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Facultad de Farmacia
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# Reconocimiento Molecular entre Quelatos de Cobre(II) con Poliaminas y el Fármaco Antiviral Aciclovir

# Molecular Recognition between Copper(II) Chelates with Polyamines and the Antiviral Drug Acyclovir

MARÍA INMACULADA PÉREZ TORO

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Memoria de Tesis Doctoral

presentada por **María Inmaculada Pérez Toro**

para aspirar al Grado de Doctor por la Universidad de Granada

Granada, Junio de 2017


María Inmaculada Pérez Toro

Los Directores

Juan Niclós Gutiérrez

Catedrático de Química Inorgánica en la Universidad de Granada

Alicia Domínguez Martín

Doctora por la Universidad de Granada

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DOCTORANDA

María Inmaculada Pérez Toro

*A mis padres,*

*a Jesús.*

*“Sólo con el corazón se puede ver bien;*
*lo esencial es invisible para los ojos”*
*El principito*

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# ABREVIATURAS

| | |
|---|---|
| ade | Adeninato |
| acv | Aciclovir |
| $Hacv^+$ | Aciclovir catiónico |
| 2aee | 2-(2-aminoetoxi)etanol |
| BCBC | N,N-bis(carboximetil)-S-benzilcisteaminato(2-) |
| bpa | Bis-(2-picolil)amina |
| bpy | 2,2'-bipiridina |
| C | Citosina |
| CCDC | Cambridge Crystallographic Data Centre |
| CSD | Cambridge Structural Database |
| cyclam | 1,4,8,11-tetraazaciclotetradecano |
| cyclen | 1,4,7,10-tetraazaciclododecano |
| dien | Dietilentriamina |
| dienol | Dietilenglicol |
| DEA | Dietanolamina |
| DMF | Dimetilformamida |
| ADN | Ácido desoxirribonucleico |
| EPR | Electron Paramagnetic Resonance |
| ESI | Información electrónica de soporte |
| FT-IR | Espectroscopía infrarroja por transformada de Fourier |
| G | Guanina |
| glygly | Glicil-glicinato |
| gua | Guanosine |
| Hade | Adenina |
| Hcyt | Citosina |
| Hhyp | Hipoxantina |
| Him | Imidazol |
| HThy | Timina |
| Hhyp | Hipoxantina |
| H(5)Meim | (5)-metilimidazol |
| IDA | Iminodiacetato |
| IUPAC | International Union of Pure and Applied Chemistry |
| M | Metal ion |
| MBPs | Metal binding patterns |
| MEPS | Molecular electrostatic potential surface |
| NMR | Resonancia Magnética Nuclear |
| phen | 1,10-fenantrolina |
| pmdta | N,N,N',N',N''-pentametildietilenotriamina |
| ppm | Partes por millón |
| RNA | Ácido ribonucleico |

| | |
|---|---|
| SQUID | Dispositivo superconductor de interferencia cuántica |
| SPN | Synthetic purine nucleoside |
| T | Timinato |
| TCC | N,N,N',N',-tetrakis(carboximetil)cistaminato(4-) |
| theo | Teofilinato |
| TG | Termogravimetría |
| tren | Tris(2-aminoetil)amina |
| trien | Trietilenetetramina |
| UV-Vis | Espectroscopía ultravioleta-visible |
| xan | Xantinato |
| XRD | Difracción de Rayos-X |

# ACRONYMS AND ABBREVIATIONS

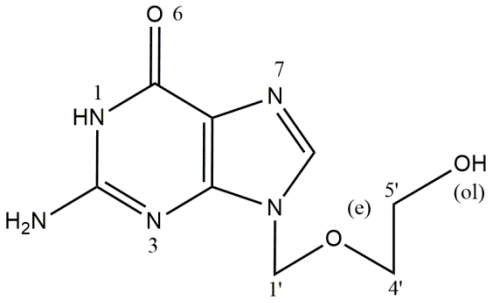
| | |
|---|---|
| ade | Adeninate |
| acv | Acyclovir |
| $Hacv^+$ | Cationic acyclovir |
| 2aee | 2-(2-aminoetoxy)ethanol |
| BCBC | N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) |
| bpa | Bis-(2-picolyl)amine |
| bpy | 2,2'-bipyridine |
| C | Cytosine |
| CCDC | Cambridge Crystallographic Data Centre |
| CSD | Cambridge Structural Database |
| cyclam | 1,4,8,11-tetraazacyclotetradecane |
| cyclen | 1,4,7,10-tetraazacyclododecane |
| dien | Diethylenetriamine |
| dienol | Diethylene glycol |
| DEA | Diethanolamine |
| DMF | Dimethylformamide |
| DNA | Deoxyribonucleic acid |
| EPR | Electron Paramagnetic Resonance |
| ESI | Electronic Support Information |
| FT-IR | Fourier Transformed - Infrared Spectroscopy |
| G | Guanina |
| glygly | Glycylglycinate |
| gua | Guanosine |
| Hade | Adenine |
| Hcyt | Cytosine |
| Hhyp | Hypoxanthine |
| Him | Imidazole |
| HThy | Thymine |
| Hyp | Hypoxanthinate |
| H(5)Meim | (5)-methylimidazole |
| IDA | Iminodiacetate |
| IUPAC | International Union of Pure and Applied Chemistry |
| M | Metal ion |
| MBPs | Metal binding patterns |
| MEPS | Molecular electrostatic potential surface |
| NMR | Nuclear Magnetic Resonance |
| Phen | 1,10-phenantroline |
| pmdta | N,N,N',N',N''-pentamethyldiethylenetriamine |
| ppm | Parts per million |
| RNA | Ribonucleic acid |

| | |
|---|---|
| SQUID | Superconducting Quantum Interference Device |
| SPN | Synthetic purine nucleoside |
| T | Thyminate |
| TCC | N,N,N',N',-tetrakis(carboxymethyl)cystaminate(4-) |
| theo | Theophyllinate |
| TG | Thermo-gravimetry |
| tren | Tris(2-aminoethyl)amine |
| trien | Triethylenetetramine |
| UV-Vis | Ultraviolet-visible Spectroscopy |
| xan | Xanthinate |
| XRD | X-Ray Diffraction |

# 1. RESUMEN/ABSTRACT

## RESUMEN

En el marco más amplio que viene desarrollando el Grupo de investigación FQM-283 "Complejos de metales de transición con interés bioinorgánico y/o terapéutico", durante casi dos décadas, sobre reconocimiento molecular entre quelatos metálicos y nucleobases o ligandos análogos, nos planteamos avanzar hacia el estudio de este fenómeno con nucleósidos derivados de bases púricas. Revisiones estructurales apropiadas, en la base *Cambridge Structural Database* (CSD) nos animaron a iniciar experiencias con aciclovir (acv): a) por tratarse de un pro-fármaco antiviral de amplia utilización, b) por la estabilidad química del N9-sustituyente acíclico, que contiene en su guanina y c) por la relativamente escasa información que se disponía de su comportamiento como ligando.




Lo conocido, por aquel entonces, dejaba claro que el átomo dador preferente de este nucleósido sintético, para iones metálicos de carácter intermedio o blando (según el criterio de Pearson) es N7, que también es el sitio preferente para su protonación. Por lo demás, se disponía de la estructura del propio aciclovir (anhidro e hidratos), de aductos orgánicos y de sales con anión orgánico o inorgánico, así como de complejos donde sólo tiene lugar el enlace metal-N7 o donde este enlace coordinado coopera con una interacción intra-molecular interligandos (O-H···O6 o N-H···O6) además de dos compuestos donde se comportaba en modo quelate-N7,O6 o en modo puente μ-N7,O(ol).

Un estudio inicial del Grupo de investigación, sobre quelatos de cobre(II) con iminodiacetato (IDA) o glicilglicinato (glygly) y acv enfatizaba la relevancia de la cooperación entre el enlace Cu-N7 y la interacción (glygly)N-H···O6. Sobre esta base surgió la idea de ampliar las fronteras del comportamiento de acv como ligando, partiendo de la idea general de investigar quelatos de cobre(II) con poliaminas como receptores de acv.

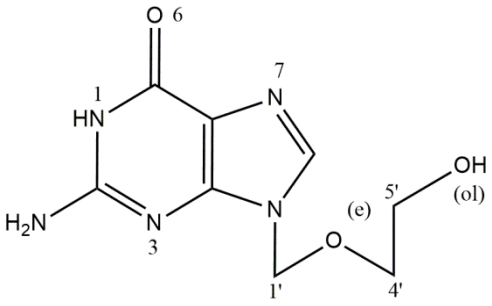
El curso de los acontecimientos ha sido objeto de cordiales discusiones de resultados y, después, ha ido perfilando nuevos objetivos, en aplicación de la más elemental metodología científica.

Los resultados obtenidos incluyen, entre otros, (a) algunos compuestos carentes de acv, por razones diversas, (b) diferentes compuestos ternarios cobre(II)-quelante-acv, (c) un complejo tetranuclear de niquel(II), molecular, conteniendo aciclovir aniónico coordinado adoptando un modo N7,O6-puente, novedoso en ambos aspectos, (d) un polímero de cobre(II) con acv monodentado y también acv multifuncional (tetradentado, puente y quelante) sin precedentes en la coordinación de nucleósidos a metales, y (e) un quelato macrocíclico de cobre(II) con acv neutro y además acv aniónico, estando ambos no coordinados al metal.

En esta Memoria, éstos y otros resultados se aportan en forma de cuatro artículos, ya publicados, un manuscrito avanzada fase de redacción y un apartado que agrupa recientes y novedosos resultados, que serán remitidos en forma apropiada para su publicación.

## ABSTRACT

During the last decades, the Research Group FQM-283 "Transition metal complexes with bioinorganic and/or therapeutic interest" has been devoted to the study of molecular recognition patterns between metal chelates and nucleobases or analogue ligands. In this context, we propose to move forward in the study of this phenomenon using synthetic nucleosides derived from purine bases. Appropriate structural revisions in the *Cambridge Structural Database* (CSD) base encourage to perform a comprehensive study on acyclovir (acv). Its interest is based on: a) acv is an antiviral drug with an extensive use, b) the chemical stability of the N9-acyclic substituent contained in its guanine moiety and c) the limited information available about its behaviour as ligand.




From previous studies, it is well-known that the preferred donor atom of this synthetic nucleoside for metal binding is N7, which is suitable for binding intermediate to soft metal ions (according to Pearson criterion). Likewise, N7 is the preferred protonation site. The structure of acyclovir (anhydrous and hydrates) as well as the structure of acv organic adducts and salts with different organic and inorganic anions have been reported already. Regarding metal complexes, the observed metal binding patterns mainly consist in a coordination bond N7-metal, or the cooperation of this bond with an intra-molecular interligand interaction (O-H···O6 or N-H···O6), with the exception of two compounds where acv acts in the N7,O6-chelating mode or in the μ-N7,O(ol)-bridging mode.

A preliminary study of our research group about copper(II) chelates with iminodiacetate (IDA) or glycilglycinate (glygly) and acv emphasized the relevance of the cooperation between the Cu-N7 bond and the (glygly)N-H···O6 interaction. On this basis, the idea of testing the potential of acv as ligand came out, expanding the metal biding abilities of acv and the capability of different copper(II)-polyamine chelates as acv receptors.

While this research was being developed, fruitful discussions regarding outcoming results lead to new goals, applying the most basic scientific methodology.

Results in this Ph.D. thesis include, among others, (a) some compounds without acv, (b) a variety of ternary copper(II)-chelating-acv complexes, (c) a tetranuclear molecular complex with nickel(II) containing coordinated anionic acv, which adopts a novel N7-O6-bridge mode, (d) a copper(II) polymer with monodentate acv and multifunctional acv (tetradentate, bridge and chelating) without precedent in the coordination of nucleosides to metals, and (e) a macrocyclic chelate of copper(II) with neutral acv and anionic acv, being both of them non-coordinated to the metal.

This Ph.D. thesis include these and other results in four articles published in indexed JCR international journals, a draft manuscript due to be submitted to a prestigious indexed journal and a section that includes recent and novel results, which will be submitted for its publication in the near future.

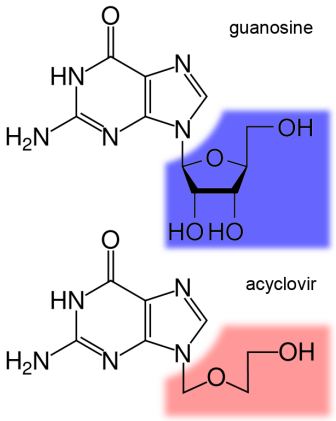
# 2. INTRODUCCIÓN/INTRODUCTION

## INTRODUCCIÓN

Durante los últimos años, el Grupo de investigación (UGR-Junta de Andalucía) FQM-283, "*Complejos de metales de transición con interés bioinorgánico y/o quimioterapéutico*"[1], viene trabajando en *reconocimiento molecular* entre quelatos metálicos y bases de los ácidos nucleicos o heterociclos nitrogenados análogos. En particular, una reciente Tesis Doctoral, que ha recibido Premio extraordinario de doctorado 2012 (Ciencias de la Salud)[2] y Premio Laza Palacios[3], se ocupa de complejos con mezcla de ligandos que incluyen un quelante incapaz de ocupar las posiciones más próximas del entorno de ion cobre(II) y adenina o ligandos relacionados, comprendiendo desde deaza-adeninas hasta aza-adeninas. Esta labor investigadora ha sido objeto de tres revisiones bibliográficas publicadas en *Coordination Chemistry Reviews* [1-3]. La referida Tesis Doctoral incluye, también, un artículo relativo a la basicidad de los átomos dadores de nucleobases en un oligonucleótido [4]. La evolución natural de esta línea de investigación va encaminada, a corto plazo, hacia el conocimiento de modos de coordinación (*metal binding patter*n) de nucleósidos con quelatos metálicos, fundamentalmente de cobre(II).

La química de coordinación de nucleósidos y nucleótidos tiene sus peculiaridades. Por una parte, los nucleósidos naturales presentan la complicación de apertura y cierre del anillo furanósico, de ribosa o desoxirribosa. Por otra parte, los nucleótidos aportan grupos fosfatos aniónicos que, por su carga, compiten eficientemente con la capacidad coordinante de su base nucleica.

Una idea atractiva, con cierto interés farmacéutico, podía ser interesarse por el comportamiento del principio activo antiviral comúnmente conocido como *aciclovir* y también como *acicloguanosina*. Este nucleósido sintético, análogo de guanosina, contiene un sustituyente en N9 portador de un átomo de oxígeno-éter, O(e) y de un átomo de oxígeno-alcohólico, O(ol):




[1] http://investigacion.ugr.es/ugrinvestiga/static/Buscador/*/grupos/ficha/FQM283
[2] http://escuelaposgrado.ugr.es/doctorado/escuelas/edcs/pages/premios_extraordinarios
[3] http://farmacia.ugr.es/noticias/Premios/RegPremioLazaPalacios.htm

El sustituyente acíclico de aciclovir en N9 tiene, por consiguiente, una notable estabilidad química, por la imposibilidad de experimentar equilibrios de apertura-cierre como los anillos furanósicos. Pese a esta gran ventaja, la química de coordinación de acv resultó relativamente limitada desde el punto de vista estructural. Una revisión estructural de aciclovir (2010) en la base de datos *Cambridge Structural Database* (CSD)[4] ponía de manifiesto el conocimiento de la estructura molecular del fármaco anhidro y varios hidratos, con casos de polimorfismo, así como de algunos *aductos* de naturaleza orgánica, una sal también de anión orgánico, un complejo de esfera externa (sal de anión complejo donde el acv no se coordina al metal), así como algunos compuestos de coordinación. En éstos últimos, el acv se coordinaba a cationes divalentes de elementos de la primera serie de transición (Co, Ni, Cu o Zn) o de Cd(II), Pt(II) o Ru(III). En todos estos complejos metálicos, la formación de un enlace coordinado implicaba la unión del átomo N7, como dador por excelencia del aciclovir, y sólo en un caso acv actuaba como ligando puente para Cd(II) (usando N7 y el O alcohólico), mientras que el acv ejercía una función quelante para Cu(II) (coordinando N7 y O6(exocíclico) al mismo centro metálico).

Un examen detenido de las estructuras descritas, por aquel entonces, revelaba que la función monodentada de acv a través de su dador N7 actuaba en varios compuestos cooperando, además, con un enlace de hidrógeno intra-molecular interligandos, de tipo O-H···O6(aciclovir) o bien de tipo N-H···O6(aciclovir). Sobre esta base, surge de inmediato la pregunta de cuándo y por qué el referido enlace de hidrógeno interligandos es operativo. Para iniciar estudios en este sentido, nuestro Grupo de investigación se planteó la conveniencia de preparar y caracterizar estructuralmente compuestos ternarios de cobre(II) conteniendo como quelantes iminodiacetato (IDA) o glicilglicinato (glygly) y, como coligando, aciclovir. La quelación del cobre(II) por IDA ofrece como dadores terminales sólo O-carboxilato por parte o bien un O-carboxilato, pero dispone de un grupo amino primario (terminal) por parte del anión $glygly^{2-}$ ($H_2NCH_2CO\text{-}NHCH_2COO$). De ese modo, la coordinación de aciclovir al quelato Cu-IDA debía esperarse sólo a través del dador N7 del nucleósido, siendo imposible el refuerzo por un enlace de hidrógeno interligandos donde O6(aciclovir) fuese el átomo aceptor. Por el contrario, la utilización de glicilglicinato(2-) como quelante abría la posibilidad de que la formación del enlace coordinado Cu-N7(aciclovir) se viera reforzada por una interacción tipo (amino, glygly)N-H···O6(aciclovir). Un artículo publicado por miembros del referido grupo de investigación, entre otros, en *Journal of Inorganic Biochemistry* (2011) [5] aporta los resultados cristalográficos que soportan la validez de esa hipótesis y que, discutidos en relación con otros datos estructurales de la bibliografía, permiten entender la afinidad del fragmento activo del fármaco antitumoral *cis*-platino por regiones de ADN en donde dos o más guaninas consecutivas se suceden en una misma hebra del ADN.

[4] https://www.ccdc.cam.ac.uk/

Los resultados del estudio inicial, en este contexto, nos animaron a plantear nuevas hipótesis, encaminadas, en una primera instancia, hacia la posibilidad de utilizar un amplio abanico de quelatos de cobre con poliaminas como receptores apropiados de aciclovir. Yendo más lejos, si fuese oportuno, podría plantearse horizontes más amplios usando análogos de poliaminas donde uno o más nitrógenos de grupos aminos primarios o secundarios fueran sustituidos por otros dadores como O-alcohólico u O-éter o bien S-tioéter o S-disulfuro. Los resultados que aporta esta Tesis Doctoral han sido obtenidos contemplando estas posibilidades.

## REFERENCIAS

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[2] D.K. Patel, A. Domínguez-Martín, M.P. Brandi-Blanco, V.M. Nurchi, J. Niclós-Gutiérrez, *Metal ion binding modes of hypoxanthine and xanthine versus the versatile behaviour of adenine*, Coord. Chem. Rev. **256** (2012) 193-211.

[3] A. Domínguez-Martín, M.P. Brandi-Blanco, A. Matilla-Hernández, H. El Bakkali, V.M. Nurchi, J.M. González-Pérez, A. Castiñeiras, J. Niclós-Gutiérrez, *Unravelling the versatile metal binding modes of adenine: Looking at the molecular recognition patterns of deaza- and aza-adenines in mixed-ligand metal complexes*, Coord. Chem. Rev. **257** (2013) 2814-2838.

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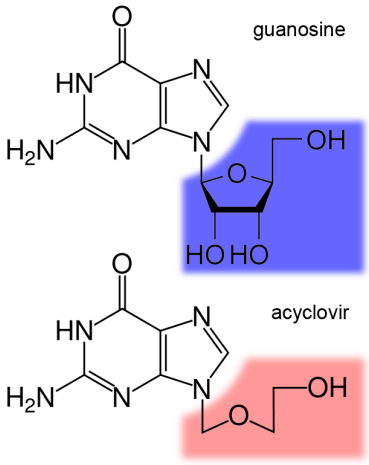
## INTRODUCTION

During the last decades, the Research Group FQM-283 "Transition metal complexes with bioinorganic and/or therapeutic interest"[1] has been devoted to the study of molecular recognition patterns between metal chelates and nucleic acids bases or nitrogen heterocyclic analogues. A recent Ph.D. Thesis defended in this research group, which received the extraordinary Ph.D. Thesis Award in Life Science[2] and the Dr. Modesto Laza Palacios Award[3], was focused on the structural characterization of metal complexes with copper(II) chelates and adenine or other related ligands, including deaza-adenines to aza-adenines. Here, the chelators used were unable to occupy the all the closest sites within the copper(II) environment. This research has been the aim of three bibliographic reviews published in *Coordination Chemistry Reviews* [1-3]. The referred Ph.D. Thesis also includes a scientific paper related to the basicity of nucleobase donor atoms in an oligonucleotide [4]. The natural evolution of this research line, in a short term, is headed towards to the knowledge of the metal binding patterns of nucleosides and metal chelates, mainly copper(II) chelates.

The coordination chemistry of nucleosides and nucleotides is very peculiar. On one hand, natural nucleotides feature the opening and closing of the furanosic ring, either ribose or deoxyribose, which hampers their coordination. On the other hand, nucleotides have a residual negative charge attributed to the anionic phosphates, which efficiently compete with the coordinating ability of the nucleobases.

An attractive idea, with potential pharmaceutical interest, would be to study the behavior of the antiviral active ingredient commonly known as *acyclovir* or *acycloguanosine*. This synthetic nucleoside, guanosine analog, has a substituent at position N9 which carries an oxygen-ether atom, O(e), and an oxygen-alcoholic atom, O(ol).




[1] http://investigacion.ugr.es/ugrinvestiga/static/Buscador/*/grupos/ficha/FQM283
[2] http://escuelaposgrado.ugr.es/doctorado/escuelas/edcs/pages/premios_extraordinarios
[3] http://farmacia.ugr.es/noticias/Premios/RegPremioLazaPalacios.htm

The N9-acyclic substituent of acyclovir has a remarkable chemical stability due to the impossibility of experiencing the opening-closing equilibrium of the furanosic ring. Despite this advantage, the coordination chemistry of acyclovir was still relatively limited from a structural point of view. In 2010, a structural review of acyclovir in the CSD[4] revealed the existence of a molecular structure of the anhydrous drug as well as several hydrates, with cases of polymorphism. Besides, some organic adducts, a salt with an organic anion, an outer sphere complex (where acyclovir is not coordinated to the metal), as well as a few coordination compounds have been reported. In these coordination compounds, acyclovir was bonded to divalent cations from the first-row transition series (Co, Ni, Cu or Zn) or to Cd(II), Pt(II) or Ru(III). Regardless of the metal ion, these metal complexes exhibit the formation of a coordination bond involving the N7(acv) atom, which is the best donor atom within acyclovir. Only two exceptions were found: (i) acyclovir played a bridging role with Cd(II) using N7 and alcoholic O donors and (ii) acyclovir showed the N7-O6(exocyclic) chelating function in a Cu(II) compound.

A thorough examination of the reported acv structures revealed that the monodentate chelating mode of acyclovir via its N7 donor cooperate in several compounds with an intra-molecular interligand hydrogen bond, type O-H⋯O6(acyclovir). This raised the question of when and why the referred interligand hydrogen bond is operative. To answer this question, our Research Group designed an experiment involving the synthesis and structural characterization of copper(II) ternary complexes containing the iminodiacetate (IDA) or glycylglycinate (glygly) chelators and acyclovir as co-ligand. The chelator IDA offers O-carboxylates as terminal donors while the anion glygly2- (H2NCH2CO-NHCH2COO) offers a primary (terminal) amino group. The coordination of acyclovir to the Cu(II)-iminodiacetate chelate led to the expected metal-N7(acv) coordination bond. A reinforcement by an interligand hydrogen bond, where O6(acyclovir) was the acceptor atom, was impossible. In contrast, the use of glycilglycinate(2-) as chelator opened the possibility of the formation of the coordination bond Cu-N7(acv) plus an intra-molecular interligand interaction type amine(glygly)N-H⋯O6(acyclovir). These results were published in 2011 on Journal of Inorganic Biochemistry [5] and provide crystallographic results that support the validity of this hypothesis. These results, discussed together with other structural data described in the literature, allow a better understanding of the affinity of the active moiety of the antitumoral drug cis-platinum to DNA regions where two or more consecutives guanines are present in the same DNA strand.

[4] https://www.ccdc.cam.ac.uk/

In this context, the results of this preliminary study encouraged us to further test the coordination abilities of acv, looking for novel acv metal binding patterns. At first instance, the possibility of using a wide range of copper(II) chelates with polyamines as appropriate acyclovir receptors was planned. Going further, broader horizons were considered, using polyamine analogues where one or more nitrogen atoms from the primary or secondary amino groups were substituted by other donors such as O-alcoholic or O-ether, or S-tioether or S-disulfide. The results provided in this Ph.D. Thesis have been obtained considering all of these possibilities.

## REFERENCES

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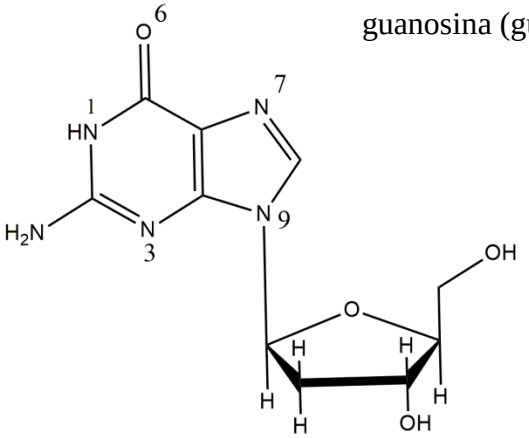
# 3. ANTECEDENTES

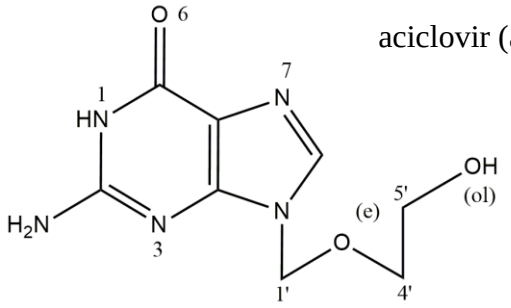
## ANTECEDENTES

El aciclovir (acv) es conocido también como aciclo-guanosina por la correlación que existe entre este nucleósido sintético y el natural guanosina (gua), tal como reflejan las fórmulas estructurales que se indican a continuación:

guanosina (gua)




aciclovir (acv)




Con carácter general, la **notación** de la parte guanina (G) debe acogerse a la propia de las purinas, incluyendo N1 (lactámico), N2 (amino exocílico), N3, N7 y N9 (heterocíclicos) y O6 (exocíclico). Para el acv, se propone en esta Tesis Doctoral referirnos como O(e) y O(ol) a los átomos de oxígeno de los grupos funcionales éter y alcohol, respectivamente, en el sustituyente acíclico sobre N9.

Las estructuras cristalinas recogidas en estos Antecedentes serán vinculadas a sus acrónimos de la base CSD (seis caracteres en mayúsculas, p.ej. CUHFGO, a veces seguidos de dos dígitos numéricos, p.ej. CUHFGO01) y/o por su cita bibliográfica entre corchetes, recogida a final de esta parte de la Memoria.

La estructura molecular del acv fue aportada, en primer lugar, para un hidrato de composición $3acv{\cdot}2H_2O$ o $acv{\cdot}0.66H_2O$ (CEHTAK [1], CEHTAK10 [2], Figura 1). En la actualidad, se conoce también la estructura de dos polimorfos para acv anhidro, cristalizados en el sistema monoclínico (MECWIC [3] o MECWIC01 [4] del grupo $P2_1/c$, Figura 2-a) y MECWIC2 o MECWIC3 del grupo $P2_12_12_1$ [4], Figura 2-b) además del hidrato superior, $acv{\cdot}2H_2O$ (WOZPAE [4], Figura 3).

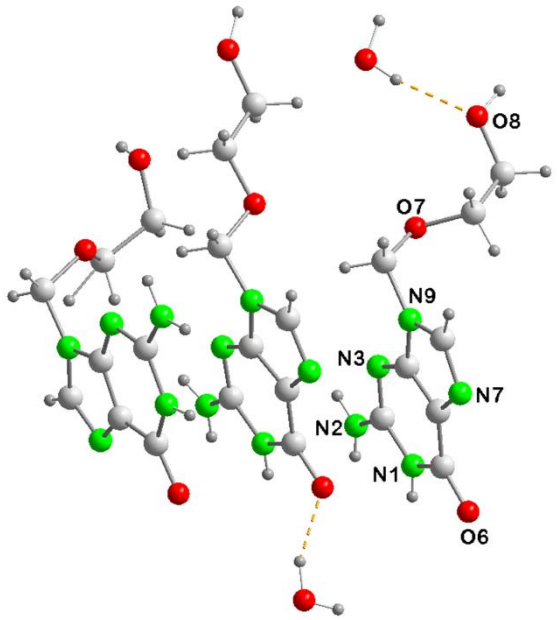



Figura 1. Estructura de 3acv·2H2O (CEHTAK10, [2]).

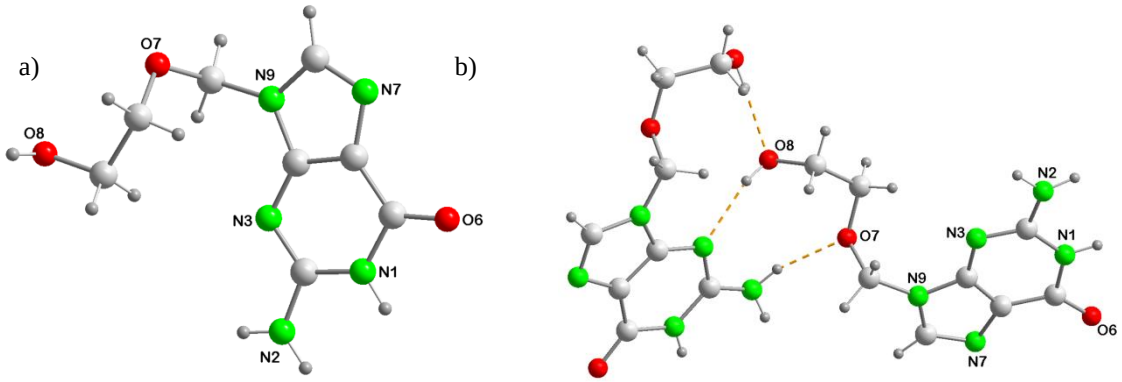



Figura 2. Polimorfos de acv (anhidro): a) MECWIC01 [4]. b) MECWIC03 [4].

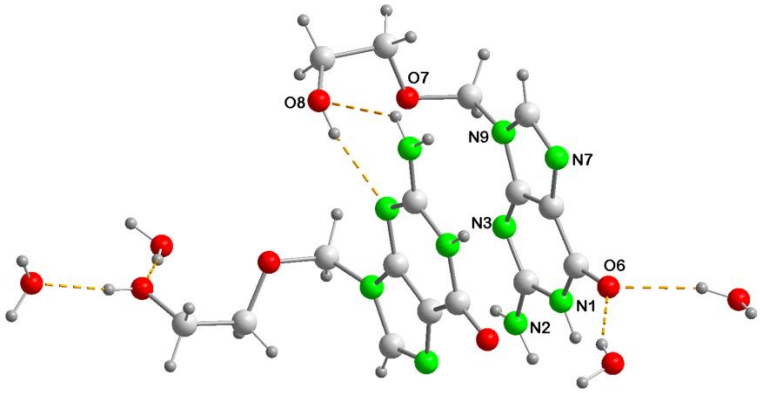



Figura 3. Estructura de acv·2$H_2O$ (WOZPAE, [4]).

Por otra parte, se ha descrito la estructura cristalina de aductos orgánicos de acv con 5-fluorocitosina (H5Fcyt:acv, MECWOI [3], Figura 4) o con los ácidos fumárico (RIGDAO) [5] o glutárico (RIGDES) [5] así como de la sal Hacv(Hmaleato) (RIGDIW [5]) para la cual se han referido muy recientemente (2017) éste (RIGDIW01 [6]) y otro polimorfo (RIGDIW02), ambos cristalizados el sistema monoclínico, grupo P-1, pero con diferente celda unidad, en razón de la distinta conformación de N9-sustituyente acíclico [6].

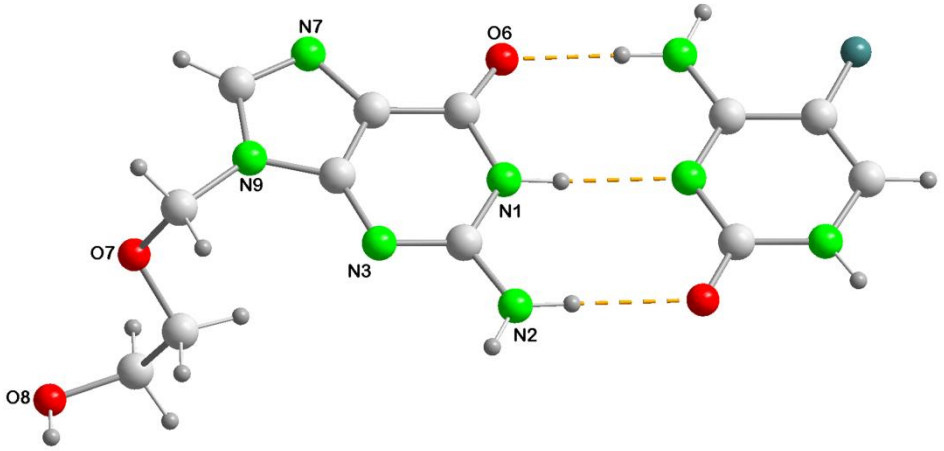



Figura 4. Estructura del aducto H5Fcyt:acv (MECWOI [3]). En la unidad asimétrica, el par de bases se relaciona con tres enlaces de hidrógeno, (acv)N1-H···N3(H5Fcyt), (acv)N2-H···O4(H5Fcyt) y (acv)O6···H-N4(H5Fcyt), de modo similar al par guanina:citosina en la forma B (Watson-Crick) de un ADN.

La **revisión estructural** que concierne al acv, unida a los resultados originales que se aportan en esta Tesis Doctoral, serán objeto de una revisión bibliográfica exhaustiva, que se remitirá próximamente para su consideración en la prestigiosa revisa ***Coordination Chemistry Review***. La parte original de esta Tesis Doctoral sustenta una ampliación de las fronteras que delimitaban el comportamiento del acv como ligando.

En lo que concierne a ***Compuestos conteniendo iones metálicos y acv***, se ha descrito un complejo de esfera externa (H(N7)acv)trans-[$Ru^{II}Cl_4$(O-dmso)(NO)] (BOPZAI [7], Figura 5) donde el nucleósido existe en forma protonada $Hacv^+$, conteniendo el protón adicional en N7 y, por consiguiente, no coordinada directamente al metal (al estar bloqueado su átomo dador preferente). En este cristal, pares de cationes $Hacv^+$ están unidos por dos enlaces de hidrógeno $N7^+$-H···O6 (2.646 Å, 161.3º) relacionados por simetría, mientras que el reconocimiento catión-anión está esencialmente restringido a la interacción N1-H···Cl (3.200 Å, 168.9º) débilmente asistida por otra interacción N2-H···Cl más débil (3.362 Å, 157.7º).

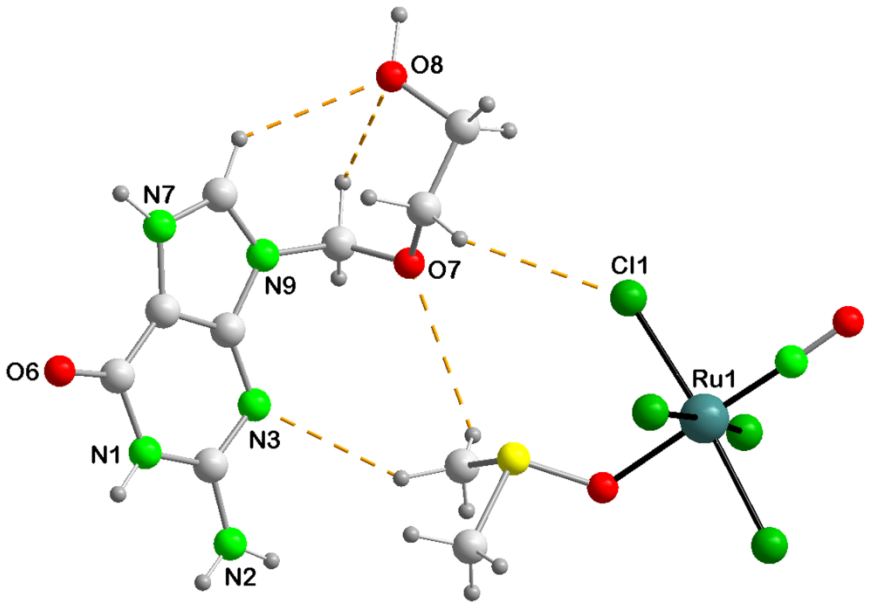



Figura 5. Asociación, por enlaces de hidrógeno, entre pares de cationes $Hacv^{+}$ y cation-anión en el coplejo de esfera externa (H(N7)acv)trans-[$Ru^{II}Cl_4$(O-dmso)(NO)] (BOPZAI, [7]).

Téngase en cuenta que una reflexión sobre la fórmula estructural del acv, permite hacer las siguientes consideraciones generales:

(a) El átomo N1 carece de interés como dador, al encontrarse el resto de guanina en forma lactámica y, por lo tanto, con el par electrónico de N1 implicado en la deslocalización electrónica (y con el átomo N1 unido a un átomo H) lo que, definitivamente, le excluye como potencial coordinante.

(b) Por otra parte, el átomo N3 de guanina, tiene muy escasa o nula posibilidades de coordinación a metales, por el notable factor estérico y las influencias inductivas que impone el grupo amino exocíclico adyacente, en la posición 2 del heterociclo.

(c) Tampoco cabe esperar la coordinación del O6 exocíclico (dador duro de Pearson) a iones metálicos de carácter intermedio o blandos, a menos que su unión a un metal (M) coopere con la coordinación por N7 (de carácter intermedio).

(d) Nula posibilidad tiene el átomo N9, portador del sustituyente acíclico.

(e) Y pocas posibilidades, aunque no ninguna, tienen los átomos O de este N9-sustituyente acíclico, O(e) y O(ol).

(f) Es obvio, por consiguiente, que el dador preferente de acv debe ser N7, en particular a iones metálicos de carácter intermedio o blando, según el criterio de Pearson.

El **comportamiento de acv como ligando**, en base a los antecedentes de esta Tesis Doctoral, puede resumirse en los siguientes modos de reconocimiento molecular:

**(a) Formación exclusiva del enlace coordinado M-N7: Modo de coordinación (a1).**

Se ha descrito en el complejo de Pt(II) cis-$[Pt(acv)_2(NH_3)_2]Cl_2\cdot 2H_2O$ (ZAYBIK [8], Figura 6) y en los complejos de Cu(II) $[Cu(acv)_2(H_2O)_3](NO_3)_2\cdot H_2O$ (RUMGAH [9] y$\{[Cu(IDA)(acv)]\cdot 2MeOH\}_n$ (IPUXIB [10], Figura 7). Nótese que los dos primeros de estos compuestos contienen una ratio acv/M 2:1, mientras que, en el tercero, el metal y el nucleósido están en relación equimolar 1:1. Es también sorprendente que en los dos primeros compuestos, donde el metal contiene, además, amoníaco o agua como ligando, la formación del enlace M-N7 no se vea reforzada por un enlace de hidrógeno intra-molecular interligandos. En ambos casos, el examen de las estructuras revela que la disposición de los restos de guanina resulta inapropiada para la formación de tal interacción interligandos. Por otra parte, la coordinación de acv al quelato de Cu(II) con iminodiacetato (IDA), que adopta una conformación-*mer* en el entorno del metal, imposibilita el referido enlace de hidrógeno interligandos, puesto que los grupos carboxilato terminales del quelante IDA no pueden actuar como *dadores* de hidrógeno (del que carecen) para una interacción tipo O-H···O6(acv).

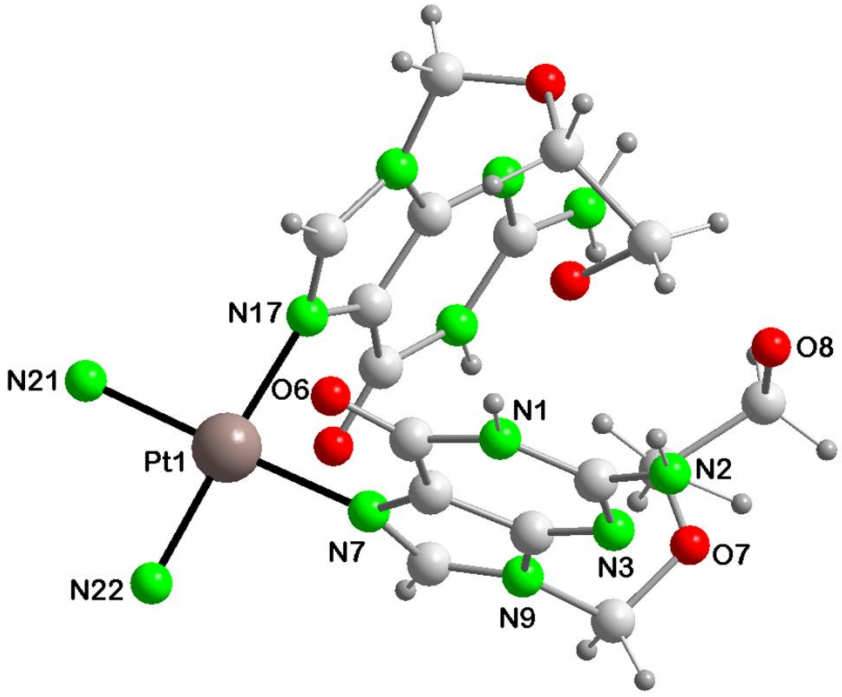



Figura 6. Estructura de cis-$[Pt(acv)_2(NH_3)_2]Cl_2\cdot 2H_2O$ (ZAYBIK, [8]).

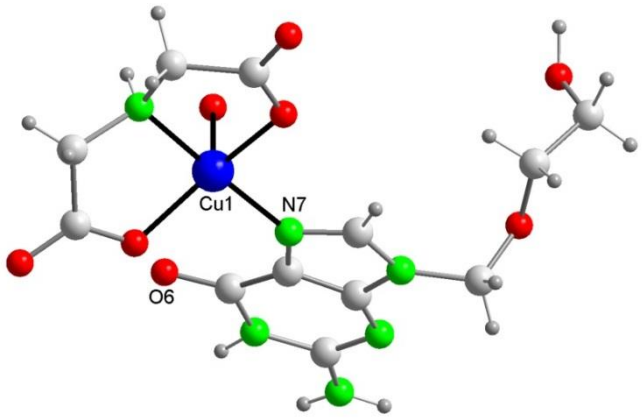



Figura 7. Entorno de coordinación del Cu(II) en el polímero $\{[Cu(IDA)(acv)]\cdot 2MeOH\}_n$ (IPUXIB, [10]).

### (b) Cooperación del enlace coordinado M-N7 con un enlace de hidrógeno intra-molecular interligandos A-H···O6(acv): Modo de coordinación (a2).

Existe un grupo razonablemente diverso de compuestos donde el modo de reconocimiento molecular del acv en un compuesto con mezcla de ligandos representa la eficiente cooperación entre el enlace M-N7 y un enlace de hidrógeno intra-molecular interligandos, de tipo OH···O6(acv) o tipo N-H···O6(acv). Estos compuestos son derivados de cationes divalentes de la primera serie de transición o de Ru(III):

| Metal | Código CSD | Formula/Comment(s) | M-N7(acv) (Å) | Interacción interligandos (O or N)-H···O6(acv) d (Å), > (º) | Ref. |
|---|---|---|---|---|---|
| Co(II) | JAJPUG | mer-[Co (o-Ihip)$_2$(acv)(H$_2$O)$_3$] | 2.171(3) | 2668, 160.25 | 11 |
| Ni(II) | HOPBOD | trans-[Ni(H$_2$O)$_4$(acv)$_2$]Cl$_2$·2acv | 2.160(2) | 2.634(2), 162.46 | 12 |
| Cu(II) | IPUXEX | [Cu(glygly)(acv)]·H$_2$O | 1.994(2) | 2.961, 140.5 | 10 |
| | ZATJIN | Trans-[Cu(acv)$_2$(H$_2$O)$_2$Cl$_2$]/Cl-apical-distal | 2.029(2) | 2.594, - | 13 |
| Zn(II) | JAJPOA | mer-[Zn(o-Ihip)$_2$(acv)(H$_2$O)$_3$] / isotype with JAJPUJ | 2.171 | 2.669, 168.19 | 11 |
| | HOPBUJ | [Zn(acv)(H$_2$O)Cl$_2$] | 2.009 | 2.845, 151.49 | 12 |
| Pt(II) | SIMMOQ | [Pt(en)(acv)$_2$][PF$_6$]$_{1.5}$Cl$_{0.5}$·H$_2$O | 2.014<br>2.032 | 2.970, 144.34<br>2.955, 146.92 | 14 |
| Ru(III) | LUFGIC | mer-[Ru$^{III}$ Cl$_3$(acv)(S-dmso)(H$_2$O)]·H$_2$O | 2.127(5) | 2.573(2), 174.94 | 15 |
| | LUFGEY | mer-[Ru$^{III}$Cl$_3$(acv)(S-dmso)(MeOH)]·0.5MeOH | 2.132(7) | 2.517(7), 176.46 | 15 |
| | ARAMOV | mer-[Ru$^{III}$Cl$_3$(acv)(S-dmso)(EtOH)]·EtOH | 2.148(6) | 2.553(8), 154.30 | 16 |

Parte de tales compuestos aportan el fragmento OH para la formación de la interacción, procedente de agua coordinada (ligando aqua), de metanol o de etanol coordinado. Otros tienen la interacción N-H···O6(acv). Es evidente que la coordinación de agua o de estos alcoholes a un centro metálico divalente o trivalente aumenta la polaridad del enlace OH, favoreciendo la formación de la interacción OH···O6(acv). Ejemplos destacables de estos compuestos son trans-[$Cu(acv)_2(H_2O)_2Cl_2$] (ZATJIN [13], Figura 8), [$Zn(acv)(H_2O)Cl_2$] (HOPBUJ [12], Figura 9 ) y [$Cu(glygly)(acv)]\cdot H_2O$ (IPUXEX [10], Fugura 10), con diferentes tipos de coordinación en sus entornos del metal.

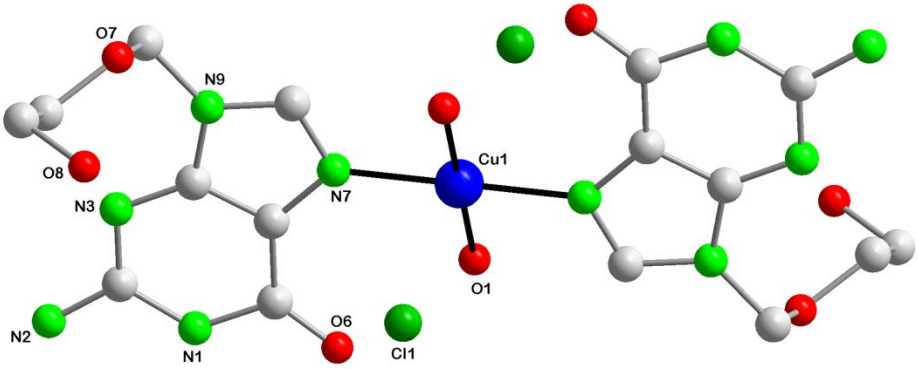



Figura 8. Estructura de trans-[$Cu(acv)_2(H_2O)_2Cl_2$] (ZATJIN [13]). En este complejo molecular, el Cu(II) adopta un entorno octaédrico alargado, centrosimétrico, con sendos ligandos cloro en las posiciones trans-apicales/distales para favorecer que ambos ligandos acv coordinen por su dador N7 en cooperación con la correspondiente interacción intra-molecular interligandos (aqua)O-H···O6(acv).

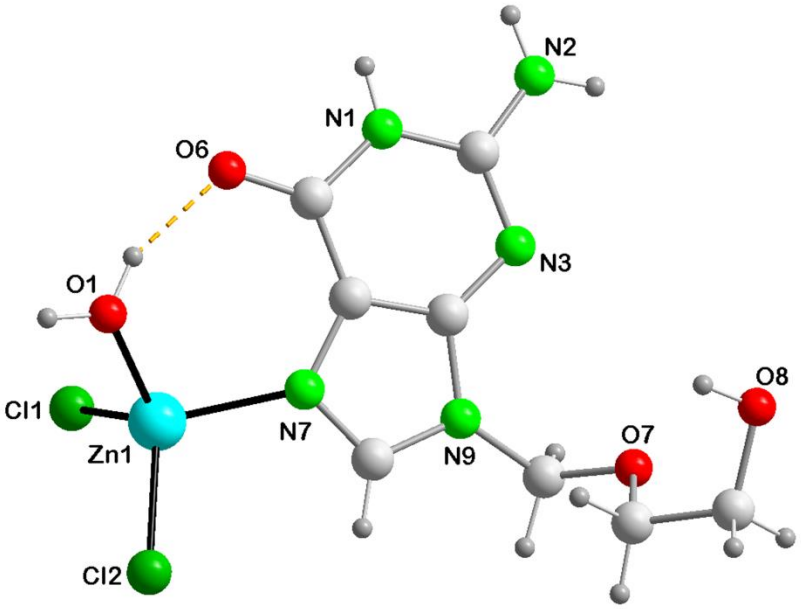



Figura 9. Estructura del complejo molecular [$Zn(acv)(H_2O)Cl_2$] (HOPBUJ, [12]). El Zn(II) está tetracoordinado, en un entorno tetraédrico, lo que implica una notable polarización del ligando aqua. La coordinación de acv por el enlace Zn-N7 se refuerza por la interacción inra-molecular interligandos (aqua)O-H···O6(acv).

La estructura del complejo [Cu(glygly)(acv)]·$H_2O$ (IPUXEX [10], Figura 10) revela que, también, en este complejo molecular plano-cuadrado donde el dipéptido $glygly^{2-}$ actúa como quelante mer-tridentado, es posible la cooperación entre el enlace Cu-N7(acv) y la interacción interligandos (glygly-NH···O6(acv)). Tal interacción debe estar propiciada por la estructura plano cuadrada del complejo de cobre(II) y la coordinación del grupo amino primario de glygly entre las cuatro posiciones más próximas del entorno del Cu(II). Es, precisamente, el conocimiento de esta estructura, lo que nos llevó a contemplar la posibilidad de investigar el modo de coordinación del acv a complejos de Cu(II) (o de otros iones metálicos) con poliaminas quelantes.

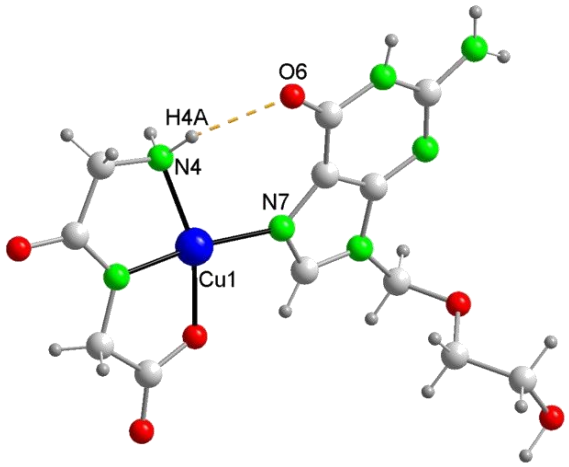



Figura 10. Estructura del complejo planocuadrado [Cu(glygly)(acv)]·$H_2O$ (IPUXEX [10]. Dado que el quelante glicil-glicinato dispone de un grupo amino primario terminal, la cooperación entre el enlace Cu-N7(acv) y la interacción intra-molecular interligandos (glygly)N-H···O6(acv) es operativa.

La cooperación de un enlace Ru-N7 con una interacción intra-molecular interligandos se da también en los compuestos moleculares donde el grupo O-H lo aporta un ligando aqua (LUFGIC [15]), metanol (LUFGEY [15]) o etanol (ARAMOV [16]), circunstancia que no deja de tener un particular interés, habida cuenta de las evidencias que se tienen sobre la conveniencia de usar disolventes menos polares que el agua en las estrategias de síntesis.

También se dispone de la estructura cristalina del complejo catiónico en $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot H_2O$ (SIMMOQ [14]) siendo *en* etilendiamina o 1,2-diaminoetano, conteniendo una relación acv/M 2:1. En este caso (y en contra de lo arriba referido para cis-$[Pt(acv)_2(NH_3)_2]Cl_2\cdot 2H_2O$, ZAYBIK, [8]), el modo de reconocimiento molecular implica, para cada uno de los ligandos acv, la formación del enlace M-N7 en cooperación con una interacción interligandos tipo (en)N-H···O6(acv).

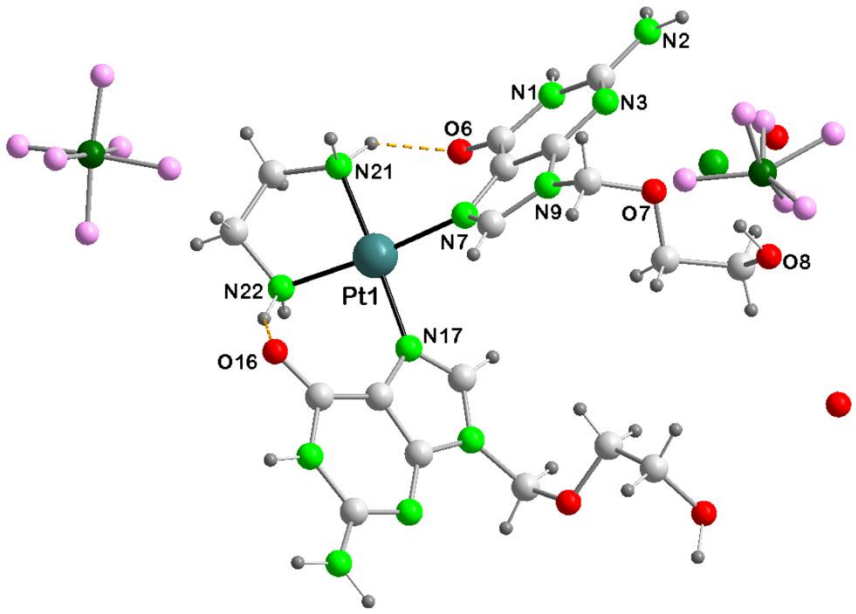



Figura 11. Estructura del complejo catiónico en el cristal de $[Pt(en)(acv)_2][PF_6]_{1.5}Cl_{0.5}\cdot H_2O$ (SIMMOQ [14]).

La estructura de los compuestos referidos en este epígrafe tiene un notable interés por cuando establece, para HOPBOD, ZATJIN y SIMMOQ, la posibilidad de coordinar hasta dos ligandos acv a un mismo centro metálico, con la eficiente cooperación de los citados enlaces de hidrógeno intra-moleculares interligandos.

Es importante destacar la relevancia del modo de coordinación a2 en complejos de diferentes iones metálicos, con mezclas de ligandos, donde el comportamiento del acv como ligando, implica el hecho común de que los enlace O-H o N-H involucrados en las interacciones O-H···O6(acv) o N-H···O6(acv) deben pertenecer a ligandos coordinados (aminas, agua, alcoholes). Además, en casos de entornos distorsionados por efecto Jahn-Teller, propios de los complejos de Cu(II), los ligandos dadores de los grupos O-H deben coordinarse al metal entre las cuatro posiciones más próximas de su entorno. Solo así se entiende que los ligandos aqua (neutros) de trans-$[Cu(acv)_2(H_2O)_2Cl_2]$ (ZATJIN [13], (Figura 8) releguen la los iones cloruro coordinados a las posiciones trans-apicales/distales del entorno tipo 4+2 del cobre(II).

**(c) Un caso singular.**

Se ha descrito también la estructura de $[Pt(en)(acv)_2]SO_4\cdot 2.5H_2O$ (MENJOE [17], Figura 12) que constituye un caso singular donde uno de los ligandos acv se coordina formando solo el enlace Pt-N7 (modo a1) mientras que el otro constituye el enlace Pt-N7 en cooperación con la interacción intra-molecular interligandos N-H···O6(acv). No se dispone de suficiente información estructural para justificar este comportamiento singular, que probablemente se deba a la influencia del empaquetamiento del cristal. En este sentido, el grupo amino implicado en la interacción intra-molecular, lo hace generando una interacción N-H···O6 intermolecular.

Además, el átomo O6 implicado en la interacción N-H···O6 intra-molecular también lo hace en una interacción similar, pero intermolecular, actuando como doble aceptor de hidrógeno.

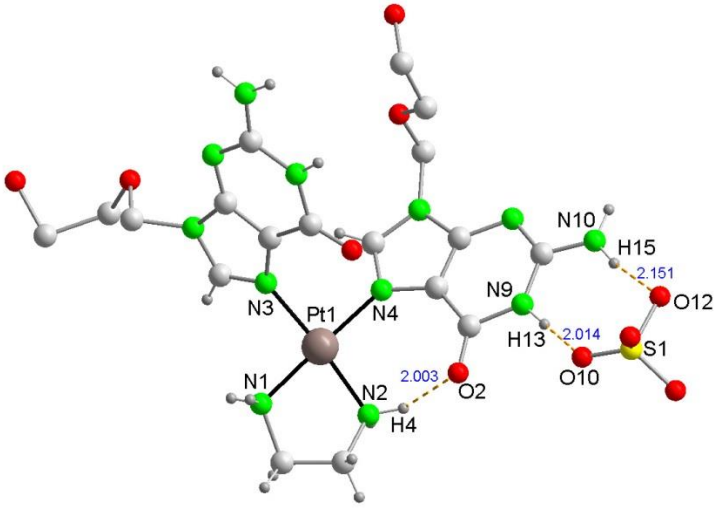



Figura 12. Estructura del cation complejo de $[Pt(en)(acv)_2]SO_4 \cdot 2.5H_2O$ (MENJOE, [17], mostrando que sólo uno de los grupos amino del quelante etilendiamina se implica en una interacción (en)N-H···O6(acv).

**(d) Acv como ligando puente.**

Se ha descrito la estructura del compuesto polimérico $(\{Cd(\mu_2\text{-}Cl)_2(\mu_2\text{-}N7,O(ol)\text{-}acv)]\cdot H_2O\}_n$ (HOPCAQ [12], Figura 13) donde el acv ejerce la función de ligando puente μ-N7-O(ol) entre dos centros metálicos, con enlaces Cd-N7 (2.402(2) Å) y Cd-O(ol) (2.305(1) Å). Cada ion Cd(II) tiene un entorno octaédrico, con dos posiciones satisfechas por el dador N7 y el dador O(ol) de dos ligandos diferentes. El polímero de coordinación se genera mediante un esqueleto de unidades $\{Cd(\mu_2\text{-}Cl)_2\}$ que se extiende a lo largo del eje a del cristal. Estas estructuras están engarzadas por los ligandos $\mu_2$-N7,O(ol)-acv, extendiendo la polimerización a entramados 2D paralelos al plano ab del cristal, que después conectan por enlaces de hidrógeno en una red 3D. En estos enlaces de hidrógeno, la implicación de la molécula de agua en tres interacciones es patente: (acv)N1-H···O(agua) (2.800 Å, 168.8º), (agua)O-H···O(e) (2.841 Å, 168.0º) y (agua)O-H···O6(acv) (2.893 Å, 158.2º). Lo más notable de este compuesto es, desde luego, la implicación del dador O(ol) de acv en la denticidad del nucleósido sintético.

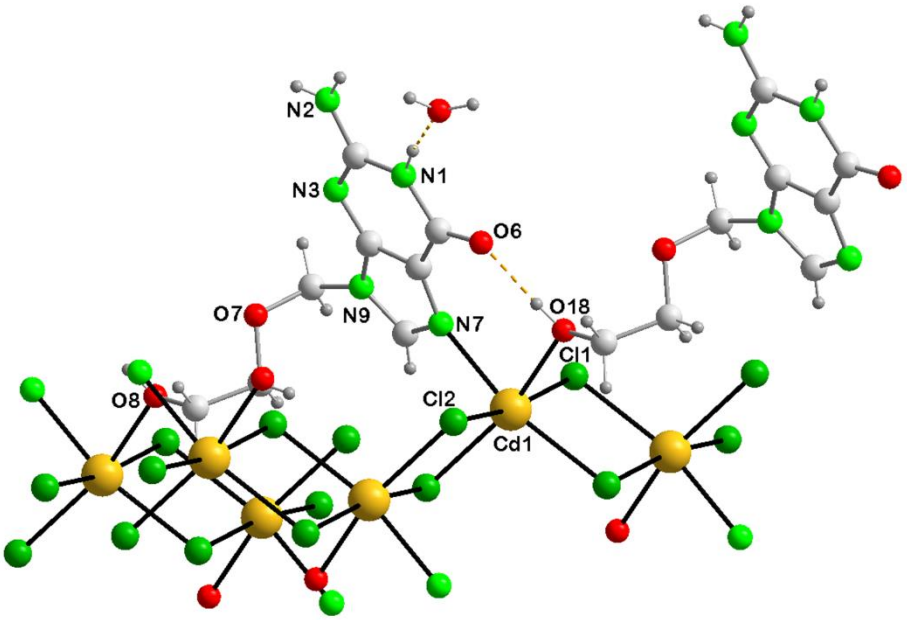



Figura 13. ({Cd($\mu_2$-Cl)$_2$($\mu_2$-N7,O(ol)-acv)]·$H_2O$}$_n$ (HOPCAQ [12]).

**(e) Función quelante del acv.**

I. Turel y cols. [18] publicaron la estructura del compuesto *trans*-[Cu(acv)$_2$($H_2O$)$_2$]($NO_3$)$_2$ (HOSQUB, Figura 14-a) describiendo la geometría de coordinación del cobre(II) en el complejo catiónico como plano-cuadrada. No obstante, el examen detenido de esta estructura deja fuera de dudas que cada ligando acv actúa como quelante asimétrico en modo $\eta_2$-N7,O6, siendo el enlace Cu-N7 (2.004(2) Å) significativamente más corto que el enlace Cu-O6 (2.698(2) Å). Este último enlace no puede ni debe ignorarse, puesto que su distancia es más corta que la suma de los radios de Van der Waals ($r_O + r_{Cu}$ = 1.50 + 1.40 = 2.90 Å). Por consiguiente, el entorno de coordinación del Cu(II) en este complejo es de tipo octaédrico alargado o 4+2, donde los dadores trans-apicales/distales son los átomos O6 de sendos ligandos acv.

Es importante notar la quelación asimétrica del acv al cobre(II), sometido a la distorsion Jahn-Teller, por su configuración electrónica $3d^9$. La afinidad del cobre(II) (ácido intermedio de Pearson) con el dador N7-acv (base intermedia de Pearson) es mucho mayor que con el dador O6-acv (base dura de Pearson), lo que sitúa a los dadores N7-acv entre los cuatro dadores más próximos al metal. Otra cuestión muy distinta es la razón por la que los dadores O6 de sendos ligandos acv son relegados a las posiciones apicales-distales, mientras que sendos ligandos aqua se sitúan en posiciones proximales al cobre(II). En el complejo catiónico de HOSQUB la distancia interatómica N7···O6 es (2.98 Å) más larga que la distancia N7(acv)···O(aqua) (2.77 Å). La razón de esto parece estar relacionada con la rigidez del esqueleto de guanina, que separa a sus dadores N7 y O6 a casi 3 Å (2.98 Å en el caso que nos ocupa). Esto hace que los dadores O6-acv, en el catión centrosimétrico *trans*-[Cu(acv)$_2$($H_2O$)$_2$]$^{2+}$ se desvíen de la verticalidad con respecto al plano [Cu(N7)$_2$(O-aqua)$_2$] en unos 10º.

Desde el punto de vista sintético, es interesante señalar, también, que el compuesto *trans*-$[Cu(acv)_2(H_2O)_2](NO_3)_2$, de color verde oscuro (HOSQUB, [18]) se obtuvo por reacción de cantidades equimolares (1.33 mmol) de $Cu(NO_3)_2{\cdot}3H_2O$ y acv en metanol (30 ml), mientras que usando una mezclas agua-metanol como medio disolvente se obtiene $[Cu(acv)_2(H_2O)_3](NO_3)_2{\cdot}H_2O$ (RUMGAH [9], Figura 14-b) donde los ligandos acv se coordinan al cobre(II) sólo y exclusivamente por su dador N7 (modo a1). Estas consideraciones ponen de manifiesto la importancia de la polaridad de medio en las síntesis de complejos de aciclovir. Parece claro que la disminución de número n de ligandos aqua al pasar de RUMGAH (n = 3) a HOSQUB (n = 1) desempeña una influencia notable.

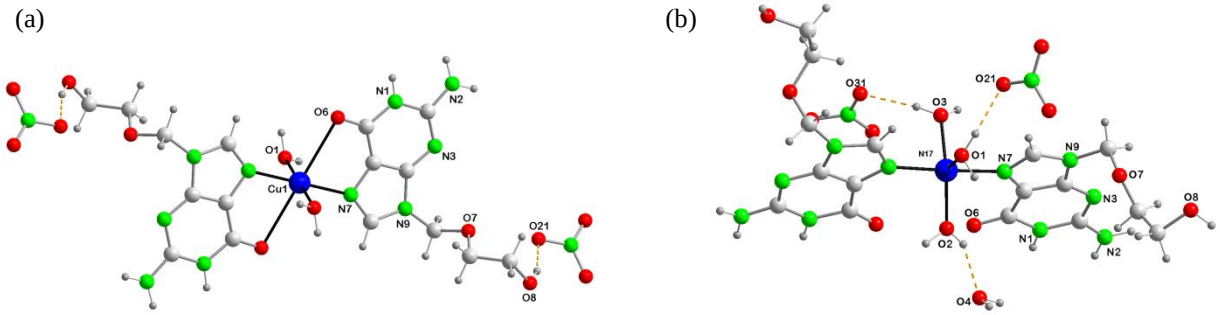



Figura 14. (a) Catión complejo centrosimétrico de trans-$[Cu(acv)_2(H_2O)_2](NO_3)_2$ (HOSQUB [18]) mostrando el modo quelante asimétrico $\eta_2$-N7,O6 de sus ligandos acv. (b) Catión complejo de $[Cu(acv)_2(H_2O)_3](NO_3)_2{\cdot}H_2O$ (RUMGAH [9]), donde los ligandos acv sólo se coordinan al Cu(II) por su dador N7 (modo a1).

En resumidas cuentas, los antecedentes de esta Tesis Doctoral ponían de manifiesto que, en todos los casos de complejos metálicos de 'esfera interna', la molécula de aciclovir coordina al ion metálico (M) a través de su dador preferente, el átomo N7, que tiene carácter de ácido intermedio de Pearson. Nótese que se conocían estructuras de complejos con cationes que son considerados ácidos intermedios de Pearson ($Co^{II}$, $Ni^{II}$, $Cu^{II}$, $Zn^{II}$, $Ru^{III}$) o ácidos blandos de Pearson ($Cd^{II}$, $Pt^{II}$). En complejos afectados por distorsiones estructurales asociadas al efecto Jahn-Teller, como es el caso de los complejos de Cu(II), el dador N7-acv ocupa una de las cuatro posiciones más próximas de su entorno, con una distancia de enlace ligeramente más corta que 2.00 Å. La formación del enlace M-N7(acv) puede cooperar con una interacción intramolecular interligandos tipo A-H···O6(acv), siendo A un O o N coordinado. La denticidad del acv puede ser superior actuando como ligando puente μ-N7,O(ol) o como quelante bidentado asimétrico η-N7,O6.Se desconocen complejos con más de dos ligandos acv coordinados al mismo dentro metálico. La coordinación de dos ligandos acv a un mismo ion metálico puede hacerse en disposición *cis* o *trans*.

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# 4. OBJETIVOS

## OBJETIVOS

Los antecedentes de este trabajo y, en particular, el estudio de las estructuras de los compuestos $[Cu(IDA)(acv)]\cdot 2MeOH\}_n$ y $[Cu(glygly)(acv)]\cdot H_2O$ ponían de manifiesto cuatro circunstancias importantes, relativas al reconocimiento molecular de acv en complejos metálicos con mezcla de ligandos:

a) La preferencia absoluta para coordinarse por su dador N7 a centros metálicos (M) con carácter de ácido intermedio o blando, según el criterio de Pearson.

b) La tendencia a la eficiente colaboración entre el enlace M-N7(acv) con una interacción intra-molecular interligandos de tipo O-H···O6(acv) o N-H···O6(acv), donde los átomos O y N portadores de H están coordinados.

c) La posibilidad de ejercer el modo quelante-N7,O6 asimétrico, con enlaces de desigual distancia ($Cu^{II}$-N7 < $Cu^{II}$-O6) que, en buena parte, se puede relacionar por la mayor afinidad mutua entre el $Cu^{II}$ (ácido intermedio de Pearson) por el dador N7-acv (base intermedia de Pearson) que por el O6-acv (base dura de Pearson.

d) La posibilidad de implicar al menos el dador O(ol) del N9-sustituyente acíclico de acv en la coordinación, como queda patente en la función puente μ-N7,O(ol) establecida para el complejo polímero de cadmio(II).

El conocimiento de estas circunstancias perfilaba un dominio sobre el que plantearse una crucial cuestión:

**¿Son éstas las fronteras definitivas del comportamiento del aciclovir como ligando o es posible plantearse nuevos retos que expandan estos límites?**

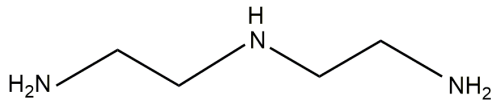
Para dar respuesta a ella, se podían definir, entre otros, diversos **Objetivos** sobre la base de la ***utilización de complejos metálicos con poliaminas quelantes (y ligandos análogos) como receptores de aciclovir***, sin distanciarse de la perspectiva de la metodología científica que, sobre la base de nuevos resultados, apunten hacia retos adicionales.

Estos (y otros) objetivos conllevan, de modo implícito, la preparación de cristales únicos apropiados para la *determinación cristalográfica de las estructuras* de los compuestos investigados. Asimismo, se estimó la conveniencia de iniciar las investigaciones con diversas oxosales de cobre(II), como fuentes de aporte del ion metálico, sabedores de que el efecto Jahn-Teller, impuesto por su configuración electrónica ($[Ar]3d^9$) y el socorrido *formalismo de los huecos*, lo que se traduce en la valiosa *plasticidad de sus entornos de coordinación* y, en concreto, en la generación de

desiguales distancias de enlaces coordinados, que *discriminan a sus átomos dadores* en *proximales* o en *apicales-distales*.

Los Objetivos inicialmente planteados se centran en la síntesis y cristalización de diversos complejos metálicos, que se pueden puntualizar como sigue:

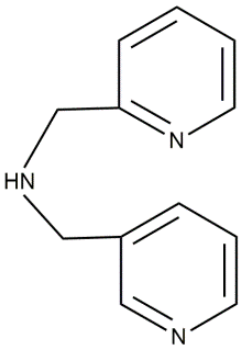
1. Complejos ternarios $Cu^{II}$-dien-acv, donde previsiblemente pueda coordinarse N7-acv a una posición proximal del metal, en cooperación con la interacción interligandos (dien)N-H···O6(avc).

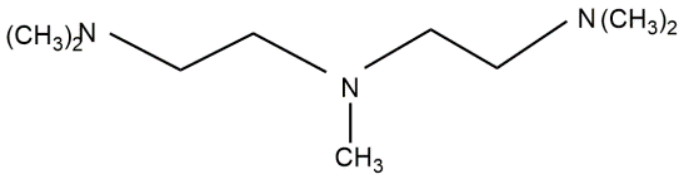



dien

Diethylenetriamine

2. Complejos análogos a $Cu^{II}$-dien-acv donde se dificulte o impida la cooperación del enlace Cu-N7(acv) con la interacción (dien)N-H···O6(avc), usando las aminas tridentadas bpa o pmdta, respectivamente.



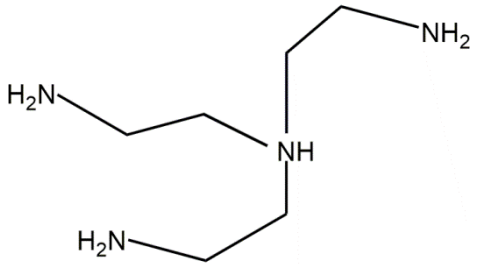

bpa

Bis-(2-picolyl)amine

pmdta

N,N,N’,N’,N’’-pentamethyldiethylenetriamine

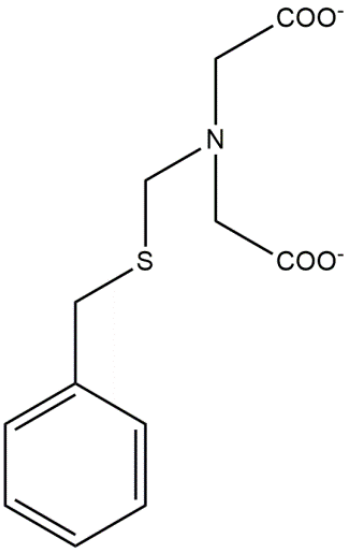
3. Complejos $Cu^{II}$-tren-acv, donde el ligando tetradentado-trípode tren pueda permitir al dador N7-acv coordinarse a una posición proximal del metal, en cooperación con la interacción interligandos (tren)N-H···O6(avc).




tren

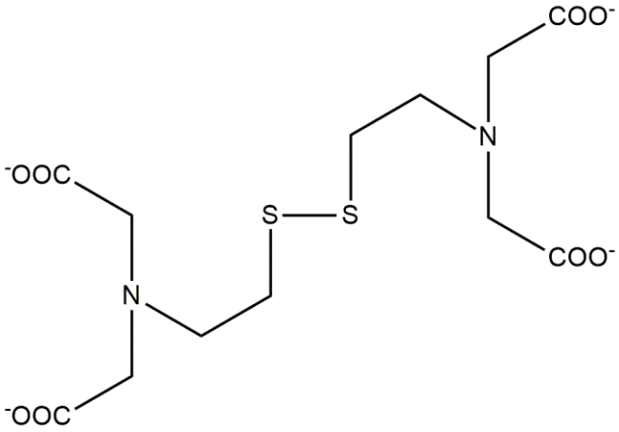
Tris(2-aminoethyl)amine

4. Complejos ternarios Cu-BCBC-acv o $Cu_2$-TCC-$(acv)_2$ donde los quelantes BCBC o TCC generen motivos por quelación $CuNO_2$+S(distal, tioeter o disulfuro) capaces de coordinar acv por N7, sin cooperación interligandos por enlace de hidrógeno.




BCBC

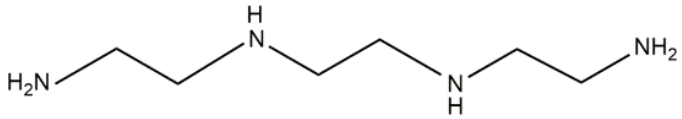
N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-)




TCC

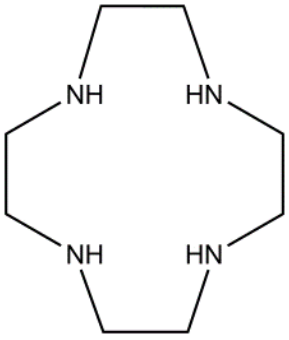
N,N,N',N'-tetrakis(carboxymethyl)cystaminate(4-)

5. Complejos de cobre(II) con tetra-aminas lineales (trien) o macrocíclicas (cyclen, cyclam) que fuercen, en su caso, la coordinación del dador N7-acv a una posición apical-distal, con posibilidad de cooperar con una interacción interligandos (tetra-anina)N-H···O6(avc).



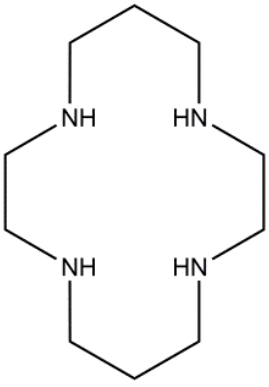

trien

Triethylenetetramine




cyclen

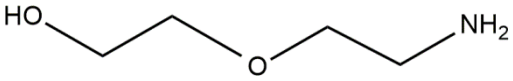
1,4,7,10-tetraazacyclododecane




cyclam

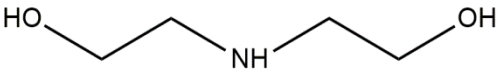
1,4,8,11-tetraazacyclotetradecane

6. Complejos relacionados con el sistema ternario $Cu^{II}$-dien-acv donde la triamina dien tenga uno o más de sus grupos amino sustituidos por grupos funcionales isolobales oxigenados ($–NH_2$ por –OH, =N-H por –O–) usando potenciales ligando como 2aee, DEA o dienol.



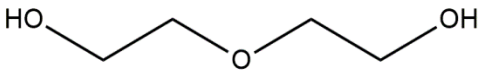

2aee

2-(2-aminoethoxy)etanol




DEA

diethanolamine



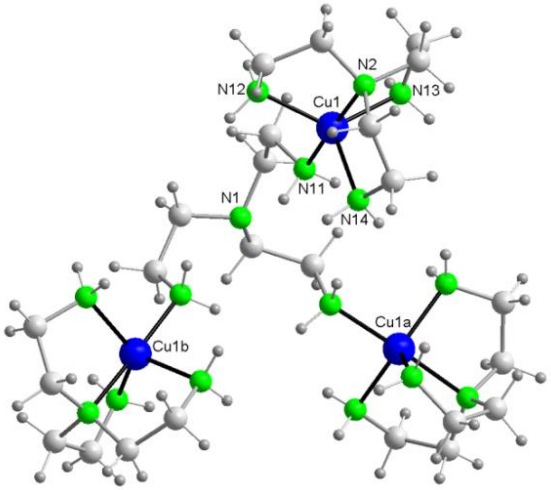

dienol

dietilenglycol

# 5. APORTACIONES/RESULTS

## 5.1. ARTÍCULO 1: SYNTHESIS, THERMOGRAVIMETRIC STUDY AND CRYSTAL STRUCTURE OF AN N-RICH COPPER(II) COMPOUND WITH TREN LIGANDS AND NITRATE COUNTER-ANIONS

### SYNOPSIS ENTRY




The N-rich salt $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ has been studied by XRD and by coupled TG and FT-IR spectroscopy of evolved gases. Under air-dry flow the thermal decomposition begins by the pyrolysis of ethylene-tren moieties.

### HIGHLIGHTS

· A novel N-rich copper(II)-tren complex has been crystallized as a 3-hydrated nitrate salt.

· Tren acts both as tripodal tetradentate and as $\mu_3$-tren bridging ligand.

· Copper(II) centers exhibit distorted trigonal bipyramidal coordination.

· Thermogravimetry and FT-IR spectra of evolved gases have been used.

· Decomposition of nitrate anions and tren ligands occurs in an overlapped step.

### RESUMEN

El compuesto $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ ha sido sintetizado, cristalizado y caracterizado por difracción de rayos X con cristal único, termogravimetría acoplada espectroscopía FT-IR de los gases emitidos, calorimetría diferencial de barrido y espectroscopías electrónica (reflectancia difusa) y FT-IR. El compuesto pierde el agua de cristalización entre temperatura ambiente y 200ºC. La descomposición de esta sal comienza con la descomposición solapada de iones nitrato y de parte de los ligandos tren, con desprendimiento de los gases $CO_2$, $H_2O$, CO, $NH_3$, $N_2O$, NO and $NO_2$ (205 -235 ºC). Después, la descomposición de los restantes ligandos tren ocurre a más altas temperaturas (235-725ºC), para dejar un residuo final de CuO.

## SYNTHESIS, THERMOGRAVIMETRIC STUDY AND CRYSTAL STRUCTURE OF AN N-RICH COPPER(II) COMPOUND WITH TREN LIGANDS AND NITRATE COUNTER-ANIONS

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# Synthesis, thermogravimetric study and crystal structure of an N-rich copper(II) compound with tren ligands and nitrate counter-anions

Inmaculada Pérez-Toro [a], Alicia Domínguez-Martín [a,1], Duane Choquesillo-Lazarte [b], Esther Vílchez-Rodríguez [a,c], Alfonso Castiñeiras [c], Juan Niclós-Gutiérrez [a,*]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada,Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain
[c] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

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ABSTRACT

The compound $[\{Cu(tren)\}_3(\mu 3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ has been synthesized, crystallized and characterized by single crystal X-ray diffraction, thermogravimetry (TG) coupled to FT-IR spectroscopy of the evolved gases, TG–differential scanning calorimetry (DSC) and electronic (diffuse reflectance) and FT-IR spectroscopies. The sample loses the crystallization water between room temperature and 200 °C. The decomposition of the salt begins with an overlapped decomposition of nitrate anions and some tren ligands where $CO_2$, $H_2O$, CO, $NH_3$, $N_2O$, NO and $NO_2$ are evolved (205–235 °C). Then decomposition of additional tren ligands takes place (235–725 °C). Finally a non-pure CuO residue is obtained at 725 °C.


## 1. Introduction

Tris(2-aminoethyl)amine (tren) is perhaps the best known ligand within the family of tripodal tetradentate polyamines [1]. A search in the structural CSD-database [2] reveals that tripodal tetradentate tren builds trigonal bipyramidal [3–8], octahedral [9–11] or other [12–14] coordination surroundings depending on the metal ion. Neutral tren can also act as a tridentate chelator (with a free 2-aminoethyl arm), e.g., in $Co^{II}$ [15], $Ni^{II}$ [16] or $Cu^{II}$ [17] complexes or simply as a $\mu_2$-bridging bidentate ligand (using two terminal primary amino groups), e.g., linking two $Co^{III}$ metal centers [18,19]. A tridentate chelating + $\mu_2$-bridging mode has also been reported for neutral tren [20–23]. The $\mu_3$-tren mode always involves the coordination of the three terminal amino groups to three metallic centers such as $Li^{I}$ [14], $Ag^{I}$ [24,25], $Mn^{II}$ [26], $Cu^{II}$ [27–29], $Cd^{II}$ [30], $Ti^{IV}$ or $Zr^{IV}$ [31]. The highest $\mu_4$-bridging tetradentate role has only been observed for a $K^{I}$-polymeric cation found in the structure of $[K_2(\mu_4\text{-tren})_2]_n(H_3O)_{4n}[Ru^{III}Cl_6]_{2n}\cdot 4nH_2O$ [32]. The structural diversity of tren–metal complexes is further increased with a variety of compounds having bidentate or tridentate $Htren^+$ or monodentate $H_2tren^{2+}$ ligands, as well as some outer-sphere complexes with $Htren^+$, $H_3tren^{3+}$ or $H_4tren^{4+}$ [33] cations.

As a part of our program on molecular recognition between $Cu^{II}$(polyamine) chelates and the acyclic synthetic nucleoside acyclovir [34], we have unintendedly obtained the salt $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$. This structure is closely related to other compounds that also show this trinuclear cation $[\{Cu(tren)\}_3(\mu_3\text{-tren})]^{6+}$ with $[Pt^{II}(CN)_4]^{2-}$ [27], $BF_4^-$ [28] and $ClO_4^-$ [29] anions, as well as to the compound $[\mu_6\text{-}[Cr^{III}(\mu_2\text{-}CN)_6\cdot\{Cu^{II}(tren)\}_6][\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(ClO_4)_{21}$ [29]. The novel compound is a good example of an N-rich $Cu^{II}$ derivative which contains the fully reduced tren polyamine and fully oxidized nitrate counter-anions. The aim of this work is to determine the crystal and molecular structure of this novel salt as well as characterize its thermal and spectroscopic behavior.

## 2. Experimental

### 2.1. Materials

Bluish $Cu(NO_3)_2\cdot 3H_2O$ was purchased from Panreac. Tris(2-aminoethyl)amine was supplied by Acros. Acyclovir (acv) was supplied by Sigma. Solvents and reagents and solvents were used as received.

* Corresponding author. Tel.: +34 958243855; fax: +34 958246219.
*E-mail address:* jniclos@ugr.es (J. Niclós-Gutiérrez).
[1] Present address: Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland.

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### 2.2. Synthesis of [{Cu(tren)}$_3$($\mu_3$-tren)]$_2$(NO$_3$)$_{12}$·3H$_2$O (1)

The studied compound **1** was unintendedly obtained from the synthesis of a ternary copper(II) complex type [Cu(tren)(acv)](NO$_3$)$_2$. The absence of acv in the formula of the compound was evidenced by single crystal X-ray diffraction (XRD). Since the structure of the compound **1** was not reported in the CSD database, efforts were made to completely characterize the novel compound. Hence, the synthesis of **1** was re-formulated according to the stoichiometric Reaction (1):

$$6Cu(NO_3)_2 \cdot 3H_2O + 8tren \rightarrow [\{Cu(tren)\}_3(\mu_3\text{-}tren)]_2(NO_3)_{12} \cdot 3H_2O + 15H_2O \quad (1)$$

0.25 mmol of copper(II) nitrate trihydrate and 0.35 mmol of tren (5% in excess) were dissolved in 100 ml of a mixture absolute EtOH:H$_2$O (95:5). The solution was heated (50 °C) and stirred for half an hour, then left to cool down and finally filtered without vacuum on a crystallization dish. The crystallization dish was placed inside a chamber where diethyl ether was present and used as an anti-solvent. After a few days, well-shaped prismatic blue crystals were formed and collected by filtration. Many of them were single crystals suitable for XRD. Additional sample of the compound can also be obtained by slow evaporation of the mother solution in the absence of diethyl ether, albeit the quality of the crystals is reduced. Yield: ~80%. Anal. Exp.: C, 24.37; H, 6.16; N, 26.12. Calc. for C$_{48}$H$_{150}$Cu$_6$N$_{44}$O$_{39}$: C, 24.54; H, 6.44; N, 26.23.

Synthesis in 100% absolute ethanol and a mixture absolute EtOH:H$_2$O (97:3) yields to the same blue prismatic crystals. Note that the copper(II) nitrate trihydrate salt provides enough water to crystallize compound **1**. However, the highest quality of the collected single crystals was observed when the synthesis was carried out in a mixture absolute EtOH:H$_2$O with 3–5% of water and in the presence of diethyl as anti-solvent.

### 2.3. Single crystal X-ray diffractometry

A blue prismatic crystal of [{Cu(tren)}$_3$($\mu_3$-tren)]$_2$(NO$_3$)$_{12}$·3H$_2$O (**1**) was mounted on a glass fiber and used for data collection. Crystal data were collected at 100(2) K, using a Bruker X8 Kappa APEXII diffractometer. Graphite monochromated MoK($\alpha$) ($\lambda$ = 0.71073 Å) was used. The data were processed with APEXII [35] and corrected for absorption using SADABS (transmissions factors: 1.000–0.903) [36]. The structure was solved by direct methods using the program SHELXS-97 [37] and refined by full-matrix least-squares techniques against $F^2$ using SHELXL-97 [37]. Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were located in difference maps and included as fixed contributions riding on attached atoms with isotropic thermal parameters 1.2 times those of their carrier atoms. The H atoms of water molecules were not located. Criteria of a satisfactory complete analysis were the ratios of rms shift to standard deviation less than 0.001 and no significant features in final difference maps. Structural figures were plotted with DIAMOND [38]. Crystal data, experimental details and refinement: crystal size 0.18 mm × 0.13 mm × 0.12 mm; trigonal system, space group R3; unit cell: $a$ = 29.393(2) Å, $b$ = 29.393(2) Å, $c$ = 19.722(1) Å, $\alpha = \beta = 90°$, $\gamma = 120°$; $Z$ = 6; $F$(0 0 0) 7392. Reflections collected/unique 70337/11146. Data/restraints/parameters 1146/1/835; GOF $S$ = 0.900. Final $R$ index: $R_1$ = 0.055, $wR_2$ = 0.790. Absolute structure parameter: 0.003(14). Largest difference peak and hole: 0.865 and −0.446 e A$^{-3}$.

### 2.4. Other physical measurements

Analytical data were obtained in a Fisons–Carlo Erba EA 1108 elemental micro-analyzer. To ensure the identity of the products obtained in the different synthesis referred herein, powder X-ray diffraction measurements were performed at room temperature on a PANalytical X'pert PRO MPD X-ray diffractometer (45 kV, 40 mA, Cu K$\alpha$ radiation, and scanning angle range $4° \leq 2\theta \leq 80°$). Bragg–Brentano geometry with automatic divergence slits was used for all the measurements. Likewise, infrared spectra from samples of the different synthesis were recorded (KBr pellets) on a Jasco FT-IR 6300 spectrometer. Coupled TG analysis (20–1000 °C, 10 °C/min) + FT-IR spectra of the evolved gases were carried out in a $CO_2$ free dry-air flow (100 ml/min) on a Shimadzu Thermobalance TGA DTG-50H instrument and a FT-IR Nicolet Magma 550 spectrometer. A Nicolet-TGA Interface provided with a thermostated (165 °C) transfer line and a thermostated analyzer chamber (225 °C) was used. The air-flow is filtered with a molecular sieve (Peak Scientific Purge gas generator) to remove possible water and $CO_2$ traces. In a TG experiment, the sample is normally grinded prior to the experiment. The grinded sample is placed in the thermo-balance and a dry-air flow (100 ml/min) is applied. During this period of time, the loss of crystallization solvent molecules in the studied compounds is rather common. The dry-air flow is kept until the weight of the sample is stabilized and then the thermal experiment itself begins. A series of ~35 time-spaced FT-IR spectra of gases was recorded for identification of the evolved gases throughout the sample decomposition. A simple TG experiment was also carried out with small crystals instead of grinded crystals. A simultaneous TG–DSC experiment was recorded in a Metler-Toledo TGA7DSC 1 instrument. The electronic (diffuse reflectance) spectrum was obtained in a Varian Cary-5E spectrophotometer.

## 3. Results and discussion

### 3.1. Crystal structure

The single crystal XRD study revealed that compound **1** is a complex salt having the cation [{Cu(tren)}$_3$($\mu_3$-tren)]$^{6+}$, nitrate counter-anions and non-coordinated water. The compound contains two non-equivalent cations: one (c1) with three equivalent metallic centers (Cu1) and another one (c2) with three slightly different and non-equivalent copper(II) atoms (Cu2, Cu3 and Cu4). Thus, the asymmetric unit of the crystal comprises only one third of c1 and one c2 cation. Fig. 1 shows one c1 and three c2 cations, i.e., appertaining to three asymmetric units. Table 1 shows a summary of coordination bond distances and the trans-N—Cu—N angles defined by the four shortest Cu—N distances for each Cu

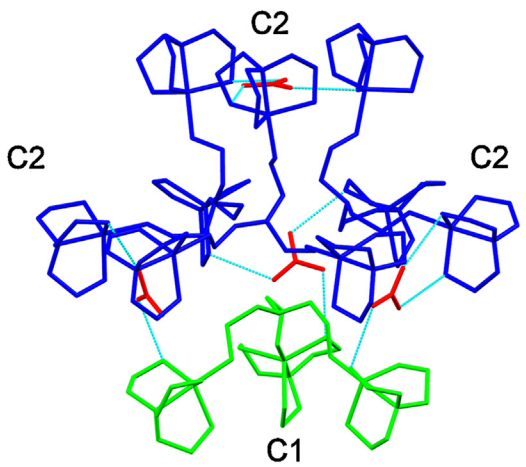


**Fig. 1.** The two non-equivalent cations [{Cu(tren)}$_3$($\mu_3$-tren)]$^{6+}$ in the crystal of compound **1** (one c1 and three c3 depicted). H-atoms, nitrate anions and non-coordinated water molecules have been omitted for clarity.

**Table 1**
Selected bond lengths (angstrom), *trans*-angles (degree) and Adison–Reedijk parameters ($\tau$) for the non-equivalent cations in the salt $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ (**1**).

| Cation c1 | Cation c2 | | |
|---|---|---|---|
| Cu1 | Cu2 | Cu3 | Cu4 |
| Cu1-N11 1.997(5) | Cu2-N21 1.980(6) | Cu3-N22 1.988(6) | Cu4-N23 2.007(6) |
| Cu1-N2 2.055(6) | Cu2-N4 2.031(6) | Cu3-N43 2.053(6) | Cu4-N51 2.067(7) |
| Cu1-N12 2.042(6) | Cu2-N32 2.056(6) | Cu3-N5 2.022(9) | Cu4-N53 2.025(8) |
| Cu1-N14 2.097(6) | Cu2-N31 2.103(7) | Cu3-N41 2.078(7) | Cu4-N6 2.051(7) |
| Cu1-N13 2.069(6) | Cu2-N33 2.078(7) | Cu3-N42 2.091(8) | Cu4-N52 2.092(8) |
| N11-Cu1-N2 177.6(2) | N21-Cu2-N4 178.1(3) | N22-Cu3-N5 177.9(3) | N51-Cu4-N53 125.9(4) |
| N12-Cu1-N13 129.3(2) | N32-Cu2-N31 122.4(3) | N43-Cu3-(N41 127.3(3) | N23-Cu4-N6 176.8(3) |
| $\tau(1)$ 0.805 | $\tau(2)$ 0.947 | $\tau(3)$ 0.843 | $\tau(4)$ 0.848 |

center. Trans-angles ($\theta > \varphi$) were used to calculate the value of the Addison–Reedijk parameter, $\tau = (\theta - \varphi/60)$, and discern between trigonal-bipyramidal ($\tau > 1.0$–$0.5$) or square-base pyramidal ($\tau < 0.5$–$0.0$) Cu(II) five-coordination polyhedron. $\tau$ values (Table 1) fall between 0.805 (Cu1) and 0.947 (Cu2). These data reveal that, as expected for $Cu^{II}$-tripodal tetradentate tren units, all Cu(II) centers in compound **1** are best described as slightly distorted trigonal bipyramidal polyhedra. Note that the shortest Cu—N distances in **1** correspond to the Cu—N bonds involving the primary amino group of the $\mu_3$-tren ligand. The steric constraints imposed by the chelating tren ligands make the Cu—N distances in **1** to fall in the range 1.997(5)–2.103(7) Å. The average of the longest Cu—N distances is 2.096 Å, ~10% longer than the averaged short distance.

The structure of the $[\{Cu(tren)\}_3(\mu_3\text{-tren})]^{6+}$ cation in compound **1** agrees with that reported for the same cation in closely related salts such as $[\{Cu(tren)\}_3(\mu_3\text{-tren})][Pt(CN)_4]_3\cdot 3H_2O$ [27], $\{Cu(tren)\}_3(\mu_3\text{-tren})](BF_4)_6$ [28], $\{Cu(tren)\}_3(\mu_3\text{-tren})](ClO_4)_6$ [29] and $[\mu_6\text{-}[Cr^{III}(\mu_2\text{-}CN)_6\cdot\{Cu^{II}(tren)\}_6][\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(ClO_4)_{21}$ [29]. In fact, the structure containing $BF_4^-$ anions also have two non-equivalent trinuclear cations, one with equivalent and another with non-equivalent Cu(II) centers, as reported here for the novel compound.

In the crystal, nitrate ions are located in a three-fold axis and connected by H-bonds to the trinuclear cations c2 (with non-equivalent Cu(II) centers). This leads to trimeric-c2 aggregates. Such units adopt an umbrella topology and are H-bonded to the trinuclear c1 cations (with three Cu(II) equivalent centers). This sub-structure is stabilized by (amino)N—H···O(nitrate) interactions. Additional H-bonds involving cations, anions and solvent water molecules build the supramolecular 3D architecture.

### 3.2. Thermogravimetric study

A grinded sample of **1** was first placed on the thermo-balance under dry-air flow (100 ml/min). Once the weight of the sample was stabilized (6.668 mg), the experiment started with an increasing heating rate of 10 °C/min (see Section 2.4). The TG-plot (Fig. 2) shows seven weight loss steps, from ~100 to 725 °C. Note that in Fig. 2 the time (*X*-axis, top) is related only to the recorded FT-IR spectra (i.e., the first FT-IR spectrum was assigned to 0 min). It should be remarked that no significant weight loss was observed until 100 °C, when the first evolved gases were detected. Fig. 3 shows a selected set of seven FT-IR spectra recorded to identify the evolved gases in each step. FT-IR spectra only allow to qualitatively recognize the gases produced during thermal decomposition of the sample. A summary of the results obtained in the thermogravimetric experiment is reported in Table 2. During the two first steps (100–160 and 160–205 °C, Exp. weight loss 1.954% – see Fig. 2 and Table 2) only $H_2O$ and $CO_2$ were evolved. This latter value is in agreement to the calculated for the loss of $3H_2O$ per formula (2.301%). Note that some preliminary loss of crystallization water from the trihydrate level might happen before the start of the TG–FT-IR measurement. Hence, below ca. 200 °C, the sample mainly lost all the non-coordinated water and yielded the anhydrous salt $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}$ (molar mass 2295.21). Indeed, a complementary TG–DSC experiment (with non-grinded sample) revealed a gradual loss of the solvent water molecules from room temperature to ca. 200 °C (see Supporting Information) without a measurable endothermic effect. The third step in the TG experiment (205–235 °C) represents the most pronounced weight loss (~43%). The corresponding FT-IR- spectra (10–14 min) shows the production of $H_2O$ and $CO_2$ plus additional N-oxides gases ($N_2O$, NO and $NO_2$). This weight loss in the third step (~43%) is larger than the calculated only for the decomposition of twelve nitrate ions per formula (31.672%). A plot monitoring the production of $N_2O$ upon time reveals a sharp peak of this gas at about 15 min while the TG–DSC plots reveal an exothermic balance (see Supporting Information). In addition, the FT-IR spectrum at 15.302 min (at the beginning of step 4 – see Table 2 and Supporting Information) shows the production of $H_2O$, $CO_2$, N-oxide gases and $NH_3$ (easily recognized by two sharp peaks at 967 and 928 $cm^{-1}$). All these results suggest that the decomposition of nitrate anions and tren ligands occur mostly contemporarily at this point. In the remaining

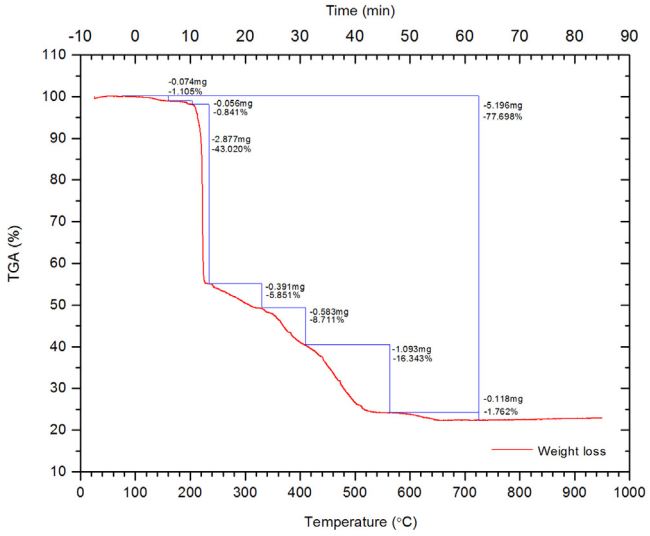


**Fig. 2.** TG-plot of $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ (**1**) under dry-air flow. Percentage of weight loss is represented against temperature (°C, bottom *X*-axis) and time (min, top *X*-axis). The time *X*-axis is related to the timing of the recorded FT-IR spectra in the experiment.

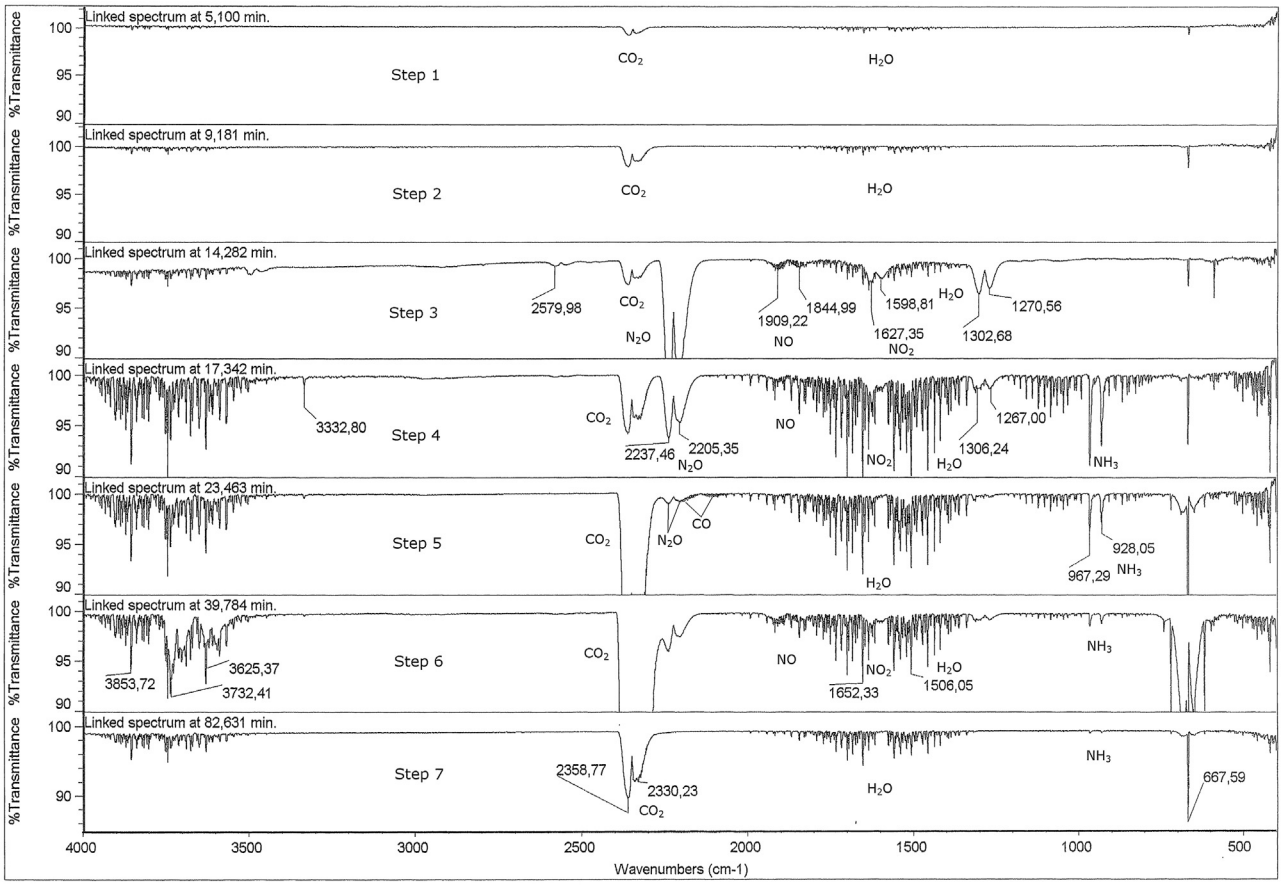


**Fig. 3.** Selected FT-IR spectra of the evolved gases during the TG-experiment of compound **1**.

steps, the decomposition of the sample continues until the formation of a copper(II) oxide residue. The amount of evolved ammonia in these final steps (4–7) is so abundant that it is observed in all FT-IR spectra recorded between 15 and 83 min. In contrast, the production of NO and $NO_2$ (initially related to the decomposition of nitrate ions) is not observed during the fifth step (330–410 °C, FT-IR spectrum at 23.463 min in Fig. 3) while $NH_3$ and $N_2O$ are present. At higher temperatures (sixth step, 410–560 °C, FT-IR spectrum at 39.484 min in Fig. 3) ammonia and all three N-oxides gases are again present, probably due to a partial oxidation of $NH_3$. The weight of the sample was briefly stabilized near 560 °C, however decomposition finally underwent until 725 °C. In the seventh step (560–725 °C, FT-IR spectrum at 82.631 min in Fig. 3), a stable thermal residue of 22.30% (~725 °C) was obtained (see Table 2). This value is within the experimental error as compared to the expected value of 20.316% for a CuO residue. The formation of a $Cu_2O$ residue has also been observed in the thermal decomposition of other copper(II) polyamines at temperatures >700 °C [39]. However, it was not observed in the novel compound even between 700 and 950 °C.

### 3.3. Vibrational and electronic spectra

The FT-IR spectrum of compound **1** shows bands ($cm^{-1}$) corresponding to stretching ($\nu$) and bending ($\delta$) modes of water [$\nu_{as}$ 3420, $\nu_s$ 3256, $\delta$ 1631] and the groups —$NH_2$ [$\nu_{as}$3306, $\nu_s$ ~3150, $\delta$ 1591] and —$CH_2$ [$\nu_{as}$ 2968, 2950 and 2923; $\nu_s$ 2881, 2850 and 2831; $\delta$ 1591] (see Supporting Information). The lack of

**Table 2**
Summary from the coupled TG + FT-IR study of compound **1**.

| Step | Temp. (°C) | Time[a] (min) | Weight loss (%) | | Gases or residue | Collected FT-IR spectra |
|---|---|---|---|---|---|---|
| | | | Experimental | Calc. | | |
| 1 | 100–160 | 0–6 | 1.11 | – | $H_2O$, $CO_2$ | 1 |
| 2 | 160–205 | 6–10 | 0.84 | – | $H_2O$, $CO_2$ | 1 |
| 3 | 205–235 | 10–14 | 43.02 | – | $N_2O$[b], NO, $NO_2$ | 3 |
| 4 | 235–330 | 14–23 | 5.85 | – | $CO_{(ta)}$[b], $NH_3$, $N_2O$, NO, $NO_2$ | 5 |
| 5 | 330–410 | 23–31 | 8.71 | – | CO[b], $NH_3$, $N_2O$ | 5 |
| 6 | 410–560 | 31–46 | 16.34 | – | $NH_3$[b], $N_2O$, NO, $NO_2$ | 9 |
| 7 | 560–725 | 46–63 | 1.76 | – | $NH_{3(ta)}$[b] | 10 |
| Residue (%) | 725 | 63–83 | 22.30 | 20.32 | CuO | – |

[a] The variable 'Time' is only referred to the recorded FT-IR spectra (i.e., the first FT-IR spectrum was assigned to 0 min). Note that at 0 min the experiment was already started, with the temperature being increased at 10 °C/min rate. However, no significant weight loss was observed between 25 and 100 °C (see Fig. 2).
[b] Besides $H_2O$ and $CO_2$. ta: trace amounts.

implication of methylene groups in H-bonding interactions is evidenced by the presence of various bands in each of the corresponding vibration modes. This is not the case of those bands related to primary amino groups and water which typically give more or less broad bands. The non-metal bonded nitrate ions are easily recognized by the very strong band at 1384 $cm^{-1}$ (usually found at 1380–1350) accompanied by a medium–low intensity band at 825 $cm^{-1}$ (normally in the range 840–815) [40]. According to the distorted trigonal bipyramidal copper(II) coordination centers of the studied compound, with a $d_z^2$ ground state, the (diffuse reflectance) electronic spectrum shows a broad band with maximum at 12,950 $cm^{-1}$ and a smooth shoulder at about 15,725 $cm^{-1}$ [41] (see Supporting Information).

## 4. Concluding remarks

Regardless the synthetic approach (with or without presence of acv, in absolute ethanol or in water–ethanol mixtures) only one unique compound is obtained (compound **1**). The use of coupled TG and FT-IR spectra shows that the N-rich studied compound gradually loses the non-coordinated water between room temperature and ~200 °C under air-dry flow. The initial water loss is then followed (205–235 °C) by an overlapped decomposition of nitrate anions and some tren ligands and finally the rest of tren ligands undergo to decomposition (235–725 °C) to yield a non-pure CuO residue (at 725 °C).

## Supporting information

CCDC991582 contains the supplementary crystallographic data for compound $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ (**1**). CIF file is provided in the Supporting Information. These data can also be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or Supplementary materials associated to this article involve a complete dossier of the main structural features (S1), X-ray powder patterns and FT-IR spectra of compound **1** out from different synthetic approaches (S2), thermal analysis (S3), the FT-IR and electronic spectra (S3) of the studied compound.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tca.2014.08.007.

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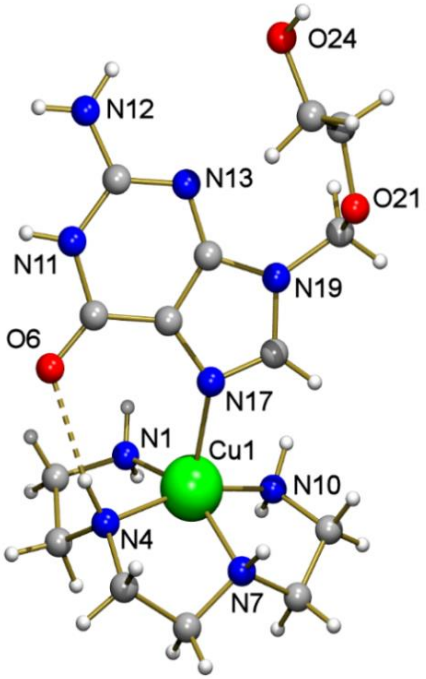
## 5.2 ARTÍCULO 2: LIGHTS AND SHADOWS IN THE CHALLENGE OF BINDING ACYCLOVIR, A SYNTHETIC PURINE-LIKE NUCLEOSIDE WITH ANTIVIRAL ACTIVITY, AT AN APICAL-DISTAL COORDINATION SITE IN COPPER(II)-POLYAMINE CHELATES

### SYNOPSIS ENTRY

To address the challenge of binding the synthetic purine-like nucleoside acyclovir at an apical Cu(II) coordination site, cyclen, cyclam and trien tetraamine chelators were used as suitable receptors. Only the Cu(trien)$^{2+}$ chelate was able to bind acyclovir as expected. The N7-acv bond cooperates with an intra-molecular N-H···O6(acv) interaction.




### HIGHLIGHTS

· The synthetic purine-like nucleoside acyclovir is used for metal recognition studies.

· Cu(II) chelates of cyclam, cyclen or trien were used as potential acyclovir receptors.

· Cu(trien)$^{2+}$ yielded the ternary complex [Cu(trien)(acv)]$^{2+}$ (sulfate or nitrate).

· Unprecedented apical coordination of the N7-acv donor in the 4+1 Cu(II) coordination.

· The Cu-N7(acv) bond is assisted by a (trien)N-H···O6(acv) interaction.

### RESUMEN

Los ácidos nucleicos y sus constituyentes o sus complejos metálicos se involucran en etapas metabólicas cruciales. Sobre esta base, el estudio de interacciones entre metales y ácidos nucleicos resulta esencial para la comprensión de tales procesos biológicos. En este trabajo se ha utilizado aciclovir (acv) nucleósido sintético derivado de guanina, como modelo acíclico de guanosina, para investigar su reconocimiento molecular con quelatos tipo Cu(II)-poliamina. La estabilidad química del N9-sustituyente acíclico de acv brinda una valiosa posibilidad de usar este principio activo antiviral para ahondar en el conocimiento de interacciones metal-nucleósido. Como potenciales receptores de este nucleósido, se han usado quelatos de Cu(II) con las

poliaminas macrocíclicas cyclam y cyclen así como la poliamina acíclica lineal trien. Los quelatos de Cu(II) formados por estas tetraaminas tienen, en común, la posibilidad de coordinar el nucleósido acv en una posición apical/distal del entorno de coordinación del metal, mediante el enlace Cu-N7(apical/distal) asistido por una interacción intra-molecular interligandos de tipo (amina)NH···O6(acv). Una serie de procedimientos sintéticos, llevados a cabo con esta finalidad, han producido los compuestos:

$[Cu(cyclam)(ClO_4)_2]$ (**1**)

$\{[Cu(cyclam)(\mu_2\text{-}NO_3)](NO_3)\}_n$ (**2**)

$\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot MeOH\}_n$ (**3**)

$\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot 5H_2O\}_n$ (**4**)

$[Cu(cyclen)(H_2O)]SO_4\cdot 2H_2O$ (**5**)

$[Cu(cyclen)(H_2O)]SO_4\cdot 3H_2O$ (**6**)

$[Cu(trien)(acv)](NO_3)_2\cdot acv$ (**7**)

$[Cu(trien)(acv)]SO_4\cdot 0.71H_2O$ (**8**).

Estos ocho compuestos han sido todos cristalizados y caracterizados por cristalografía de rayos-X (con cristales únicos) y espectroscopía FT-IR. Los resultados revelan que ambos macroquelatos, $Cu(cyclen)^{2+}$ y $Cu(cyclam)^{2+}$, resultan incapaces de coordinar acv en una posición apical/distal del entorno de coordinación del cobre(II). En claro contraste, el quelato $Cu(trien)^{2+}$ se ha mostrado como un eficiente receptor de acv, en **7** y **8**. En el complejo ternario $[Cu(trien)(acv)^{2+}]$ de **7** u **8**, el acv se reconoce con el quelato metálico $Cu(trien)^{2+}$ mediante la formación del enlace Cu-N7(distal) en cooperación con una interacción intra-molecular interligandos tipo (amina primaria o secundaria)N-H···O6(acv).

Comparaciones apropiadas de nuestros resultados con otros muchos, aportados en la bibliografía, revelan que tal coordinación de N7-acv en una posición distal del entorno de Cu(II) debe relacionarse directamente con la naturaleza acíclica y flexible del quelante trien y con la habilidad del quelato binario $Cu(trien)^{2+}$ para construir complejos pentacoordinados de tipo 4+1.

# LIGHTS AND SHADOWS IN THE CHALLENGE OF BINDING ACYCLOVIR, A SYNTHETIC PURINE-LIKE NUCLEOSIDE WITH ANTIVIRAL ACTIVITY, AT AN APICAL-DISTAL COORDINATION SITE IN COPPER(II)-POLYAMINE CHELATES

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# Lights and shadows in the challenge of binding acyclovir, a synthetic purine-like nucleoside with antiviral activity, at an apical–distal coordination site in copper(II)-polyamine chelates

Inmaculada Pérez-Toro [a], Alicia Domínguez-Martín [a,*], Duane Choquesillo-Lazarte [b], Esther Vílchez-Rodríguez [a], Josefa María González-Pérez [a], Alfonso Castiñeiras [c], Juan Niclós-Gutiérrez [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain
[c] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

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ABSTRACT

Several nucleic acid components and their metal complexes are known to be involved in crucial metabolic steps. Therefore the study of metal–nucleic acid interactions becomes essential to understand these biological processes. In this work, the synthetic purine-like nucleoside acyclovir (acv) has been used as a model of guanosine recognition with copper(II)-polyamine chelates. The chemical stability of the N9-acyclic arm in acv offers the possibility to use this antiviral drug to deepen the knowledge of metal–nucleoside interactions. Cu(II) chelates with cyclam, cyclen and trien were used as suitable receptors. All these copper(II) tetraamine chelates have in common the potential ability to yield a Cu–N7(apical) bond assisted by an appropriate (amine)N–H···O6(acv) intra-molecular interligand interaction. A series of synthesis afforded the following compounds: $[Cu(cyclam)(ClO_4)_2]$ (**1**), $\{[Cu(cyclam)(\mu_2\text{-}NO_3)](NO_3)\}_n$ (**2**), $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot MeOH\}_n$ (**3**), $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot 5H_2O\}_n$ (**4**), $[Cu(cyclen)(H_2O)]SO_4\cdot 2H_2O$ (**5**), $[Cu(cyclen)(H_2O)]SO_4\cdot 3H_2O$ (**6**), $[Cu(trien)(acv)](NO_3)_2\cdot acv$ (**7**) and $[Cu(trien)(acv)]SO_4\cdot 0.71H_2O$ (**8**). All these compounds have been characterized by X-ray crystallography and FT-IR spectroscopy. Our results reveal that the macrochelates $Cu(cyclen)^{2+}$ and $Cu(cyclam)^{2+}$ are unable to bind acv at an apical site. In contrast, the $Cu(trien)^{2+}$ complex has proved to be an efficient receptor for acv in compounds (**7**) and (**8**). In the ternary complex $[Cu(trien)(acv)]^{2+}$, the metal binding pattern of acv consists of an apical Cu–N7 bond assisted by an intra-molecular (primary amino)N–H···O6(acv) interligand interaction. Structural comparisons reveal that this unprecedented apical role of acv is due to the acyclic nature of trien together with the ability of the $Cu(trien)^{2+}$ chelate to generate five-coordinated (type 4 + 1) copper(II) complexes.



## 1. Introduction

Metal–nucleic acid complexes are known to play a crucial role in our metabolism [1,2]. Thus, the coordination of different metal ions with nucleobases, nucleosides and nucleotides has been extensively studied along the past decades [3–10]. The vast majority of these studies are related to crystallographic studies on small ternary complexes, which are used as models to understand the affinity of metal ions for the different N-donors of these biologically relevant molecules [3–8]. Likewise, the relevance of non-covalent interaction such as H-bonds or pi,pi-stacking interactions in molecular recognition processes has also been widely addressed [7,9,10]. The final aim is to provide a comprehensive view on the behavior of these model systems and therefore a close vision of the rationale of metal–nucleic acid chemistry in biology.

Acyclovir (acv, also called acycloguanosine) is a well-known synthetic purine-like nucleoside used as an antiviral first-line prodrug against viruses of the alpha sub-family of *Herpesviridae*. Due to its momentous pharmacological interest, physical properties and co-crystallization engineering, this synthetic purine-like nucleoside analog has been thoughtfully studied along the past decades. Single crystal structure determinations have been carried out for anhydrous acv [11], $acv\cdot 0.67H_2O$ [12] and $acv\cdot 2H_2O$ [13]. Anhydrous acyclovir exits as two polymorphs. The conversion between these polymorphs is influenced by humidity and temperature [14]. However, the two polymorphs do not directly convert into each other but undergo water mediated transformations instead, yielding the above referred hydrates. Some adducts have also been structurally characterized with different

* Corresponding author at: Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland. Tel.: +34 958243855, +41 446354640; fax: +34 958246219.
*E-mail addresses:* alicia.dominguez@chem.uzh.ch, adominguez@ugr.es (A. Domínguez-Martín).

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co-crystal formers such as fumaric [15], glutaric [15] or tartaric acids [16] as well as 5-fluorocytosine [11] or other purine nucleoside phosphorylases [17,18]. The structure of two salts of the H(N1)acv$^{+}$ cation and hydrogen malate(1−) [15] or $[Ru^{II}(NO)(O\text{-}DMSO)Cl_4]^{-}$ anions [19] has also been reported. The chemical stability of the acyclic N9-arm of this nucleoside analog has favored the synthesis and crystal structure determination of various metal complexes with Co(II) [20], Ni(II) [21], Cu(II) [22–25], Zn(II) [10,11], Cd(II) [21], Pt(II) [26–28] and Ru(III) [29,30]. These works were early promoted by I. Turel et al. [19,22,24,25,29,30] and A. Terrón et al. [20,21] and showed to the following metal binding patterns (MBPs) for acv (Fig. 1):

(a) The formation of a single M–N7(acv) bond as described in $\{[Cu(\mu_2\text{-IDA})(acv)]\cdot MeOH\}_2$ (IDA = iminodiacetate ligand) [23], $[Cu(acv)_2(H_2O)_3](NO_3)_2$ [24] and cis-$[Pt(acv)_2(NH_3)_2]Cl_2\cdot 2H_2O$ [28].

(b) The cooperation of the M–N7(acv) bond and an intra-molecular interligand H-bonding interaction. This is the most common MBP of acv. Most commonly, the O–H···O6 interligand interaction is built by aqua ligands [20,21,25,30] or involves coordinated MeOH [30] or EtOH [29]. Alternatively the M–N7(acv) bond can also be assisted by an N–H···O6 interligand interaction provided an appropriate N–H group is supplied, for instance a primary amino group of an ethylenediamine ligand (en) [26,27] or the glycylglycinate(2−) ligand [23]. Surprisingly, this acv MBP was not observed in the just referred related complex cis-$[Pt(acv)_2(NH_3)_2]Cl_2\cdot 2H_2O$ [28]. Note that both interligand O–H···O6 and N–H···O6 interactions, when present, involve coordinated O–H or N–H bonds.

(c) The chelating acv–N7,O6 mode. This has only been reported for the elongated–octahedral complex $[Cu(acv)_2(H_2O)_2](NO_3)_2$ [22], showing short Cu–O(aqua) (1.953(2) Å) and Cu–N7(acv) (2.004(2) Å) bonds but the rather long Cu–O6(acv) bond (2.698(2) Å). Hence, in this compound the O-aqua and N7–acv atoms are the four closest donors of the metal, whereas the O6–acv occupies the trans-apical/distal site of the coordination polyhedron.

(d) The bridging $\mu_2$-N7,O(ol) mode, where the O(ol) donor is the alcoholic O-atom in the acyclic-N9 arm. The only example is found in a polymeric Cd(II) compound [21]. Curiously this polymeric structure features an inter-molecular O(ol)–H···O6 interligand interaction between two acv ligands linked to neighboring metallic centers.

These four MBPs involve the N7-donor within the guanine moiety that is clearly the most suitable coordination site of neutral acv. There is only one compound reported having the H(N7)acv(1+) cation [19]. In this compound, the protonation of the N7 atom does not favor the formation of a different metal–N(donor) bond, e.g. the use of the hindered N3 donor atom, thus resulting in an outer-sphere metal complex.

In 2010, K. Aoki et al. [31] proved that purine-like univalent anions such as adeninate (ade), hypoxanthinate (hyp), theophyllinate (theo) and xanthinate (xan) were able to bind at the apical coordination site of the $Cu(cyclen)^{2+}$ chelate. In these compounds the apical Cu–N9(ade or hyp) bond plus the (cyclen)N–H···N3 interaction and the apical Cu–N7(hyp, theo or xan) bond plus the (cyclen)N–H···O6 interaction were observed. These interesting structures prove that the referred purinate(1−) anions are actually able to bind their N9 or N7 donors at the apical coordination site available in the $Cu(cyclen)^{2+}$ macrochelate. However, the same has not been proved for neutral forms of these biologically relevant purine-like ligands. As part of our research program devoted to better understand the interaction between metal ions and nucleosides [23], the main aim of this work is to promote and probe a new MBP for neutral acv, moving this purine-like nucleoside to an apical/distal coordination site. To this purpose, representative tetradentate polyamines (cyclam, cyclen and trien — see Fig. 2) have been chosen in order to block the four closest N-donor atoms of the copper(II) coordination. The choice of the copper(II) as metal center is based on the plasticity of this ion tied to the Jahn–Teller consequences imposed by its one-hole electronic configuration ($3d^9$). The typical Cu(II) 4 + 2 and 4 + 1 coordination polyhedra will provide four nearly coplanar shorter bonds of ca. 2 Å for appropriate N- and O-(acv) donors plus two or one clearly longer bonds (~2.3–2.8 Å) that fulfill the apical–distal sites, respectively. Such discriminating structural distortions are difficult to reach using other biologically significant first-row transition ($Co^{II}$, $Ni^{II}$) or post-transition ($Zn^{II}$, $3d^{10}$) metal ions, for which electronic configuration does not apply the Jahn–Teller effect. The obtained results would expand the frontiers of the coordination possibilities of this kind of neutral purine-like nucleosides.

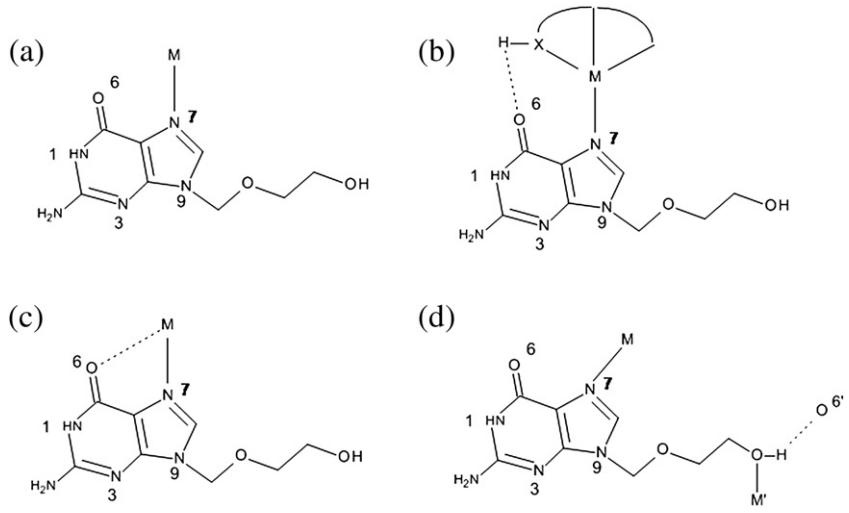


**Fig. 1.** Metal binding patterns of acyclovir. (a) Unidentate mode, with the metal–N7(acv) bond. (b) Unidentate mode assisted with an intra-molecular interligand H-bonding X-H···O6(acv) (X = N or O). (c) Bidentate N7,O6-chelating role. (c) $\mu_2$-N7,O(ol N9-side chain) bridging mode.

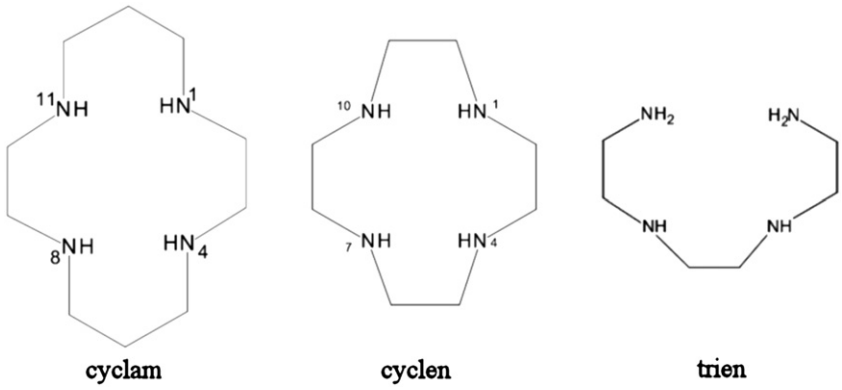


**Fig. 2.** Formulas of the three Cu(II) chelating tetraamines used in this work.

## 2. Experimental

### 2.1. Materials

Acycloguanosine (acv) can be purchased in Sigma-Aldrich and other suppliers. Acv samples were systematically checked by FT-IR spectroscopy, thermogravimetry and powder X-ray diffraction in order to ascertain the used hydrate form, identified as acv·0.66$H_2O$ [12]. The copper(II) oxo-salts ($Cu(ClO_4)_2·6H_2O$, $Cu(NO_3)_2·3H_2O$ and $CuSO4·5H_2O$) were supplied by Acros or Alfa Aesar. *Caution! Perchlorate salts of transition metal complexes and organic ligands are hazardous and may explode. Only small quantities should be prepared and handled with great care*. The tetraamines were obtained from Aldrich or Acros. Solvents were obtained from commercial sources. All reactants and solvents were of high purity and used as received.

### 2.2. Synthesis

According to previous works of I. Turel et al. [22] and our research group [23], the metal binding of acyclovir seems to be favored by the use of solvents with slightly lower polarity than water such as methanol and other alcohols or even water–alcohol mixtures. In this work methanol has been used as preferred solvent. The small water content of the acv ligand and the copper(II) oxo-salts was not considered relevant. The general procedure can be described as follows. First, methanol mother solutions of both the appropriate amine and the appropriate copper(II) oxo-salt are prepared. Then acyclovir is added drop wise to the Cu(polyamine) oxo-salt methanol solution maintaining permanent stirring until a clear solution is obtained. Finally, the reacting mixture is filtered without vacuum into a crystallizing dish. The solution can be placed into a diffusion chamber in which diethyl-ether is used as anti-solvent or left stand at room temperature allowing slow evaporation of the solvent. In most of studied systems colored and colorless crystals appeared at the same time. Separation of both types of crystals was performed by hand with the help of a magnifying glass and products were monitored by FT-IR spectroscopy in order to confirm their nature. Colorless crystals were always identified as free acv ligand. Colored crystals correspond to binary or ternary copper(II) complexes having the corresponding Cu(polyamine) oxo-salt without or with acyclovir (only compounds **7** and **8** — see below). Cu(polyamine) oxo-salts (binary compounds) were isolated from the solution when crystallization of free acv was persistent along the evaporation process. The presence (or absence) of acv in the colored crystals could be easily identified by FT-IR spectroscopy due to the presence (or absence) of one or two overlapped bands near 1700 $cm^{-1}$ due to the $\nu$(C═O) mode and a sharp and medium to intense band at 1385 $cm^{-1}$

**Table 1**
Summary of crystal data and structure refinement.

| Compound | Crystalline system | Space group | Unit cell | Final R |
|---|---|---|---|---|
| $[Cu(cyclam)(ClO_4)_2]$ (**1**) | Triclinic | P-1 | a = 7.941(3) Å, α = 113.222(4)°<br>b = 8.208(3) Å, β = 116.256(4)°<br>c = 8.402(3) Å, γ = 95.325(4)° | 0.0254 |
| $\{[Cu(cyclam)(\mu_2\text{-}NO_3)](NO_3)\}_n$ (**2**) | Monoclinic | P21/n | a = 9.206(6) Å, α = 90°<br>b = 13.646(10) Å, β = 97.206(9)°<br>c = 12.703(9) Å, γ = 90° | 0.0300 |
| $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]·MeOH\}_n$ (**3**) | Monoclinic | P21/c | a = 13.774(2) Å, α = 90°<br>b = 13.961(2) Å, β = 90.025(4)°<br>c = 16.528(2) Å, γ = 90° | 0.0392 |
| $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]·5H_2O\}_n$ (**4**) | Monoclinic | C2/c | a = 9.023(5) Å, α = 90°<br>b = 15.489(2) Å, β = 91.184(2)°<br>c = 27.298(2) Å, γ = 90° | 0.0511 |
| $[Cu(cyclen)(H_2O)]SO_4·2H_2O$ (**5**) | Orthorhombic | P21 21 21 | a = 10.710(5) Å, α = 90°<br>b = 10.875(5) Å, β = 90°<br>c = 13.121(5) Å, γ = 90° | 0.0259 |
| $[Cu(cyclen)(H_2O)]SO_4·3H_2O$ (**6**) | Monoclinic | P21/n | a = 7.887(2) Å, α = 90°<br>b = 14.102(1) Å, β = 99.435(2)°<br>c = 14.724(2) Å, γ = 90° | 0.0330 |
| $[Cu(trien)(acv)](NO_3)_2·acv$ (**7**) | Monoclinic | C2/c | a = 39.086(8) Å, α = 90°<br>b = 7.567(2) Å, β = 122.888(7)°<br>c = 26.769(5) Å, γ = 90° | 0.0521 |
| $[Cu(trien)(acv)]SO_4·0.71H_2O$ (**8**) | Monoclinic | P2(1) | a = 7.422(2) Å, α = 90°<br>b = 22.230(1) Å, β = 95.463(4)°<br>c = 12.860(2) Å, γ = 90° | 0.0363 |

corresponding to the δ(O–H) of acyclovir [23]. Various commercial samples of acv·0.66$H_2O$ absorb at 1720 ± 3 plus 1695 ± 2 $cm^{-1}$ and ~1387 ± 3 $cm^{-1}$. Caution: Samples having free nitrate ions and/or apical-Cu(II) bonded $NO_3^-$ ligand(s) can also absorb at 1380–1350 $cm^{-1}$. In these cases, the observation of the ν(C═O) band(s) must be identified to confirm the presence of acv. Note that crystal separation by hand has to be fairly precise otherwise binary complexes plus acv contamination can be misinterpreted as ternary complexes by FT-IR analysis.

The binary Cu(polyamine) oxo-salts reported in this manuscript containing free nitrate ions were also synthesized separately (without the addition of the synthetic nucleoside) and their FT-IR performed. The spectra of colored crystals that did not show the aforementioned 1385 $cm^{-1}$ band had the same FT-IR footprint as the corresponding binary Cu(polyamine) oxo-salt, confirming the absence of acv in that compound.

### 2.2.1. [Cu(cyclam)($ClO_4$)$_2$] (**1**)

To an equimolar (0.25 mmol) solution of Cu($ClO_4$)$_2$·6$H_2O$ and cyclam in MeOH (30 ml) a suspension of acv (0.25 mmol) in methanol (40 ml) was added. The evaporation of the solvent promptly yields colorless crystals of free acv and dark pink crystals of compound **1**. In addition, nice dark pink crystals of **1** can be obtained by slow evaporation of equimolar amounts (0.25 mmol) of Cu($ClO_4$)$_2$·6$H_2O$ and cyclam dissolved in 40 ml of methanol. Yield: 65%. The elemental analysis of this compound was not carried out due to the perchlorate content! FT-IR (KBr disk, $cm^{-1}$): cyclam ν(N–H) 3242 and 3165, $\nu_{as}(CH_2)$ 2976 and 2939, $\nu_s(CH_2)$ 2890 and 2880, $ClO_4^-$ absorptions 1137, 1121, 1094 and 1038 or 1017 [32].

### 2.2.2. {[Cu(cyclam)($\mu_2$-$NO_3$)]($NO_3$)}$_n$ (**2**)

An equimolar (0.5 mmol) solution of Cu($NO_3$)$_2$·3$H_2O$, cyclam and acv in methanol (125 ml) yields colorless crystals of free acv and dark pink crystals of compound **2**. Alternatively, nice dark pink crystals of this compound were isolated by slow evaporation of equimolar amounts (0.25 mmol) of Cu($NO_3$)$_2$·3$H_2O$ and cyclam in 50 ml of methanol. Yield: 80%. Anal. exp. (%): C, 30.99; H, 6.32; N, 21.60. Calc. for $C_{10}H_{24}CuN_6O_6$: C, 30.96; H, 6.24; N, 21.67. FT-IR (KBr disk, $cm^{-1}$): cyclam ν(N–H) 3229 and 3165, $\nu_{as}(CH_2)$ 2940 and 2905, $\nu_s(CH_2)$ 2878 and 2865; free and coordinated nitrate ν($NO_3^-$) 1385 (very intense and broad) and 839 or 825 (weak) [32].

### 2.2.3. {[Cu(cyclam)($\mu_2$-$SO_4$)]·MeOH}$_n$ (**3**)

An equimolar (0.5 mmol) solution of $CuSO_4$·5$H_2O$, cyclam and acv in methanol (125 ml) yields colorless crystals of free acv and dark pink crystals of compound **3**. Dark pink crystals of this compound were also obtained by slow evaporation of equimolar amounts (0.5 mmol) of $CuSO_4$·5$H_2O$ and cyclam dissolved in 80 ml of methanol. Suitable crystals for X-ray crystallography were ground using diethyl ether as anti-solvent. Yield: 77%. Anal. exp. (%): C, 33.66; H, 7.12; N, 14.25. Calc. for $C_{11}H_{28}CuN_4O_5S$: C, 33.71; H, 7.20; N, 14.29. FT-IR (KBr disk, $cm^{-1}$): MeOH band ν(O–H) ~3443 (broad and intense) and δ(O–H) 1385 (in this case, weak and defined but not accompanied of a ν(C═O) band near 1695 $cm^{-1}$ of acv!), cyclam ν(N–H) 3229 and 3165, $\nu_{as}(CH_2)$ 2935 and 2905, $\nu_s(CH_2)$ 2866 and shoulder at ~2830, $\mu_2$-$SO_4$ $\nu_3$ 1195, 1106 (intense), 1075 and 1063 (weak peaks), $\nu_1$ 963 (medium and defined), $\nu_4$ 620 (medium and defined) and $\nu_2$440 (weak) [32]. The electronic spectrum of this dark pink compound, as obtained by diffuse reflectance, shows a band with $\lambda_{max}$517 nm ($\nu_{max}$ 19,340 $cm^{-1}$) with a shoulder near 670 nm (ν ~15,000 $cm^{-1}$). This spectrum is representative for all pink Cu-cyclam derivatives here reported, with an elongated octahedral coordination, type ~4 + 2. The shape of his spectrum does not enable a geometrical estimation of an intensity barycenter.

### 2.2.4. {[Cu(cyclam)($\mu_2$-$SO_4$)]·5$H_2O$}$_n$ (**4**)

Dark pink crystals of this hydrate were obtained from a similar synthesis to that referred for compound **3** but using a $H_2O$:MeOH (1:1)

**Table 2**
Bond lengths [Å] and *trans*-coordination angles (°) around the metal ion in compounds **1** to **4**.

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Cu–N(cyclam) | 2.025(2) | 2.015(1) | 2.016(3) | 2.019(2) |
| | 2.025(2) | 2.0168(1) | 2.023(3) | 2.018(2) |
| | 2.029(2) | 2.018(2) | 2.024(3) | 2.0148(2) |
| | 2.029(2) | 2.023(2) | 2.028(3) | 2.014(2) |
| Cu–O($ClO_4$) | 2.547(1) | – | – | – |
| | 2.547(1) | – | – | – |
| Cu–O($NO_3$) | – | 2.510(2) | – | – |
| | – | 2.603(2) | – | – |
| Cu–O($SO_4$) | – | – | 2.449(2) | 2.544(2) |
| | – | – | 2.519(2) | 2.544(2) |
| N(cyclam)–Cu–N(cyclam) | 180.00(9) | 179.62(7) | 178.79(11) | 178.51(8) |
| | 180.00(7) | 178.05(7) | 179.32(11) | 178.51(8) |
| O($ClO_4$)–Cu–O($ClO_4$) | 180.00(8) | – | – | – |
| O($NO_3$)–Cu–O($NO_3$) | – | 171.24(5) | – | – |
| O($SO_4$)–Cu–O($SO_4$) | – | – | 175.20(8) | 175.39(8) |

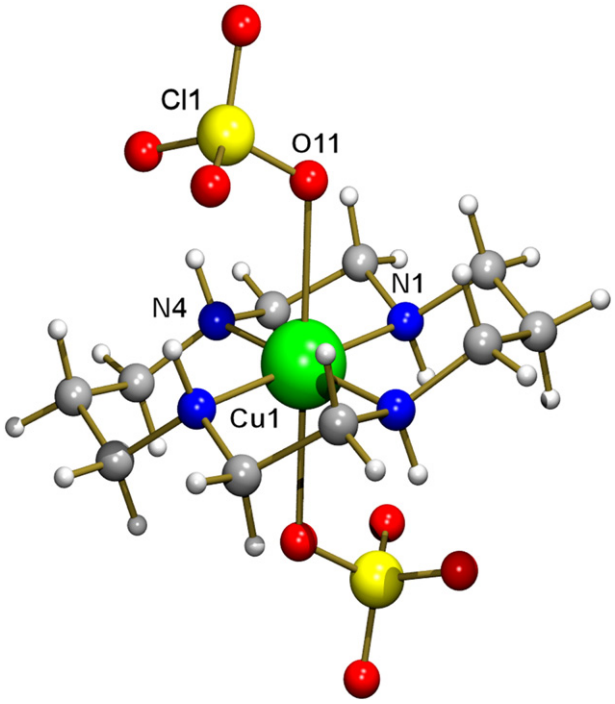


**Fig. 3.** Structure of the complex molecule trans-[Cu(cyclam)($ClO_4$)$_2$] in the crystal of compound **1**.

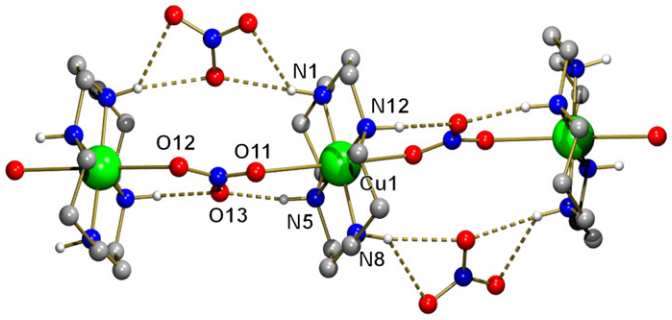


**Fig. 4.** Fragment of the polymeric chain of compound **2**, {[Cu(cyclam)($\mu_2$-$NO_3$)]($NO_3$)}$_n$, showing different N–H···O interactions connecting cyclam (as H-donor) and free and coordinated nitrate ions (as O-acceptors). H-atoms not involved in H-bonds omitted for clarity.

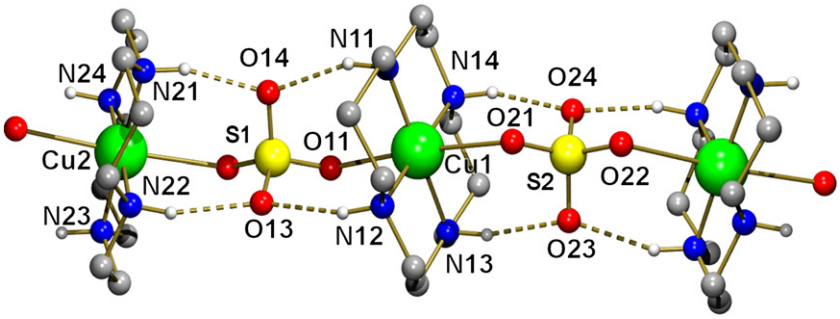


**Fig. 5.** Fragment of the polymeric chain of compound **3**, {[Cu(cyclam)($\mu_2$-$SO_4$)]·MeOH}$_n$, showing the N–H···O interactions connecting cyclam and bridging-sulfate ligands. Methanol and H-atoms not involved in H-bonds omitted for clarity.

mixture as solvent. The crystals afforded by this reaction were studied by X-ray crystallography and correspond to the penta-hydrated compound **4**. Yield: 26%. Anal. exp. (%): C, 26.73; H, 7.68; N, 12.28. Calc. for $C_{10}H_{34}CuN_4O_9S$: C, 26.69; H, 7.62; N, 12.45. FT-IR (KBr disk, $cm^{-1}$): $H_2O$ bands $\nu_{as}(H_2O)$ ~3458 (broad and intense) and $\delta(H_2O)$ 1631, cyclam $\nu$(N–H) 3227 and 3168, $\nu_{as}(CH_2)$ 2933 and 2906, $\nu_s(CH_2)$ 2877, 2861 and 2850, $\mu_2$-$SO_4$ $\nu_3$ 1139, 1121 (intense), 1078 and 1065 (weak peaks), $\nu_1$ 963 (medium and defined), $\nu_4$ 619 (medium and defined) and $\nu_2$ 434 (weak) [32].

*2.2.5. [Cu(cyclen)($H_2O$)]$SO_4$·2$H_2O$ (**5**)*

To an equimolar (0.15 mmol) solution of $CuSO_4$·5$H_2O$ and cyclen in methanol (25 ml), 0.3 mmol of acv was added with stirring and heating (50 °C) until complete solution of reactants. The solution was filtered with vacuum. Colorless crystals of acv were formed and removed by filtration. Blue crystals were also formed and picked off for X-ray diffraction. Compound **5** was also obtained by mixing $CuSO_4$·5$H_2O$ (0.5 mmol) dissolved in 10 ml of MeOH and cyclen (0.5 mmol) in 10 ml of MeOH. The dark blue solution was filtered without vacuum into a crystallizing dish. The slow evaporation of the solvent leads to the compound in a 35% yield. Anal. exp. (%): C, 24.75; H, 6.84; N, 14.48. Calc. for $C_8H_{26}CuN_4O_7S$: C, 24.90; H, 6.79; N, 14.52. FT-IR (KBr disk, $cm^{-1}$): $H_2O$ bands $\nu_{as}$ 3439, $\delta(H_2O)$ ~1630, cyclen $\nu$(N–H) 3170, $\nu_{as}(CH_2)$ 2960, 2936 and 2920, $\nu_s(CH_2)$ 2872 and 2824, free $SO_4^{2-}$ $\nu_3$ 1119 (intense and broad) and $\nu_4$ 618 [32].

*2.2.6. [Cu(cyclen)($H_2O$)]$SO_4$·3$H_2O$ (**6**)*

To an equimolar (0.15 mmol) solution of $CuSO_4$·5$H_2O$ and cyclen in methanol (25 ml), 0.3 mmol of acv was added with stirring and heating (50 °C) until complete solution of reactants. The solution was filtered with vacuum. Colorless crystals of acv were formed and removed by filtration. A blue precipitate appeared and collected in a yield of 21%. FT-IR (KBr disk, $cm^{-1}$): $H_2O$ bands $\nu_{as}$ 3428, $\delta(H_2O)$ ~1630, cyclen $\nu$(N–H) 3171, $\nu_{as}(CH_2)$ 2957, 2933 and 2921, $\nu_s(CH_2)$ 2871 and 2853, free $SO_4^{2-}$ $\nu_3$ 1123 (intense and broad) and $\nu_4$ 620 [32]. Suitable single crystals for X-ray diffraction were grown by recrystallization of the initial blue precipitate (which had evident contamination of acv) in a water:DMF mixture (80:20). The electronic spectrum of this blue compound, as obtained by diffuse reflectance, shows an asymmetric d–d band with $\lambda_{max}$ 595 nm ($\nu_{max}$ 16,800 $cm^{-1}$). This spectrum is representative for all blue Cu-cyclen derivatives here reported, with an elongated square base pyramidal coordination, type 4 + 1. The shape of his spectrum enables the geometrical estimation of an intensity barycenter ($\lambda$ 670 nm, $\nu$ 15,000 $cm^{-1}$).

*2.2.7. [Cu(trien)(acv)]($NO_3$)$_2$·acv (**7**)*

To an equimolar (1 mmol) solution of Cu($NO_3$)$_2$·3$H_2O$ and trien in isopropanol (150 ml), acv (1 mmol) was added in small aliquots. When the initial turbidity disappeared, the blue solution was filtered without vacuum into a crystallizing dish. With or without the use of diethyl-ether as anti-solvent, the formation of colorless (acv) and needle-like blue crystals was observed. The blue crystals were separated by hand and recrystallized in MeOH (10 ml). Yield: 30%. Anal. exp. (%): C, 33.62; H, 5.07; N, 28.43. Calc. for $C_{22}H_{40}CuN_{16}O_{12}$: C, 33.70; H, 5.14; N, 28.58. FT-IR (KBr disk, $cm^{-1}$): $\nu$(O–H) of acv 3434 (broad), $\nu_{as}(NH_2)$ ~3316 and $\nu$(N–H) 3136 (overlapped bands of trien and acv), only trien $\nu_{as}(CH_2)$ 2962 and 2925, $\nu_s(CH_2)$ 2856, acv $\nu$(C═O) 1696, $\delta$(O–H) of acv and $\nu$(free $NO_3^-$) 1384 of acv (very intense and sharp!) [32].

*2.2.8. [Cu(trien)(acv)]$SO_4$·0.71$H_2O$ (**8**)*

To an equimolar (0.5 mmol) solution of $CuSO_4$·5$H_2O$ and trien in methanol (25 ml), 0.5 mmol of acv in MeOH:DMF (3:1, 40 ml) was added while stirring. The resulting solution was filtered with vacuum. Colorless crystals of acv were formed and removed by filtration. Needle-like blue crystals were formed in ten days, some of them

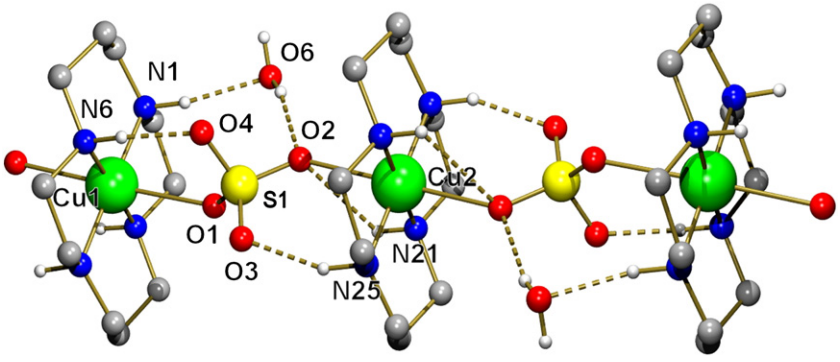


**Fig. 6.** Fragment of the polymeric chain of compound **4**, {[Cu(cyclam)($\mu_2$-$SO_4$)]·5$H_2O$}$_n$, with N–H···O interactions connecting cyclam and bridging-sulfate ligands. Non-coordinated water molecules and H-atoms not involved in H-bonds omitted for clarity.

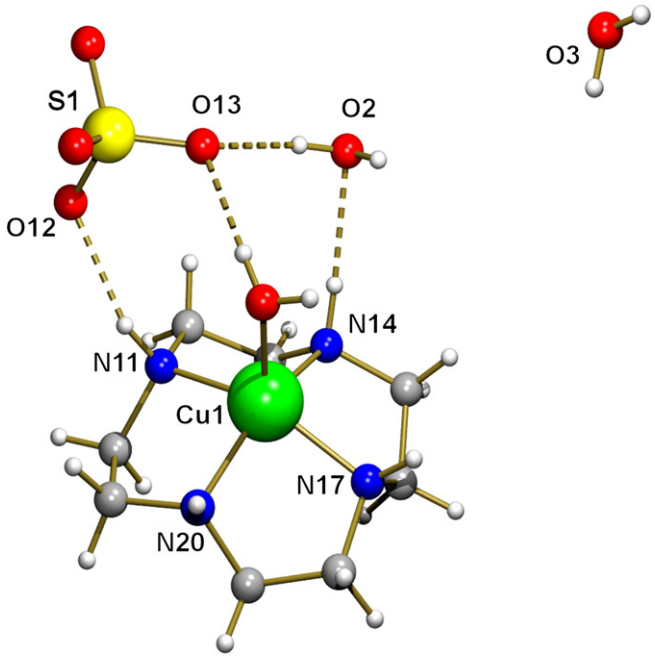


**Fig. 7.** Asymmetric unit in the crystal of compound **5**, $[Cu(cyclen)(H_2O)]SO_4 \cdot 2H_2O$, showing three H-bonding interactions between the macrochelate cation and sulfate counter-anions.

suitable for X-ray diffractometry. Additional samples were successively collected by filtration. Yield: 60%. Anal. exp. (%): C, 30.85; H, 5.59; N, 23.09. Calc. for $C_{14}H_{30.42}CuN_9O_{7.71}S$: C, 30.92; H, 5.64; N, 23.18. FT-IR (KBr disk, $cm^{-1}$): $\nu$(O–H) acv + $\nu_{as}(H_2O)$ 3434 (overlapped, broad), overlapped acv and trien $\nu_{as}(NH_2)$ ~3304, $\nu_s(NH_2)$ ~3257 and $\nu$(N–H)

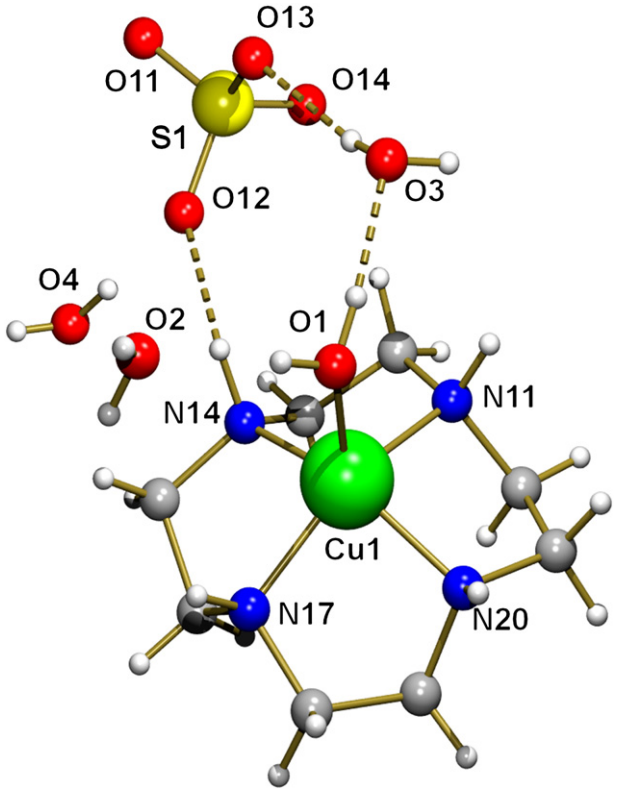


**Fig. 8.** Asymmetric unit in the crystal of compound **6**, $[Cu(cyclen)(H_2O)]SO_4 \cdot 3H_2O$, showing only two H-bonding interactions between the macrochelate cation and sulfate counter-anions.

**Table 3**
Bond lengths [Å] and trans-coordination angles (°) around the metal ion in compounds **5** to **8**.

| | 5 | 6 | 7 | 8 |
|---|---|---|---|---|
| Cu–N(cyclen) | 2.017(3) | 2.023(2) | – | – |
| | 2.021(3) | 2.0248(1) | – | – |
| | 2.025(3) | 2.027(2) | – | – |
| | 2.030(3) | 2.027(2) | – | – |
| | – | – | 2.007(3) | 2.008(4) |
| Cu–N(trien) | – | – | 2.021(3) | 2.032(4) |
| | – | – | 2.024(3) | 2.026(3) |
| | – | – | 2.047(3) | 2.022(3) |
| Cu–O($H_2O$) | 2.124(2) | 2.184(2) | – | – |
| Cu–N(acv) | – | – | 2.193(3) | 2.235(3) |
| N(cyclen)–Cu–N(cyclen) | 150.93(11) | 149.46(6) | – | – |
| N(cyclen)–Cu–N(cyclen) | 148.92(11) | 149.12(6) | – | – |
| N(trien)–Cu–N(trien) | – | – | 162.49(13) | 160.46(14) |
| N(trien)–Cu–N(trien) | – | – | 145.28(13) | 150.32(14) |

3137 (overlapped), only trien $\nu_{as}(CH_2)$ 2950, $\nu_s(CH_2)$ 2885, only acv $\nu$(C═O) 1696 and $\delta$(O–H) 1381, free $SO_4^{2-}$ $\nu_3$ 1114 (intense and broad) and $\nu_4$ 621 [32]. The electronic spectrum of this blue compound, as obtained by diffuse reflectance, shows an asymmetric d–d band with $\lambda_{max}$ 595 nm ($\nu_{max}$ 16,800 $cm^{-1}$). This spectrum is representative for both blue Cu–trien derivatives here reported, with an elongated square base pyramidal coordination, type 4 + 1. The shape of his spectrum enables the geometrical estimation of an intensity barycenter ($\lambda$ 650 nm, $\nu$ 15,400 $cm^{-1}$). As can be anticipated, these data are closing similar to those above referred for compound **6**.

### 2.3. X-ray diffraction studies

Measured crystals were prepared under inert conditions immersed in perfluoropolyether as protecting oil for manipulation. Suitable crystals were mounted on MiTeGen Micromounts™, and these samples were used for data collection. Data were collected with Bruker Kappa ApexII (compounds **1**, **3**, **5** and **6**, 100 K), Bruker SMART CCD 100 (compound **2**, 100 K), Bruker D8 Venture (compounds **4** and **8**, 100 K) or Bruker X8 Proteum (compound **7**, 296 K) diffractometers. The data were processed with APEX2 [33] programs and corrected for absorption using SADABS [34]. The structures were solved by direct methods, which revealed the position of all non-hydrogen atoms. These atoms

**Table 4**
Relevant H-bonding interactions in compounds **1** to **8**. Crystallographic symmetry codes omitted (see Figs. 1 to 8 and Supplementary data S2 to S9).

| Compound | D–H···A | d(D···A) (Å) | <(DHA) (°) |
|---|---|---|---|
| **1** | N(1)–H···O(13) | 3.208(2) | 146.5 |
| | N(4)–H···O(14) | 3.236(2) | 142.6 |
| **2** | N(1)–H···O(13) | 2.968(3) | 149.8 |
| | N(8)–H···O(13) | 2.887(3) | 162.7 |
| **3** | N(11)–H···O(14) | 2.940(3) | 161.7 |
| | N(12)–H···O(13) | 2.926(3) | 157.5 |
| | N(13)–H···O(23) | 2.899(3) | 160.2 |
| | N(14)–H···O(24) | 2.918(3) | 165.3 |
| | N(21)–H···O(14) | 2.962(3) | 161.0 |
| | N(22)–H···O(13) | 2.872(3) | 163.3 |
| **4** | N(1)–H···O(6) | 3.035(3) | 163.5 |
| | N(6)–H···O(4) | 2.819(3) | 161.8 |
| **5** | N(11)–H···O(12) | 2.910(4) | 149.4 |
| | O(1)–H···O(13) | 2.742(3) | 178.8 |
| | N(14)–H···O(2) | 3.020(4) | 175.6 |
| | O(2)–H···O(13) | 2.752(3) | 164.3 |
| **6** | N(14)–H···O(12) | 2.860(2) | 136.8 |
| | O(1)–H···O(3) | 2.704(2) | 173.1 |
| | O(3)–H···O(13) | 2.733(2) | 162.3 |
| **7** | N(44)–H···O(6) | 2.811(4) | 150.2 |
| **8** | N(1)–H···O(46) | 3.028(4) | 171.5 |
| | N(37)–H···O(46) | 3.067(4) | 149.7 |
| | N(4)–H···O(6) | 3.010(4) | 150.7 |

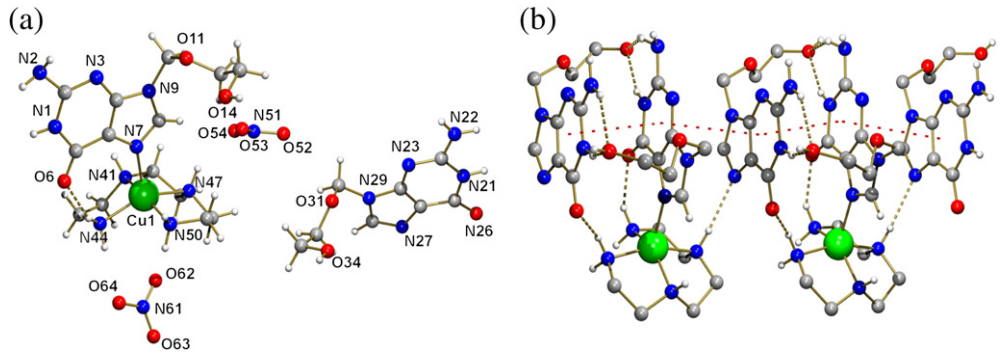


**Fig. 9.** Structure of compound **7**, [Cu(trien)(acv)]$(NO_3)_2$·acv. A) Asymmetric unit showing the Cu–N7(acv) bond cooperating with the (primary amino)N–H···O6(acv) interligand interaction within the ternary complex cation. B) π,π-Multi-stacked chains involving the six-membered heterocyclic rings of acyclovir solvate and $[Cu(trien)(acv)]^{2+}$ ions in cooperation with different H-bonds.

were refined on $F^2$ by a full-matrix least-squares procedure using anisotropic displacement parameters [35]. All hydrogen atoms were located in difference Fourier maps and included as fixed contributions riding on attached atoms with isotropic thermal displacement parameters 1.2 times those of the respective atom. Geometric calculations and drawings were carried out with PLATON [36]. Additional crystal data and more information about the X-ray structural analyses are shown in Supporting information S2 to S9. In compound **8**, one of the coordinated acyclovir molecules exhibits disorder over two sites in the hydroethoxymethyl-arm in a 0.65:0.35 ratio. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 1033794–1033801. Copies of this information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44 1223 336 033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

### 2.4. Other physical measurements

Analytical data were obtained in a Fisons-Carlo Erba EA 1108 elemental micro-analyzer. Infrared spectra were recorded by using KBr disks on a Jasco FT-IR 6300 spectrophotometer. Thermogravimetric (TG) analyses of commercial acv samples (295–900 °C) were carried out in a Shimadzu thermogravimetric analyzer TGA-50H instrument (Supplementary information S1.3). Also commercial samples of acyclovir were analyzed by powder X-Ray diffraction in a Bruker D8 Advance diffractometer (Supplementary information S1.2).

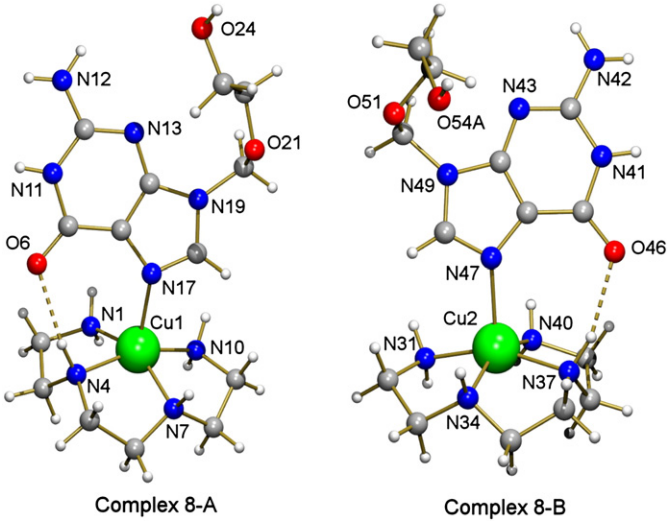


**Fig. 10.** The two independent ternary complex cations in the crystal of compound **8**, [Cu(trien)(acv)]$SO_4$·0.71$H_2O$. For clarity reasons only one of the two N9-side chain conformations of acv ligand is plotted for complex 8-B.

## 3. Results and discussion

The studied structures in this work have not been previously reported in the CSD database (compounds **2**–**6**) with the single exception of compound **1**, which was reported long time ago with lower resolution (CSD code PTZDCU) [37]. Only Cu(II)–trien complexes contain acyclovir. Table 1 shows detailed information about the crystal data of compounds **1-8**.

### 3.1. Cyclam copper(II) complexes

Cyclam is a symmetrical 14-membered N4-macrocycle able to insert the Cu(II) atom in the plane of its four N-donors. It most frequently tends to give elongated octahedral copper(II) complexes with a ~4 + 2 coordination. Numerous examples can be found, e.g. in the cation $[Cu(cyclam)(H_2O)_2]^{2+}$ [38–41] or related compounds where the trans-apical ligands are other molecular solvents (N,N-dimethylformamide [42,43] and acetonitrile [44–46]) or anionic ligands such as cyanide [47] and azide [48,49]. Nevertheless, square based pyramidal (type 4 + 1) complexes [50] and the square-planar $[Cu(cyclam)]^{2+}$ cation [51] have also been reported. According to these data, the Cu(II)–cyclam chelate could be considered as an appropriate receptor for the apical coordination of one (or even two) acv ligand(s), coordinated via its N7-donor and assisted by an intramolecular interligand interaction (cyclam)N–H···O6(acv). However, all our results in this sense failed. Instead, we obtained compounds **1**–**4**. The structure of $[Cu(cyclam)(ClO_4)_2]$ (**1**) was reported in 1975 and determined at room temperature (PTZDCU in CSD database) with a final R1 value of 0.056 [37] while our results show an improved R1 value of 0.025 with data collected at 100 K. Structures of compounds **2**–**4** have not been reported previously in the CSD database. Coordination bonds and selected angles for compounds **1**–**4** are summarized in Table 2. As expected, these four compounds exhibit a 4 + 2 copper(II) coordination, with the four closest Cu–N(cyclam) bonds being in the range 2.02–2.03 Å. The trans-apical distances of the Cu–O(oxoanion) bond are 2.45–2.60 Å. Compound **1** consists of centro-symmetrical complex molecules where the perchlorate anions are only weakly coordinated (Fig. 3). (Cyclam)N–H···O6(acv) interligand interactions are missing in this molecular crystal.

Compounds **2**–**4** have in common the bridging role of the nitrate or the sulfate anion between $[Cu(cyclam)]^{2+}$ units. In these compounds there are a variety of intra-molecular N–H···O interactions. In the polymeric 1D chain $\{[Cu(cyclam)(\mu_2NO_3)]^+\}_n$ of **2** (Fig. 4), each bridging nitrate ligand builds a Cu–O11 bond (2.510(2) Å) that cooperates with the N1–H1···O13 interaction (2.968(3), 149.87°) and a longer Cu1–O12 bond (2.603(2) Å). Additional H-bonds involve the non-coordinated nitrate counter-anion. In compound **3** (Fig. 5), each Cu1–O(11 or 12) or Cu2–O21 or O22 bond of the $\mu_2$-sulfate ligand is reinforced by two (cyclam)N–H···O(sulfate) interligand interactions in

such a way that each of these non-coordinated O-μ-sulfate atoms acts twice as H-acceptor. The hydrated compound **4** also consists of 1D-polymeric chains where the bridging sulfate ligand reinforces the Cu–O bonds with two N–H···O (non-coordinated) interactions and one water-mediated N–H···O (coordinated) interaction (Fig. 6). These structures illustrate the ability of the Cu(cyclam)$^{2+}$ chelate to give Cu–O(oxoanion) bonds and to reinforce these bonds with H-bonding interligand interactions. Taking into account that acv is a neutral ligand, our results strongly suggest that acv has a dislike for cyclam binding due to the weakness of trans-apical Cu(II) coordination sites.

### 3.2. Cyclen copper(II) complexes

Cyclen is a well-known 12-membered N4-macrocycle that is not able to insert the Cu(II) atom in the plane of its N-donor atoms. Thereby it gives Cu(II) macrochelates with a frequent 4 + 1 coordination, with only one apical site. At this apical position we can found aqua [52,53], acetonitrile [54] and various anions, including the purinate(1−) anionic ligand studied by K. Aoki et al. [31]. On this basis, the possibilities of binding acv at the apical coordination site were expected to be improved. However, once more, none of the isolated Cu–cyclen compounds had acyclovir in its formula. Compounds **5** and **6** have in common the [Cu(cyclen)($H_2O$)]$^{2+}$ cation and a sulfate counter-anion, differing in the number of non-coordinated water molecules. In the crystal of compound **5** (Fig. 7), there are anion–cation interactions featured by the (cyclen)N11–H11···O12(sulfate) and (aqua)O1–H1···O13(sulfate) interactions as well as water mediated (cyclen)N14–H–14···O2(water)–H2A···O13(sulfate) interaction. In compound **6** (Fig. 8), the anion–cation interactions are restricted to the (cyclen)N14–H14···O12(sulfate) interaction and the water mediated (aqua)O1–H1A···(water)O3–H3A···O13(sulfate) interaction. These structures remain however puzzling because of the incapability of the N7–acv donor atom to displace the apical–aqua ligand from the [Cu(cyclen)($H_2O$)]$^{2+}$ cation. Note that the O(water) atom is a hard Pearson base while and the N7–acv donor is a borderline Pearson base and the Cu(II) ion is a borderline Pearson acid.

### 3.3. Ternary copper(II) complexes with trien and acyclovir

Triethylenetetramine (trien) is an acyclic and flexible N4-ligand. The number of Cu–trien structures found in the CSD database is limited to 22 items and include some derivatives having the [Cu(trien)($H_2O$)]$^{2+}$ (Cu–O 2.37(1) Å) [55] and [Cu(trien)($NH_3$)]$^{2+}$ (Cu–$NH_3$ 2.12(1)–2.18(1) Å) [56] cations with neutral apical ligands. In addition, related [Cu(trien)(L)]$^{-}$ complex units have been reported where L is an unidentate anionic ligand, such as iodide [57], S-thiocyanate [58], N-isothiocyanate [59], [$PF_6$]$^{-}$ [60], dicianamido(1−) [61] or a $\mu_2$-bridging(1−) anionic ligand as cyanide [62–65], azide [66], imidazolate [67] or a 1,2,4-triazolo-derivative [68]. Without exception, in all these compounds the tetradentate trien ligand supplies the four closest N-donors to the elongated square-base pyramidal copper(II) coordination, type 4 + 1, thus moving the donor atom of the neutral or anionic co-ligand to the apical coordination site. Therefore the Cu(trien)$^{2+}$ complex can be considered as a suitable model receptor for Cu(II)–acv apical binding.

A summary of coordination bond length and angles of compounds **7** and **8** is reported in Table 3. Intra-molecular H-bonding interactions of these compounds are in Table 4. Compound **7** consists of the [Cu(trien)(acv)]$^{2+}$ cation, nitrate counter-anions and free acv as solvate (Fig. 9A). In this ternary Cu(II) complex, trien supplies the four closest N-donor atoms of the 4 + 1 copper(II) surrounding (averaged Cu–N(trien) distance of 2.025 Å). The Cu–N7–acv bond is the longest Cu–N bond (2.193(3) Å) and cooperates with the (primary amino trien)N44–H44B···O6(acv ligand) intra-molecular interligand interaction (2.811(4) Å, 150.2°). In the crystal **7**, among other H-bonds, each ternary complex cation is related to a neighboring acv solvate by the following H-bonding interactions: (acv ligand)N1–H1···O34 (2.833(4) Å, 158.2°) and (acv ligand)N2–H2A···O34 [2.984(5) Å, 138.5°] with the O-alcoholic of N9 arm from the free-acv solvate plus (primary amino trien)N50–H50A···O26(exocyclic free-acv) (2.965(5) Å, 143.0°) as well as (acv solvate)N21–H21···O14 (2.867(4) Å, 156.8°) and (acv solvate)N22–H22B···O14 3.025(4) Å, 146.6° with the O-alcoholic atom of the N9 arm from the acv ligand. These interactions favor π,π-stacking between the six-membered aromatic rings of the acv ligand and the acv solvate (with an inter-centroid distance of 3.798(2) Å and interplanar distance of 3.755(2) Å) thus building multi-π,π-stacked chains along the b-axis of the crystal (Fig. 9B).

Compound **8** agrees with the simplified formula [Cu(trien)(acv)]$SO_4$·0.71$H_2O$. In the asymmetric unit there are two non-equivalent mixed-ligand complex cations (hereafter referred as cations 8-A and 8-B, see Fig. 10), two sulfate anions and 1.42 water molecules. Besides their role in H-bonding interactions, the main difference between both molecules is the disorder located in the N9-acyclic arm of acv ligand in cation 8-B (not shown in Fig. 10). Both Cu(II) complex ions exhibit a close similar copper(II) coordination, type 4 + 1, with the Cu–N7(acv) bond distances of 2.239(3) Å or 2.235(2) Å in 8-A and 8-B, respectively (see Table 3). The most striking feature of this compound is the apical coordination of neutral acv via N7 within the Cu(II) polyhedron. These Cu–N7(acv) bonds are reinforced by intra-molecular interligand interactions (N4–H4···O6 2.968(4) Å, 150.7° for 8-A and N37–H37···O46 3.067(4) Å, 149.7° for 8-B cations — see Table 4). In the crystal additional H-bonding interactions are present, e.g. the exocyclic O6–acv atoms of both complex cations participate in inter-molecular interactions, thus acting as double acceptors. Moreover π,π-stacking interactions between the six-membered aromatic rings of acv ligands of both independent cations are found, with a inter-centroid distance of 3.776(1) Å and a rather short inter-planar distance of 3.404(2) Å.

### 3.4. The discriminating behavior of the studied Cu–tetraamine chelates as receptors for acyclovir

The disability of the Cu(cyclam)$^{2+}$ chelate to bind neutral acv as an apical ligand seems to be related to its preference for an elongated octahedral coordination, type ~4 + 2, which features a remarkable weakness of the trans-apical bonds. Regardless of the absence (compound **1**) or presence (compounds **2** to **4**) of intra-molecular interactions type (cyclam)N–H···O(oxoanion), the Cu–O(aqua, apical bond) distances in compounds **1**–**4**, with different oxo-anions, are significantly longer (2.45–2.60 Å) than the Cu–O(aqua) in the five-coordinated Cu–cyclen compounds **5** and **6** (2.12 Å and 2.18 Å, respectively) and the Cu–O6(acv) bond distances observed in the also five-coordinated compounds **7** (2.19 Å) and **8** (2.22 or 2.24 Å). Indeed, it is well documented that an increase of the coordination number represents an elongation of the coordination bonds.

To ascertain the origin of the inability of the [Cu(cyclen)($H_2O$)]$^{2+}$ macrochelate to bind acv in the apical coordination site of the copper(II) center (by substitution of the apical aqua ligand), the comparison of the five-coordinated Cu–cyclen (**5** and **6**) and Cu–trien (**7** and **8**) compounds here reported seems to be crucial. In Cu–cyclen compounds, the N–Cu–N angles of the four five-membered chelate rings, at the basal Cu(II) coordination plane, are very close to 85°. This feature is also observed for the five-membered chelate rings formed in the Cu–cyclam chelates. In contrast, the acyclic trien tetraamine only builds three five-membered chelate rings with N–Cu–N angles of ~85° while the value of the non-chelate (primary amino)N–Cu–N(primary amino) angle is about 10–12° higher (97.37° in **7** and 95.61° or 94.37° in **8**). Note that the intra-molecular (trien)N–H···O6(acv) interaction involves a primary amino group of trien in **7** but a secondary amino group in **8** although with similar structural consequences.

### 3.5. Concluding remark

We conclude that the successful role of the $Cu(trien)^{2+}$ chelate as a receptor for acv at the apical–distal Cu(II) coordination site is related to the concurrence of two circumstances: (a) the acyclic and flexible nature of trien and (b) the ability of trien to generate square-base pyramidal copper(II) complexes (type 4 + 1) where its four N-atoms occupy the four closest coordination sites of the metal.

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## Appendix A. Supplementary data

FT-IR, thermal analysis and powder X-ray diffraction of commercial acv are shown in S1. Basic crystallographic tables are reported for all studied compounds (S2–S9) as well as FT-IR spectra (S10). For further information about the spectral properties (FT-IR, UV–Vis) or thermal analyses (TGA) carried out to all the reported compounds, please contact with the corresponding author. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jinorgbio.2015.03.006.

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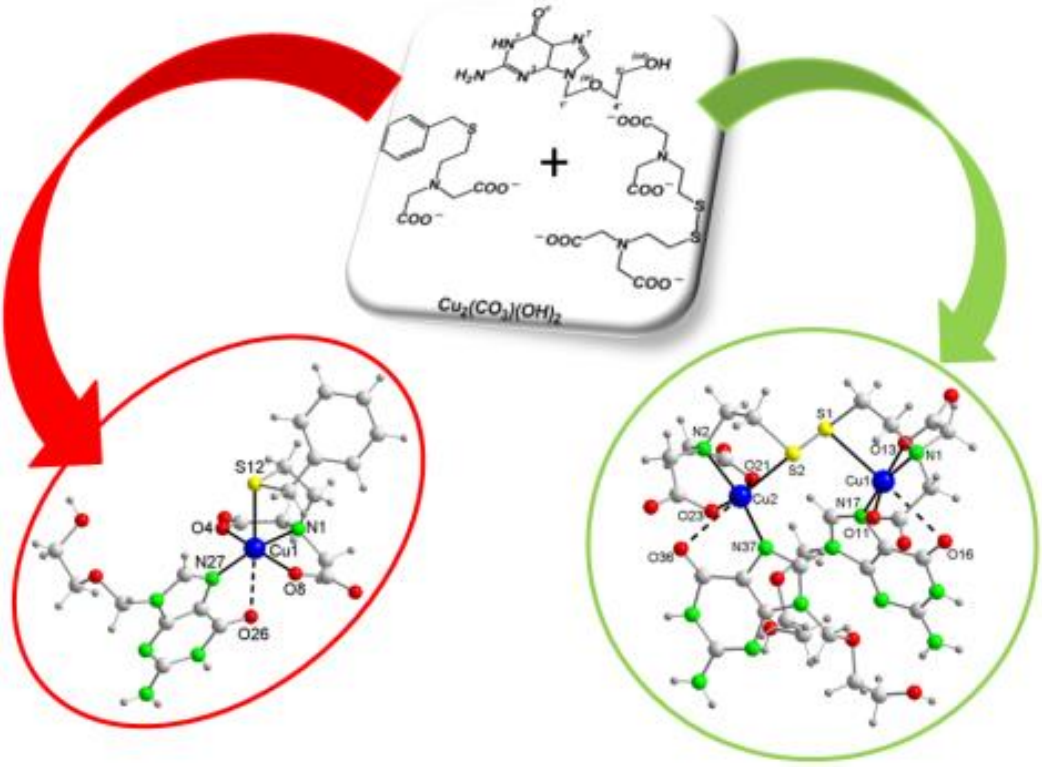
## 5. 3. ARTÍCULO 3: METAL BINDING PATTERN OF ACYCLOVIR IN TERNARY COPPER(II) COMPLEXES HAVING AN S-THIOETHER OR S-DISULFIDE $NO_2S$-TRIPODAL TETRADENTATE CHELATOR

### SYNOPSIS ENTRY

Metal binding pattern of acyclovir in ternary copper(II) complexes having an S-thioether or S-disulfide $NO_2S$-tripodal tetradentate chelator are investigated. The molecular and crystal structure of two novel Cu(II) complexes with $NO_2S$-tripodal tetradentate chelators and acyclovir coligands are reported. Acyclovir features the rather uncommon N7,O6-chelating metal binding mode. The metal exhibits an asymmetric elongated octahedral coordination, type 4+1+1, with S-(thioether or disulfide) and O6-acyclovir atoms in trans-apical/distal Cu(II) coordination sites.




### HIGHLIGHTS

· Copper(II) complexes with two $NO_2S$-tripodal tetradentate chelators are investigated.

· S-donor atoms within chelators belong to a thioether or a disulfide group.

· Acyclovir features the N7,O6-chelating binding mode in the novel ternary complexes.

· S-chelator and O6-acv donor atoms occupy both trans-apical Cu(II) coordination sites.

## RESUMEN

Este trabajo aporta, entre otras cosas, la síntesis y la estructura cristalina y molecular de dos nuevos complejos ternarios de cobre(II) conteniendo un quelante tetradentado trípode-$NO_2S$, que proporcionan información adicional acerca del modo de reconocimiento molecular entre el nucleósido sintético aciclovir (acv) y los correspondientes quelatos del referido metal. Con tal fin, se han utilizado los quelantes aniónicos N,N-bis(carboximetil)-S-bencilcisteaminato(2-) (BCBC) y N,N,N',N',-tetrakis(carboximetil)cistaminato(4-) (TCC) que contienen azufre tioéter o azufre disulfuro, respectivamente, entre sus potenciales átomos dadores. Los compuestos ternarios de $[Cu(BCBC)(acv)]\cdot 2.5MeOH\cdot 0.5H_2O$ (**3**) y $[Cu_2(TCC)(acv)_2]\cdot 6H_2O$ (**5**) contienen al átomo metálico en una coordinación octaédrica, asimétricamente alargada, tipo 4+1+1* (donde * indica una muy débil enlace de coordinación, entre el átomo de Cu(II) y el dador O6-exocíclico de acv, con una distancia interatómica de ~3Å). Esto último es esencialmente consecuencia de dos circunstancias. De una parte, el ligando acv actúa como quelante-N7,O6, un modo bastante inusual (solo previamente documentado por Iztok Turel et al. para trans-$[Cu(acv)_2(H_2O)_2](NO_3)_2$, con una distancia Cu–O6(acv) de ~2.7 Å). Por otro lado, la debilidad de la interacción Cu···O6(acv) en los nuevos compuestos guarda una estrecha relación con la relativamente corta distancia del enlace en trans-Cu-S(tioéter o disulfuro) apical/distal. En este artículo se aporta, también, la síntesis y estructura del complejo binario precursor de $[Cu_2(TCC)(H_2O)_2]$ (**4**) que revela una singular estabilización intra-molecular mediante dos enlaces de hidrógeno, (aqua)OH···O(carboxilato) (2.722(1) Å, 169º), equivalentes entre sí por razones de simetría y que conectan ambas mitades de la molécula. Además, se aportan las estructuras del ácido $H_2BCBC$ (**1**) y de su solvato hemiacetona $H_2BCBC\cdot 0.5C_3H_6O$ (**2**), que muestran sus iones dipolares $H_2BCBC\pm$ estabilizados por enlaces de hidrógeno, aunque de un modo desigual.

## METAL BINDING PATTERN OF ACYCLOVIR IN TERNARY COPPER(II) COMPLEXES HAVING AN S-THIOETHER OR S-DISULFIDE $NO_2S$-TRIPODAL TETRADENTATE CHELATOR

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Research paper

# Metal binding pattern of acyclovir in ternary copper(II) complexes having an S-thioether or S-disulfide $NO_2S$-tripodal tetradentate chelator

Josefa María González-Pérez [a,*], Duane Choquesillo-Lazarte [b,*], Alicia Domínguez-Martín [a,1], Esther Vílchez-Rodríguez [a], Inmaculada Pérez-Toro [a], Alfonso Castiñeiras [c], Oihane K. Arriortua [d], María Eugenia García-Rubiño [e], Antonio Matilla-Hernández [a], Juan Niclós-Gutiérrez [a]

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain
[b] Laboratorio de Estudios Cristalográficos, IACT, CSIC-University of Granada, Avenida de las Palmeras 4, Armilla, 18100 Granada, Spain
[c] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain
[d] Department of Inorganic Chemistry and BC Materials, University of Basque Country, E-48080 Bilbao, Spain
[e] Department of Organic and Pharmaceutical Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain

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ABSTRACT

Synthesis and crystal structures of two novel ternary copper(II) complexes with a $NO_2S$-tripodal tetradentate chelator and acyclovir (acv) are reported, providing new insights into the metal binding pattern (MBP) of this synthetic purine nucleoside. N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) (BCBC) and N,N,N′,N′,-tetrakis(carboxymethyl)cysteaminate(4-) (TCC) chelators supply S-thioether or S-disulfide donor atoms, respectively. In $[Cu(BCBC)(acv)]\cdot 2.5MeOH\cdot 0.5H_2O$ and $[Cu_2(TCC)(acv)_2]\cdot 6H_2O$ the copper(II) atom exhibits an asymmetrical elongated octahedral coordination (type 4+1+1*, where (*) indicates a very weak coordination bond, ~3 Å), and acv displays the rather uncommon N7,O6-chelating mode, (early reported by Turel for trans-$[Cu(acv)_2(H_2O)_2](NO_3)_2$ (with a Cu–O6(acv) bond distance of ~2.7 Å). The weakness of the (acv)O6···Cu interaction is related to the shortness of the Cu-S(thioether or disulfide) apical/distal bonds. A 'molecular form' of the binary parent-complex $[Cu_2(TCC)(H_2O)_2]$ (**4**) is also reported and features a relevant intra-molecular stabilization by two symmetry related (aqua)O–H···O(carboxylate) interactions (2.722(1) Å, 169.0°) linking together both halves of the complex molecule. The structure of $H_2BCBC$ and its hemi-acetone solvate $H_2BCBC\cdot 0.5C_3H_6O$ shows distinct intra-molecular H-bonding stabilizations in their $H_2BCBC^{\pm}$ zwitterions.



## 1. Introduction

Bio-ligands or synthetic pharmaceuticals with 'soft' S donor atoms (thiolate, thioether or disulfide) have focused an increasing interest during past decades [1–3]. They have predictable affinity to 'soft' Pearson acids such as Cu(I), Ag(I), Au(I), Cd(II) or Hg(I or II) as well as some 'soft-borderline' metal ions, such as Pb(II) [1]. For this reason, S-chelating agents are useful for treatment of intoxications (Cd, Hg, Pb) or metabolism disorders (Cu) [1], as well as for ($^{99m}$Tc) carriers [2]. We have recently reported the synthesis of two branched polydentate S-chelators: N,N-bis(carboxymethyl)-S-benzylcysteaminate(2-) and N,N,N′,N′-tetrakis(carboxymethyl)-cysteaminate(4-) (BCBC and TCC, respectively, Fig. 1). These ligands were designed as $NO_2S$-tripodal tetradentate chelators and form ternary Cu(II) complexes with purine nucleobases [4].

BCBC and TCC are known by long time [2]. However new synthetic methods were reported for $H_2BCBC\cdot 0.5H_2O$ and $H_4TCC\cdot 3H_2O$ [4]. Also the crystal structure of the polymer $\{[Cu_2(\mu_4\text{-}TCC)(H_2O)_2]\cdot 4H_2O\}_n$ was reported [5] and has been considered as the 'binary Cu(II)-TCC compound'. It reacts with imidazole (Him) [6], (5)-methylimidazole (H(5)Meim [7], with two tautomers), adenine (Hade), 2,2'-bipyridine (bpy) or 1,10-phenantroline (phen) [4] yielding molecular ternary compounds. Besides $H_4TCC\cdot 3H_2O$, only $[Cu_2(BCBC)_2(\mu\text{-}N3,N7\text{-}H(N9)ade)(H_2O)_2]\cdot H_2O$ and $[Cu_2(BCBC)_2(\mu\text{-}N7,N9\text{-}H(N3)dap)(H_2O)_2]\cdot 4H_2O$ have been structurally characterized [4] with purine ligands two different tautomers [8].

Molecular recognition studies between metal complexes and nucleic acid constituents should also include natural and/or synthetic nucleosides [9]. For instance, acyclovir (acv) is a well-known synthetic purine nucleoside (SPN) related to guanosine (Fig. 1) but

* Corresponding authors. Tel.: +34 958243855; fax: +34 958246219.
*E-mail addresses:* jmgp@ugr.es (J.M. González-Pérez), duane.choquesillo@csic.es (D. Choquesillo-Lazarte).
[1] Present address: Department of Chemistry, University of Zurich, CH-8057 Zurich, Switzerland.

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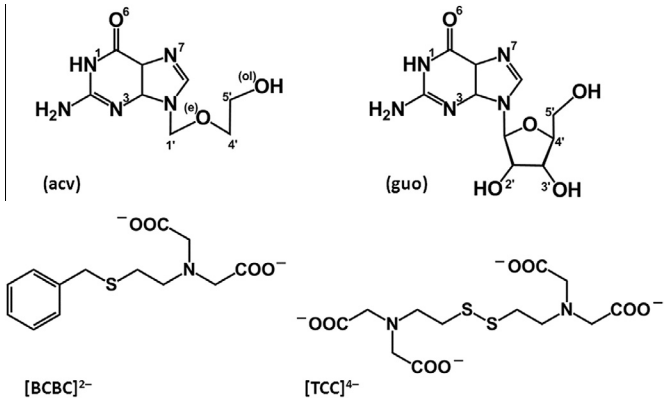


**Fig. 1.** BCBC and TCC chelators along with the SPN acyclovir (acv) and the natural guanosine (guo) nucleoside.

highest chemical stability of its acyclic N9-pendant arm. During the past twenty-five years, Turel [10–15], Terrón [16–18], Natile [19,20] and we [21–25], became particularly interested in the MBPs of acv, summarized as follows (M = metal ion): (a) the formation of a 'non-assisted' M–N7 bond, (b) the cooperation between a M–N7 bond with an intra-molecular A–H···O6(acv) interligand interaction (A = coordinated O or N), (c) the N7,O6-chelating mode, (d) $\mu_2$-N7,O(ol) bridging mode, and (e) the unprecedented multifunctional $\mu_3$-N7,O6,O(e),O(ol) mode [25]. These results point towards the attractive possibility of expanding the frontiers of acv coordination [23].

Here we report the structures of two ternary compounds [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**3**) and [$Cu_2$(TCC)(acv)$_2$]·6$H_2O$ (**5**), as well as the 'molecular form' for the binary Cu(II)-TCC chelate (compound **4**) and those of two distinct crystals of the $H_2$BCBC acid (compounds **1** and **2**).

## 2. Experimental

### 2.1. Materials and physical measurements

$H_2$BCBC·0.5$H_2O$ and $H_4$TCC·3$H_2O$ acids were prepared as previously reported [4]. All other reagents are commercially available (Sigma–Aldrich, Acros) and were used as received. The SPN was identified as acv·0.66$H_2O$ (FW = 237.09) by FT-IR spectroscopy, thermogravimetry and powder X-ray diffraction [23]. Analytical data were obtained in a Thermo-Scientific (Flash 2000) elemental micro-analyzer. FT-IR spectra (KBr pellets) were recorded using a Jasco FT-IR 6300 spectrometer. Thermogravimetric (TG) analyses were carried out in air-dry flow (100 ml/min) by a Shimadzu thermo-balance TGA-DTG-50H instrument, coupled with a FT-IR Nicolet Magma 550 spectrometer. X-band EPR measurements were carried out on a Bruker ELEXSYS 500 spectrometer equipped with a super-high-Q resonator ER-4123-SHQ. Q-band EPR spectra were recorded on a Bruker EMX system equipped with an ER-510-QT resonator. Computer simulation: WINEPR-Simfonia, version 1.5 (Bruker). Magnetic susceptibility measurements (5–300 K) were performed in a Quantum Design MPMS-7 SQUID magnetometer. Diamagnetic corrections were estimated from Pascal's constants.

### 2.2. Synthesis of the S-containing chelating ligands and novel copper(II) complexes

#### 2.2.1. Synthesis of $H_2$BCBC (**1**) and $H_2$BCBC·0.5$C_3H_6O$ (**2**) acids

$H_2$BCBC·0.5$H_2O$ acid (samples of 50 mg) were dissolved in various solvents and solvent mixtures with the aim of further purifying it and obtain single crystals. The solutions were filtered without vacuum into appropriate crystallization flasks, which were covered with a plastic film to control evaporation of solvents. From anhydrous methanol (30 ml), suitable single crystals of $H_2$BCBC acid (**1**) for X-ray diffraction studies were obtained in a few days (yield ~ 65%). *Anal.* Calc. for $C_{13}H_{17}NO_4S$ (FW 283.33): C, 55.11; H, 6.05; N, 4.94; S, 11.32. Found: C, 55.02; H, 6.12; N, 4.89; S, 11.26%. Selected IR (KBr, $\nu_{max}/cm^{-1}$): 3417 (m,br) $\nu$(O–H), 3026–3001 (w), 2965–2915 (w), 2868–2845 (w) $\nu$(C–H) + $\nu(CH_2)$, 1680 (s,br) $\nu$(C=O), 1640 (sh) $\nu_{as}$(COO), 1557–1537 (m) $\delta(N^+–H)$, 1401 (m) $\nu$(C–O) + $\delta$(O–H), 1381 (m) $\nu_s$(COO), 766–703 (m) $\pi$(C–H), 619–610 (m) $\nu$(C–S). From a 1:4 water:acetone solution also single crystals of $H_2$BCBC·0.5$C_3H_6O$ (**2**) were obtained (yield ~ 25%). *Anal.* Calc. for $C_{14.5}H_{20}NO_{4.5}S$ (FW 312.36): C, 55.75; H, 6.45; N, 4.48; S, 10.26. Found: C, 55.63; H, 6.36; N, 4.41; S, 10.20%. Selected IR (KBr, $\nu_{max}/cm^{-1}$): 3430 (m,br) $\nu$(O–H), 3031(w), 3012 (w), 2967 (w), 2945 (w), 2917 (w) $\nu$(C–H) + $\nu(CH_2)$ + $\nu(CH_3)$, 1725 (s) $\nu$(C=O, acetone), 1706 (s) $\nu$(C=O, carboxylic), 1681 (m) skeletal, 1638 (m) $\nu_{as}$(COO), 1550–1500 (vw) $\delta(N^+–H)$, 1403 (m) $\nu$(C–O)+$\delta$(O–H), 1381 (m) $\nu_s$(COO), 760–707 (m) $\pi$(C–H), 614 (m) $\nu$(C–S).

#### 2.2.2. Synthesis of [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**3**)

Basic copper(II) carbonate ($Cu_2CO_3(OH)_2$, 0,5 mmol, 110.6 mg) and $H_2$BCBC·0.5$H_2O$ (1 mmol, 0.29 g) were reacted in 100 ml of methanol under stirring and heating (50–70 °C) for several hours [4]. To the resulting solution, acyclovir (1 mmol, 237.1 mg) was added in small amounts and the reaction mixture was stirred for two hours. Afterwards the solution was filtered without vacuum into a crystallizing flask and covered with a plastic film to control the evaporation of the solvent. When the volume was reduced by half, the plastic film was removed and the crystallizing flask placed in a desiccator under diethyl ether diffusion. A few blue crystals suitable for X-ray diffraction measurements were collected. Additional sample was obtained by filtration and used for other physical studies. Yield: 55 %. *Anal.* Calc. for $C_{23.5}H_{37}CuN_6O_{10}S$ (FW 1318.38): C, 42.82; H, 5.66; N, 12.75; S, 4.86. Found: C, 42.77; H, 5.60; N, 12.65; S, 4.79%. Selected IR (KBr, $\nu_{max}/cm^{-1}$ – see SI 1.a): 3410 (s,br), 3340 (s,br) $\nu$(O–H), 3120 (m,sh) $\nu$(N–H), 2918–2870 (m) $\nu(CH_2)$, 1696 (s) $\nu$(C=O), 1630 (s) $\delta(H_2O)$ + $\delta(NH_2)$, 1541 (m) $\nu_{as}$(COO) + $\delta$(N–H), 1380 (s) $\nu_s$(COO) + $\delta$(O–H), 1120(m) $\delta$(C–O–C), 630 (w) $\nu$(C–S), 560 (w) $\nu$(S–S).

#### 2.2.3. Synthesis of [$Cu_2$(TCC)($H_2O$)$_2$] (**4**)

A methanol solution (50 ml, 50 °C) of {[$Cu_2$(TCC)($H_2O_2$]·4$H_2O$}$_n$ [5]. (180 mg, 0.29 mmol) was filtered without vacuum into a crystallization flask and doped with a drop of benzyl alcohol. The solution was covered with a plastic film and the slow evaporation of the solvent was followed daily until the first crystals appeared. The solution was filtered once more in a similar manner and the crystallization flask placed in a desiccator for diethyl ether diffusion. In one month well shaped parallelepiped blue crystals were formed, some of them suitable for X-ray diffraction purposes. Yield: 85 %. *Anal.* Calc. for $C_{12}H_{20}Cu_2N_2O_{10}S_2$ (FW 543.54): C, 26.52; H, 3.71; N, 5.15; S, 11.80. Found: C, 26.47; H, 3.75; N, 5.11; S, 11.73%. Selected IR (KBr, $\nu_{max}/cm^{-1}$ – see SI 1.b): 3380, 3260, 3155 (m,br) $\nu$(OH), 2992 (w), 2942(w), 2922 (w), 2865 (w) $\nu(CH_2)$, 1650 (s) $\delta(H_2O)$, 1600 (s,br) $\nu_{as}$(COO), 1367 (s) $\nu_s$(COO), 630 (w) $\nu$(C–S), 545 (w) $\nu$(S–S).

#### 2.2.4. Synthesis of [$Cu_2$(TCC)(acv)$_2$]·6$H_2O$ (**5**)

Basic copper carbonate, $Cu_2CO_3(OH)_2$ (1 mmol, 221.1 mg,) was reacted with $H_4$TCC·3$H_2O$ (1 mmol, 438.5 mg) in methanol (100 ml) under continuous stirring and heating (60 °C) for various hours. To this solution, acv·0.66$H_2O$ (1 mmol, 237.1 mg) was added in small amounts. The reaction mixture was left stirring for about two hours, after which it was filtered in a crystallizing flask and

covered with a plastic film. When the volume was reduced by half, the flask was introduced in a desiccator for diethyl ether diffusion. This synthesis is carried out upon the assumption maintained by I. Turel that 'an excess of metal compound favors the crystallization of the ternary compound'. Nonetheless this seems not be the sole factor which leads to the success since the preparation of this compound has turned out a tedious task. Finally, long needle-like crystals were observed. (Yield < 10%). *Anal.* Calc. for $C_{28}H_{50}Cu_2N_{12}O_{20}S_2$ (FW 1066.00): C, 31.55; H, 4.73; N, 15.77; S, 6.02. Found: C, 31.42; H, 4.60; N, 15.71; S, 6.03%. Selected IR (KBr, $\nu_{max}/cm^{-1}$ – see SI 1.c): 3430–3200 (s,br) $\nu(H_2O) + \nu(NH_2)$, 3126 (m) $\nu$(N–H), 3026–2931 (w) $\nu$(C–H) + $\nu_{as}(CH_2)$, 1695 (s) $\nu$(C=O, acv), 1635–1616 (s,br) $\delta(H_2O) + \delta(NH_2)$, 1600 (s,sh) $\nu_{as}$(COO), 1541 (w) $\delta$(N–H), 1383 (s) $\nu_s$(COO) + $\delta$(O–H), 1114 (w) $\delta$(C–O–C), 634 (w) $\nu$(C–S).

### 2.3. X-ray crystallography

Diffraction data were collected at 100(1) K using a Bruker D8 Venture (**1**–**3**) or a Bruker X8 Kappa APEXII (**4**,**5**) diffractometer from crystals mounted on glass fibers. Data were collected using Cu Kα radiation (λ = 1.54184 Å)(**2**) or Mo Kα radiation (λ = 0.71073 Å) (**1**, **3**–**5**). Data were processed with the APEX2 software [26] for reduction and cell refinement. Multi-scan absorption corrections were applied by using the DIFABS program for area detector [27]. Structures were solved by the direct methods [28] and refined on $F^2$. Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were located in difference maps (**1**–**4**) and included as riding with $U_{iso}(H) = 1.2$ or 1.5 $U_{eq}$(non-H). In **5**, hydrogen atoms were included in geometrically idealized positions. In compound **2**, one carboxylic proton of each molecule is disordered over two positions and the occupancy factor for each was refined to values of 0.58(6) for H4 and H28, and 0.42(6) for H8 and H24. For compound **3**, the structure was refined as for twined crystal with two components in a 0.55 (9):0.45(9) ratio, and also a disorder of the methanol molecule was refined anisotropically on two positions with occupancies of 0.78 for C90A–O91A and of 0.22 for C90B–O91B. In compound **5**, atoms of O20 and O30 water molecules and the C310–O311–C312–C313–O314 pendant group which showed very high thermal motion were refined isotropically, and hydrogen atoms on water molecules were not located. Molecular graphics were generated with DIAMOND [29]. The crystal data, experimental details and refinement results are summarized in Table 1.

## 3. Results and discussion

The results here reported mainly concern to structural aspects and the infrared spectra of the five novel compounds, magnetic properties of copper(II) compounds **3**–**5** and thermal stabilities of compounds **1**–**4**. Supporting information is provided as Supplementary material in Appendix A.

### 3.1. Structure of $H_2$BCBC acid

Because of the unsuccessful attempts to crystallize a binary Cu-BCBC chelate, efforts were made to further purify, by re-crystallization, the free ligand in acid form, which was early synthesized and characterized by elemental analysis, NMR and FT-IR spectroscopies as $H_2BCBC{\cdot}0.5H_2O$ [4]. Here this amino diacid has been crystallized as the 'free-of-solvents' form as well as a hemi-acetone solvate.

Colorless needles-like crystals of the $H_2$BCBC acid (**1**) were obtained by re-crystallization of $H_2BCBC{\cdot}0.5H_2O$ in anhydrous (absolute) methanol. The compound consists of S-benzyl-N-carboxymethyl-glycine $H_2BCBC^{\pm}$ zwitterions (Fig. 2a), with a free N-acetic arm and only one intra-molecular $N1^+$–H1···O8(carboxylate) interaction (2.617(2) Å, 103.85°). In the crystal, $N1^+$–H1···$O9^b$(carboxylate) interactions (2.820(2) Å, 157.1°, $b = -x + 1/2, y + 1/2, z$) associate zwitterions in chains parallel to the *b* axis (Fig. 2b). Furthermore (carboxylic)O4–H4···$O8^a$(carboxylate) interactions (2.491(2) Å, 163.6°, $a = x + 1, y, z$) connect such chains in H-bonded 2D-layers parallel the ab plane (Fig. 2c), where the hydrophilic and hydrophobic moieties of the $H_2BCBC^{\pm}$ zwitterions point out towards opposite external surfaces of the 2D- framework. Weak Van der Waals forces connect layers by two hydrophilic or two hydrophobic faces to build the 3D crystal. No π,π-stacking interactions between aromatic BCBC-rings were found in this crystal.

Slow evaporation of the water–acetone (1:4) solution of $H_2BCBC{\cdot}0.5H_2O$ yields colorless needless crystals of the hemi-acetone solvate $H_2BCBC{\cdot}0.5C_3H_6O$ (**2**, see SI 2.1.a). The asymmetric unit of **2** consists of two independent but very similar $H_2BCBC^{\pm}$ zwitterions and one acetone molecule. These zwitterions are intra-stabilized by two intra-molecular $N^+$–H···O(carboxy) interactions (2.65(2) Å and 111° or 103°). H-carboxylic atoms involved in –COOH···$COO^-$ interactions (2.45(2) Å and 180° or 167°) are delocalized in two positions. Noteworthy the O-acetone atom is not involved as acceptor in conventional H-bonds (i.e. O–H···O(acetone) or $N^+$–H···O(acetone) interactions). Again π,π-stacking interactions between benzyl-aromatic rings are missing in this crystal. The crystal packing consists of H-bonded (–COOH···$COO^-$) zigzag chains of $H_2BCBC^{\pm}$ zwitterions running parallel to the c axis and acetone molecules weakly linked together by Van der Waals forces. The shortest C–H···O distances are >3.45 Å. The chains generate hydrophilic–hydrophobic holes running parallel to the *a* axis, where acetone molecules are put up with methyl groups and carbonyl moieties are oriented towards the hydrophobic and hydrophilic regions, respectively (SI 2.1.b). This framework exhibits an unexpected thermal stability. Most (but not all) acetone molecules are lost (100–170 °C) as a first step before the thermal decomposition of the zwitterions present in the crystal (see Section 3.4.3).

A comparison of the crystal structures of the 'free-of-solvent' amino-diacid $H_2$BCBC (**1**) and the acetone solvate $H_2BCBC{\cdot}0.5C_3H_6O$ (**2**) evidences the noticeably distinct conformations of the $H_2BCBC^{\pm}$ zwitterions. Note the presence of one or two intra-molecular N–H···O(carboxyl) interactions, despite the apparently irrelevant role of acetone in **2**. To this respect, one can consider that the acetone solvate in **2** is a novel example of a zwitterion structure, as found in some crystals of N-substituted-aminodicarboxylic acids with a non-coordinating N-bulky substituent, i.e. N-(1-adamantyl)-iminodiacetic acid [30]. In contrast, the N-carboxymethyl-glycine-like structure of the zwitterion here reported for the 'free-of solvent' $H_2$BCBC acid (**1**) has also been reported for N-substituted-aminodicarboxylic acids with less bulky non-coordinating arms such as N-(2-phenyethyl)-iminodiacetic acid ($H_2$pheida) [31], N-(*tert*-butyl)-iminodiacetic acid ($H_2$TEBIDA) [32] or N-isopropyl-iminodiacetic acid ($H_2$iPIDA) [33]. The crystal packing of $H_2$BCBC is closely related to those of $H_2$pheida and $H_2$TEBIDA (with more symmetrical non-coordinating N-arm) but rather distinct to that of $H_2$iPIDA. These considerations lead us to the idea that the kind of non-coordinating N-arm in an N-substituted-iminodiacetic acid strongly influences the nature of the intra-molecular H-bonding pattern of the zwitterion and therefore the corresponding inter-molecular interactions and crystal packing.

### 3.2. Molecular and crystal structure of [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$

The asymmetric unit in the crystal of compound (Fig. 3) consists of two non-equivalent but close similar ternary complex molecules (molecules 1 and 2, with Cu(1) and Cu(2) atoms, respectively) as

**Table 1**
Summary of crystal data, structure solution and refinement for the studied compounds.

| Crystal↓/compound→ | $H_2$BCBC (**1**) | $H_2$BCBC·0.5$C_3H_6O$ (**2**) | [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**3**) | [$Cu_2(\mu_2$-TCC)$(H_2O)_2$] (**4**) | [$Cu_2(\mu_2$-TCC)$(acv)_2$]·6$H_2O$ (**5**) |
|---|---|---|---|---|---|
| Empirical formula | $C_{13}H_{17}NO_4S$ | $C_{14.5}H_{20}NO_{4.5}S$ | $C_{47}H_{74}Cu_2N_{12}O_{20}S_2$ | $C_{12}H_{20}Cu_2N_2O_{10}S_2$ | $C_{28}H_{50}Cu_2N_{12}O_{20}S_2$ |
| Formula weight | 283.33 | 312.36 | 1318.38 | 543.50 | 1066.00 |
| Crystal system | orthorhombic | triclinic | monoclinic | monoclinic | triclinic |
| Space group | *Pbca* | $P\bar{1}$ | $P2_1/c$ | $C2/c$ | $P\bar{1}$ |
| *Unit cell dimensions* | | | | | |
| $a$ (Å) | 8.4387(9) | 5.4650(5) | 14.2797(6) | 21.9252(7) | 11.288(4) |
| $b$ (Å) | 9.5677(6) | 11.9144(11) | 20.9609(7) | 7.0496(5) | 18.144(6) |
| $c$ (Å) | 31.625(2) | 23.765(2) | 20.8188(8) | 12.8962(3) | 22.403(8) |
| $\alpha$ (°) | 90 | 87.910(4) | 90.00 | 90 | 105.90(2) |
| $\beta$ (°) | 90 | 84.637(5) | 90.018(2) | 114.054(2) | 96.89(2) |
| $\gamma$ (°) | 90 | 88.579(4) | 90.00 | 90 | 102.11(2) |
| $V$ (Å$^3$) | 2553.4(4) | 1539.2(2) | 6231.4(4) | 1820.19(9) | 4237(3) |
| $D_{calc}$ (Mg m$^{-3}$) | 1.474 | 1.348 | 1.405 | 1.983 | 1.671 |
| $Z$ | 8 | 4 | 4 | 4 | 4 |
| Absorption coefficient (mm$^{-1}$) | 0.264 | 2.034 | 0.828 | 2.624 | 1.195 |
| $F$(000) | 1200 | 664 | 2760 | 1104 | 2208 |
| $\theta$ range | 2.576–27.522 | 3.713–65.075 | 2.176–26.067 | 2.034–30.507 | 0.962–19.782 |
| Collected/independent reflections | 32636/2935 | 17558/5147 | 46995/12323 | 20152/2772 | 64644/7634 |
| Data/restraints/parameter | 2935/0/172 | 5147/0/386 | 12323/6/761 | 2772/0/127 | 7634/78/1098 |
| Goodness-of-fit (GOF) on $F^2$ | 1.026 | 1.260 | 1.096 | 1.080 | 1.090 |
| Final $R_1$ index [$I < 2\sigma(I)$] | 0.0385 | 0.0758 | 0.0320 | 0.0199 | 0.1244 |
| Largest difference peak and hole (e Å$^{-3}$) | 0.346 and −0.286 | 0.467 and −0.329 | 0.988 and −0.423 | 0.505 and −0.356 | 2.176 and −2.641 |

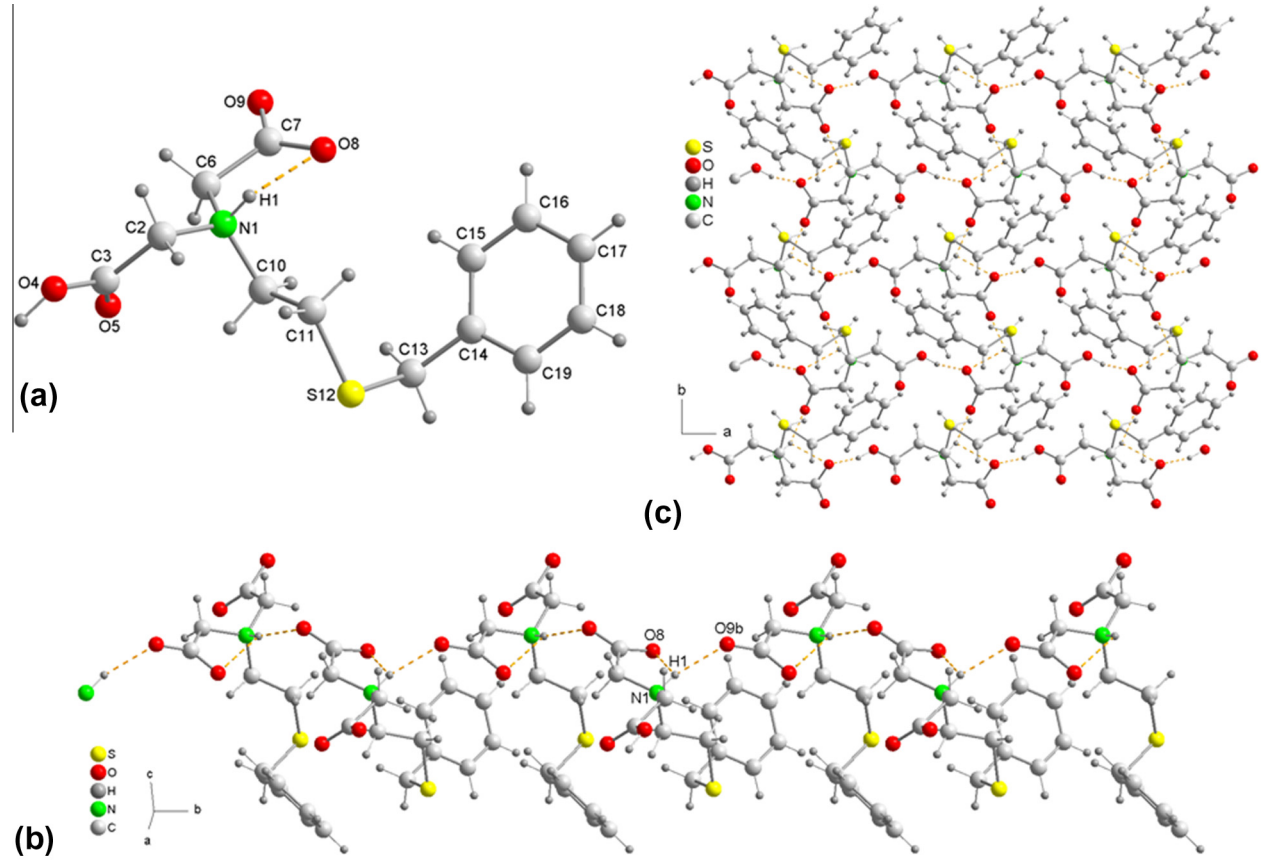


**Fig. 2.** Structure of the 'free-of-solvent' $H_2$BCBC acid (**1**). (a) The $H_2BCBC^{\pm}$ zwitterion intra-stabilized by only one intra-molecular N+–H···O(carboxy) interaction. (b) Chains of zwitterions along $b$ axis connected by inter-molecular $N1^+$–H1···$O9^b$(carboxylate) interactions ($b = -x + 1/2,\ y + 1/2,\ z$). (c) Inter-molecular (carboxylic)O4–H4···$O8^b$ (carboxylate) interactions ($b = x + 1,\ y,\ z$) link chains in 2D-molecular frameworks of zwitterions (parallel to the *ab* plane).

well as five methanol and one water solvent molecules. A methanol molecule is disordered in two positions. The copper(II) centers exhibit an asymmetric elongated octahedral coordination, type 4+1 +1∗ (∗ represents a very weak coordination or interaction). The four shortest and nearly coplanar coordination bonds are built by the N-amino and two O-carboxylate donors from the *mer*-iminodiacetate moiety of BCBC plus the N7-acv atom. The trans-apical/distal coordination sites are occupied by the S(thioether)-BCBC atom

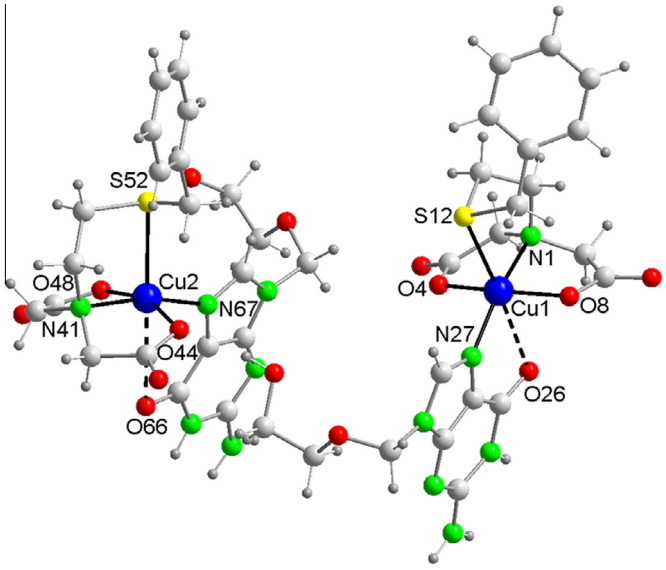


**Fig. 3.** Structure of the two complex molecules in the asymmetric unit of [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**3**). Solvent molecules omitted for clarity. Coordination bond (Å) lengths and trans-angles (°): Molecule 1, Cu(1)–O(4) 1.964(2), Cu(1)–O(8) 1.968(2), Cu(1)–N(1) 2.015(2), Cu(1)–N(27) 1.971(2), Cu(1)–S(12) 2.643(1), Cu(1)–O(26) 2.9441(4), O(4)–Cu(1)–O(8) 163.79(9), N(27)–Cu(1)–N(1) 163.86(10), S(12)–Cu(1)–O(26) 174.62(1). Molecule 2: Cu(2)–O(48) 1.953(2), Cu(2)–O(44) 1.965(2), Cu(2)–N(41) 2.019(2), Cu(2)–N(67) 1.963(2), Cu(2)–S(52) 2.580(1), Cu(2)–O(66) 3.046(1), O(48)–Cu(2)–O(44) 159.28(9), N(67)–Cu(2)–N(41) 166.75(10), S(52)–Cu(2)–O(66) 172.89(1). Please note that crystallographic numbering is different from that normally used for purine molecules.

and the O6-acv atom, with rather unequal bond distances (Cu–S < Cu–O6). The Cu–O6(acv) distances (~3.00(5) Å) slightly exceeds the sum (2.90 Å) of the Van der Waals radii of Cu (1.40 Å) and O (1.50 Å). Noteworthy the trans-S(BCBC)–Cu–O6(acv) coordination angles are close to the linearity (173(1)°). Table 2 summarizes some structural information related to Cu-BCBC complexes. Those compounds with bridging adenine or 2,6-diaminopurine as N-heterocyclic coligands exhibit an asymmetric elongated octahedral coordination, with the trans-apical/distal aqua ligand opposite to the S-(thioether)-BCBC atom. In the Hdap complex, the shortest distance corresponds to the Cu–S bond while the longest is the Cu–O(aqua) [4]. The Cu–S(thioether) distance in Hade and Hdap complexes ranges between 2.658 and 2.977 Å, with an average value of 2.829 Å. In compound **3** the averaged Cu–S (thioether) distance is 2.61(4) Å and that strongly influences the elongation of the Cu–O6(acv) distance leading to a weak coordination or interaction. Hence, in compound **3**, the BCBC chelator acts as a tripodal tetradentate $NO_2$ + S(apical/distal) ligand while the acv ligand plays a hardly asymmetric N7,O6-bidentate chelating role. The main difference between the complex molecules of 3 concerns the torsion angles within the N-arm of the iminodiacetate moiety of BCBC: (phenyl)C(13)–S(12)–C(11)–C(10) (63.61(4)°) or (phenyl)C(53)–S(52)–C(51)–C(50) (−67.33(4)°) for molecules 1 and 2, respectively. In the crystal, the complex molecules follows a series 1-1-2-2-1-1-2-2 along the *a* axis building a weak multi-π,π-staking interaction between the six-membered aromatic rings of acv ligands. The interactions 1-1 or 2-2 have dihedral angle between stacked ring planes $\alpha = 0°$ and inter-planar distances of 3.21 or 3.28 Å respectively, but high values for the slipping angles ($\beta = \gamma = 35°$ or 28° respectively) and long inter-centroid distances (3.93 Å or 3.76 Å) as considered for efficient stacking. The interaction 1-2 has an inter-planar dihedral angle $\alpha = 7.2°$ and very low values for slipping angles ($\beta$ or $\gamma$ 15.5 or 16.0°) but long and similar averaged inter-planar distance (3.74 Å) and inter-centroid distance (3.88 Å). The crystal is further stabilized by many O–H···O H-bonds and the expected (acv)N1–H···O interactions.

### 3.3. Molecular and crystal structure of the novel Cu(II)-TCC derivatives $[Cu_2(\mu_2\text{-TCC})(H_2O)_2]$ and $[Cu_2(\mu_2\text{-TCC})(acv)_2]\cdot 6H_2O$

As mentioned before, from a variety of attempts to obtain ternary copper(II)-TCC complexes (with acv and other coligands) in water and some mixtures of solvents, only nice parallelepiped single-crystals of the molecular complex $[Cu_2(\mu_2\text{-TCC})(H_2O)_2]$ (**4**), instead of the early reported polymeric form $\{[Cu_2(\mu_4\text{-TCC})(H_2O)_2]\cdot 4H_2O\}_n$ [6], were obtained.

The novel center-symmetric complex molecules (Fig. 4a) crystallizes in the monoclinic system *C*2/*c*. The copper(II) center exhibits an axially elongated square-base pyramidal coordination, type 4+1, in contrast to the elongated octahedral coordination (type 4+1+1) reported for the corresponding polymer [6]. As all known structures of dinuclear Cu(II)-TCC complexes [4–7], each half of the TCC ligand displays a $NO_2S$-tripodal tetradentate chelating role, with the iminodiacetate moiety in mer-$NO_2$ conformation and the S-disulfide donor at the apical/distal coordination site. Among the four closest donors of the metal, the trans-position to the Cu–N(amino) bond is occupied by the O1 donor of one aqua ligand. This is the main reason for the below referred stability for this compound (see Section 3.4.3). This five-coordination polyhedron has two unequal trans-basal bonds, N1–Cu1–O1 ($\theta$ = 178.45(4)°) > O11–Cu1–O13 ($\varphi$ = 161.44(4)°) leading to an Addison-Reedijk parameter [34] value of $\tau = (\theta - \varphi)/60 = 0.12$. The metal atom is displaced 0.13 Å from the mean-basal coordination plane towards the S-apical/distal donor atom. The most striking structural feature of this dinuclear complex molecule is the implication of an O–H bond from the aqua ligand of each half-molecule in an intra-molecular H-bonding interaction with an O-coordinated carboxylate acceptor of the other half-molecule: O1–H1A···O11[a] (2.722(1) Å, 169.0°, symmetry transformation $a = -x$, $y$, $-z + 1/2$) (Fig. 4a). Two of this intra-molecular interactions contribute to some extend to the shortening of the Cu–S(disulfide) bond (2.652(1) Å) and the

**Table 2**
Structural information of copper(II)-BCBC complexes.

| Formula | Cu(II) coord. number (polyhedron geometry) | Cu–S (Å) | Coligand | Cu–N (heterocyclic) (Å) | Cu–O6 (exocyclic) (Å) | Intra-molecular interligand N–H···O (coord. Carboxyl.) Interaction (Å, °) | Refs. |
|---|---|---|---|---|---|---|---|
| $[Cu_2(BCBC)_2(\mu_2\text{-N3,N7-H(N9)ade})(H_2O)_2]\cdot H_2O$ | 6 (4+1+1) | 2.812(3)<br>2.977(3) | H(N9)adenine | Cu–N3 1.987(7)<br>Cu–N7 1.998(7) | – | 2.698(10), 174.6<br>2.782(7), 140.08 | [4] |
| $[Cu_2(BCBC)_2(\mu_2\text{-N7,N9-H(N3)dap})(H_2O)_2]\cdot 4H_2O$ | 6(4+1+1) | 2.658(3)<br>2.867(3) | H(N3)-2,6-diaminopurine | Cu–N7 1.968(5)<br>Cu–N9 1.961(5) | – | 2.774(7), 169.1<br>2.732(7), 139.9 | [4] |
| [Cu(BCBC)(acv)] · 2.5MeOH·0.5$H_2O$ (two non-equivalent complex molecules) | 6 (4+1+1) | 2.643(1)<br>2.580(1) | Cu1–S12 2.643(1)<br>Cu2–S52 2.580(1) | Cu–N27 1.971(2)<br>Cu–N67 1.963(2) | 2.944(4)<br>3.046(4) | – | This work |

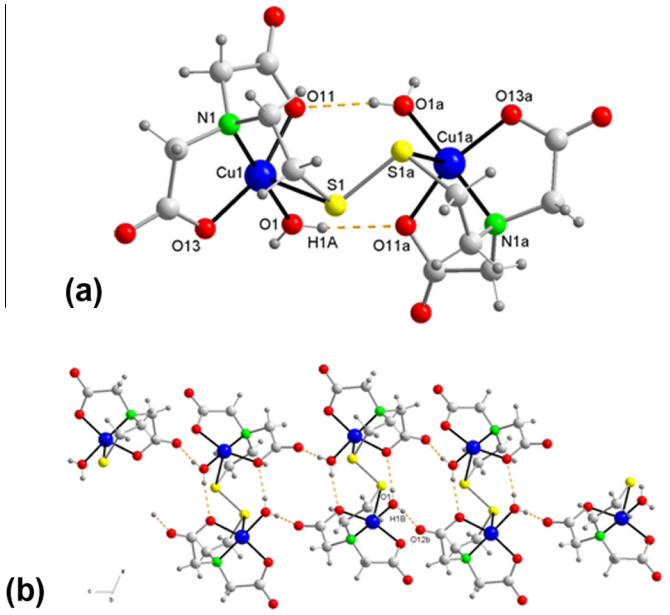


**Fig. 4.** Molecular and crystal structure of $[Cu_2(\mu_2\text{-TCC})(H_2O)_2]$ (**4**). (a) A pair of symmetry related O1–H1A···O11[a] ($a = -x, y, -z + 1/2$) interactions link together both half-complex molecules. (b) 2D chain showing H-bonding interactions including supramolecular homosynthoms of $R_2^2$ motif (orange dashed lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

small lengthening of the S–S bond (2.057(1) Å), in contrast to the reported data for the polymeric form $\{[Cu_2(\mu_2\text{-TCC})(H_2O)_2]\cdot 4H_2O\}_n$ [6] (2.721(3), 4.632(2) and 2.043(5) Å respectively) and all other known Cu(II)-TCC derivatives (see Table 3). Cu···Cu intra-dimer interatomic distance is 4.588(1) Å. The data of **3** should be better compared to those of $[Cu_2(\mu_2\text{-TCC})(H5Meim)_2\ (H_2O)_2]\cdot 2H_2O$, having a 4+1 copper(II) coordination and 5-methylimidazole as coligand (Cu–S 2.798(1), Cu···Cu 5.707(1) and S–S 2.038(2) Å). It seems clear that intra-molecular H-bonds contribute to the stability of the dinuclear complex molecule **4**. In addition, pairs of symmetry related inter-molecular (aqua)O1–H1B···O12[b] (non-coordinated carboxylate) H-bonds (2.650(2) Å, 167.8°, symmetry transformation $b = x, -y + 2, z - 1/2$) build zigzag chains parallel to the c axis of the crystal (Fig. 4b). Both intra- and inter-molecular H-bonds also contribute to the thermal stability of **4**. Chains of complex molecules connect in the crystal by weak interactions, among them C11–H11B···O14[d] (3.116(2) Å, 123.3°, $d = -x - 1/2, -y + 3/2, -z$), C16–H16A···O14[e] (3.113(2), 119.2°, $e = -x - 1/2, -y + 1/2, -z$).

Needle-like crystal of compound $[Cu_2(\mu_2\text{-TCC})(acv)_2]\cdot 6H_2O$ (**5**) have been obtained in various attempts by reaction in a methanol solution of $\{[Cu_2(\mu_4\text{-TCC})(H_2O)_2]\cdot 4H_2O\}_n$ and acv, and by diffusion of diethyl ether. First results afforded very little crystals and only a small sample, which IR spectrum clearly suggested the implication of acv in the sample. Only after several months of being the reaction mixture under diethyl ether diffusion suitable crystals for X-ray diffraction studies appeared. Crystal resolution and refinement from diffraction data do not fit to good standard parameters (see Table 1). However results are interesting and have enough relevance from the chemical point of view, providing a reasonable picture of the mixed-ligand complex, the molecular structure and the crystal packing. Our results revealed two complex molecules and twelve crystallization water molecules in the asymmetric unit (Fig. 5a). Coordination bond lengths and trans-angles are listed in Table 4. These data agree with averaged bond distances of Cu–O (TCC) 1.93(2), Cu–N(TCC) 2.01(2), Cu–S(TCC) 2.66(2), Cu–N7(acv) 1.96(2) and Cu···O6(acv) 3.02(8) Å. Each complex molecule also has two non-equivalent copper(II) centers, all of them with similar asymmetric elongated octahedral coordination, type 4+1+1∗ (∗ refers to a very weak coordination or interaction). The non-equivalence of such metallic centers is favored by two intra-molecular (acv)C8–H···O(coordinated carboxylate) interactions linking two halves of each dinuclear complex molecule. In molecule 1 (with Cu1 and Cu2) C38–H38···O11(3.03(3) Å, 164.1°) and in molecule 2 (with Cu3 and Cu4) C78–H78···O43 (3.14(3) Å, 176.7°). The counterparts of these interactions are not efficient enough to be

**Table 3**
Copper(II) coordination data and selected interatomic distances in TCC complexes.

| Formula | Cu(II) coordination number (polyhedron geometry) | Cu–S (Å) | S–S (Å) | Intra-dimer Cu···Cu (Å) | Refs. |
|---|---|---|---|---|---|
| $[Cu_2(\mu_2\text{-TCC})(H_2O)_2]$ MOLECULAR | 5 (4+1) | 2.652(1) | 2.057(1) | 4.588(1) | This work |
| $\{[Cu_2(\mu_4\text{-TCC})(H_2O)_2]\cdot 4H_2O\}_n$ | 6 (∼4+2) | 2.721(3) | 2.043(5) | 4.632(2) | [5] |
| $[Cu_2(\mu_2\text{-TCC})(Him)_2(H_2O)_2]\cdot 2H_2O$ | 6 (4+1+1) | 2.937(2)<br>2.981(2)<br>2.959* | 2.036(1) | 5.970(1) | [6] |
| $[Cu_2(\mu_2\text{-TCC})(H5Meim)_2(H_2O)_2]\cdot 2H_2O$ | 5 (4+1) | 2.798(1) | 2.038(2) | 5.707(1) | [7] |
| $[Cu_2(\mu_2\text{-TCC})(Hade)_2(H_2O)_2]\cdot 10H_2O$ | 6 (4+1+1) | 2.932(4) | 2.027(7) | 5.429(4) | [4] |
| $[Cu_2(\mu_2\text{-TCC})(acv)_2]\cdot 6H_2O$ | 6 (4+1+1) | 2.649(6)<br>2.632(7)<br>2.702(6)<br>2.660(7)<br>2.661* | 2.048(10)<br>2.056(10)<br>2.052* | 4.854(4)<br>4.984(4) | This work |
| $[Cu_2(\mu_2\text{-TCC})(bpy)_2(H_2O)_2]\cdot 15H_2O$ | 6 (4 + 1 +1) | 2.924(2)<br>2.919(2)<br>2.918(2)<br>2.897(2)<br>2.915* | 2.050(2)<br>2.039(1) | 5.915(1)<br>5.724(1) | [4] |
| $[Cu_2(\mu_2\text{-TCC})(phen)_2(H_2O)_2]\cdot 14H_2O$ | 6 (4+1+1) | 2.864(1)<br>2.971(1)<br>2.800(1)<br>2.917(1)<br>2.888* | 2.046(1)<br>2.042(1) | 5.738(1)<br>5.616(1) | [4] |
| Range of interatomic distances** | | 2.652–2.981 | 2.036–2.057[1] | 5.42–5.97 | |

* Averaged distance in the compound.
** Range of distances in the mixed-ligands compounds with N-coligands.
[1] 2.049(1) Å en free $H_4TCC\cdot 3H_2O$ acid.

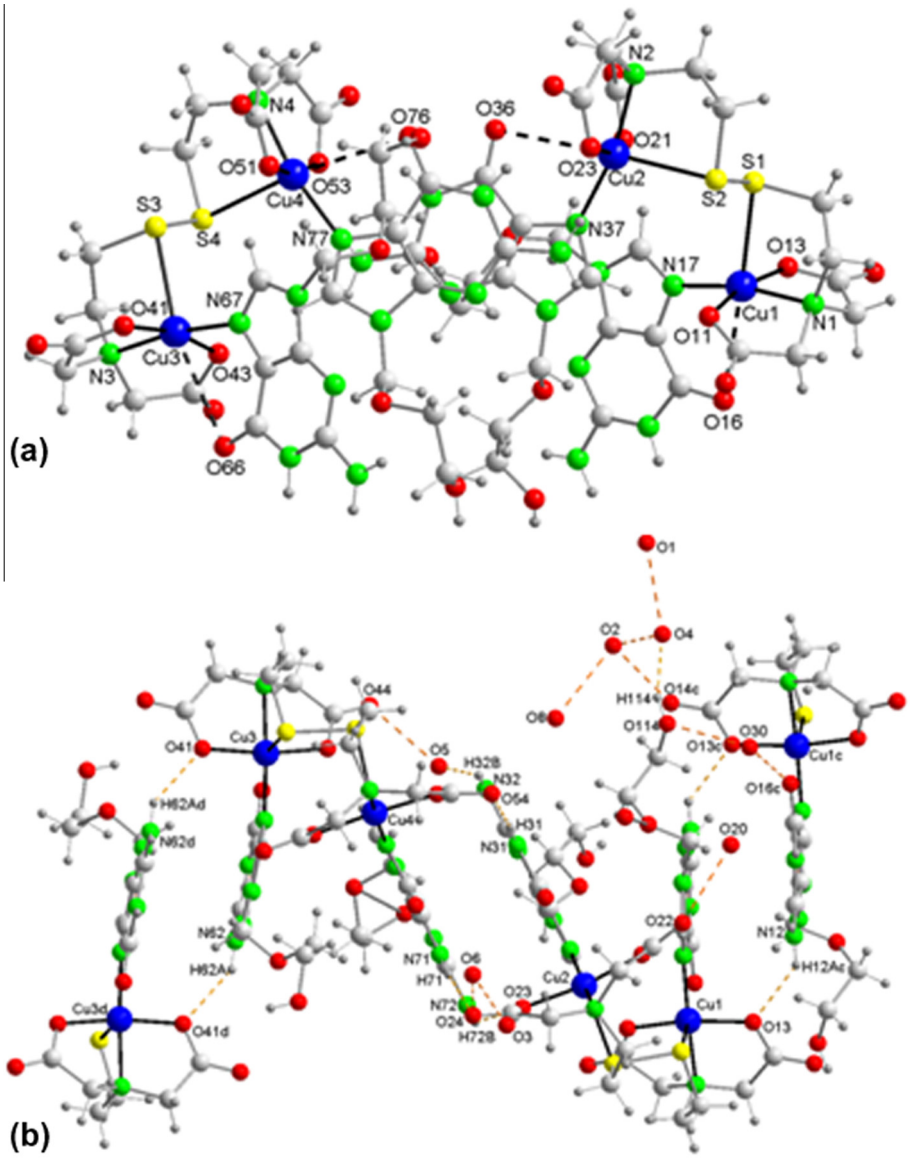


**Fig. 5.** Molecular and crystal structure of $[Cu_2(\mu_2\text{-TCC})(acv)_2]\cdot 6H_2O$ (**5**). (a) The two complex molecules in the asymmetric unit, with four non-equivalent but close similar copper(II) coordination centers (water omitted for clarity). Averaged bond distances: Cu–O(TCC) 1.93(2) Å, Cu–N(TCC) 2.01(2) Å, Cu–S(TCC) 2.66 (2) Å, Cu–N7(acv) 1.96(2) Å, Cu···O6(acv) 3.02(8) Å. (b) Fragment of crystal packing showing details of the intermolecular hydrogen bonding (orange dashed lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

considered as interactions (C18–H18···O22 and C68–H68···O52, with C···O distances of 4.30(1) Å) (Fig. 5b). As expected, in these coordination polyhedra each half-TCC ligand displays a tripodal tetradentate $NO_2$ + S(apical/distal) role and the N7-acv donor lies at the trans-site to the Cu–N(TCC) bond. The Cu–N7(acv) bonds are shorter than the Cu–N(TCC) bonds. This is because the N7-heterocyclic donor is a borderline Pearson base with higher affinity for the borderline Pearson copper(II) than the hard base N-amino(TCC) atom, both being non-charged donor atoms. One can appreciate that the Cu–S(thioether) bonds have an averaged bond distance (2.661 Å) very similar to that of the molecular compound $[Cu_2(\mu_2\text{-TCC})(H_2O)_2]$ (**4**) (2.652(1) Å) but shorter than all other known Cu-TCC-N(heterocyclic) ternary compounds (2.721(3)-2.981(2) Å, see Table 3), including the H5Meim derivative (with 4 +1 Cu(II) coordination). All these Cu-S(thioether) bond distances emphasize the weakness of the Cu···O6(acv) coordination in **5**, again with an average bond distance 3.02 Å (3.00 Å in **3**). Hence something longer than the sum of Van der Waals radii ($r_{vdw}$(Cu) + $r_{vdw}$ (O) = 1.40 + 1.50 = 2.90 Å).

### 3.4. Spectral, magnetic and thermal properties of the studied compounds

#### 3.4.1. Infrared spectra

The broad bands of strong intensity observed between 3450 and 3000 cm-1 for the complexes **3**–**5** suggest the stretching vibrations $\nu$(OH) and $\nu$(NH) of hydrogen bonds. There is no absorption peaks around 1700 $cm^{-1}$, which indicates that all carboxyl groups of $H_2$BBC in the complex **3,** and $H_4$TTC, in the complexes (**4** and **5**) are deprotonated completely. On the contrary, the asymmetric and symmetric bands of the carboxylate groups can be found between 1650–1630 $cm^{-1}$ and 1385–1365 $cm^{-1}$, respectively, indicating that these groups are coordinated to the metal center. In **3** and **5** wherein the acv is present as a ligand, a strong band that

**Table 4**
Coordination bond lengths (Å) and angles (°) for $[Cu_2(TCC)(acv)_2]\cdot 6H_2O$ (**5**).

| Metal | Bond | Distance (Å) | Trans-angle | Value |
|---|---|---|---|---|
| **Cu(1)** | Cu(1)–O(11) | 1.902(16) | O(11)–Cu(1)–O(13) | 167.1(6) |
| | Cu(1)–O(13) | 1.935(15) | N(17)–Cu(1)–N(1) | 167.5(7) |
| | Cu(1)–N(17) | 1.940(16) | S(1)–Cu(1)–O(16) | 177.6(3) |
| | Cu(1)–N(1) | 2.006(16) | | |
| | Cu(1)–S(1) | 2.649(6) | | |
| | Cu(1)–O(16) | 2.931(14) | | |
| **Cu(2)** | Cu(2)–O(21) | 1.948(15) | O(21)–Cu(2)–O(23) | 162.1(6) |
| | Cu(2)–N(37) | 1.949(17) | N(37)–Cu(2)–N(2) | 166.3(9) |
| | Cu(2)–O(23) | 1.954(15) | S(2)–Cu(2)–O(36) | 175.9(4) |
| | Cu(2)–N(2) | 2.015(17 | | |
| | Cu(2)–S(2) | 2.632(7) | | |
| | Cu(2)–O(36) | 2.989(18) | | |
| **Cu(3)** | Cu(3)–O(41) | 1.908(17) | O(41)–Cu(3)–O(43) | 166.4(6) |
| | Cu(3)–O(43) | 1.950(18) | N(67)–Cu(3)–N(3) | 170.5(7) |
| | Cu(3)–N(67) | 1.983(17) | S(3)–Cu(3)–O(66) | 167.4(3) |
| | Cu(3)–N(3) | 2.025(18) | | |
| | Cu(3)–S(3) | 2.702(6) | | |
| | Cu(3)–O(66) | 3.109(14) | | |
| **Cu(4)** | Cu(4)–O(53) | 1.929(16) | O(53)–Cu(4)–O(51) | 165.7(6) |
| | Cu(4)–O(51) | 1.950(15) | N(77)–Cu(4)–N(4) | 168.7(7) |
| | Cu(4)–N(77) | 1.981(16) | S(4)–Cu(4)–O(76) | 167.3(4) |
| | Cu(4)–N(4) | 1.995(17) | | |
| | Cu(4)–S(4) | 2.660(7) | | |
| | Cu(4)–O(76) | 3.041(14) | | |

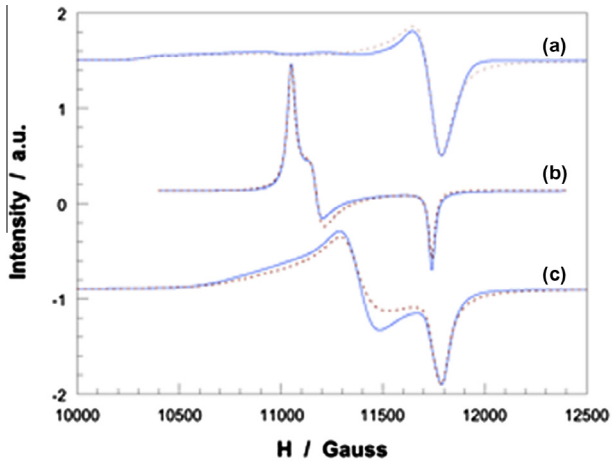


**Fig. 6.** Room temperature Q-band EPR spectra. (a), compound **3**, (b) compound **4** and (c) compound **5.** Dashed lines represent the best fits: see text for the fitting parameters.

appears in both complexes around 1695 $cm^{-1}$ is assigned to the stretching modes $\nu$(C=O) of acv which is shifted at more low frequencies relative to free acv (1715 $cm^{-1}$) [4,35]. This is consistent with the C=O group involved in coordination.

### 3.4.2. Magnetic properties of copper(II) compounds

X and Q band EPR measurements were carried out on powdered samples of compounds **3**–**5** at room temperature. The X-band EPR spectra exhibit near axial symmetries for the g tensor in the $\Delta M_s = \pm 1$ region. However, an appreciable extent of rhombic influence can be detected operating at Q-band in all cases (Fig. 6). The spin Hamiltonian parameters were estimated by comparison of the experimental spectra with those obtained by a computer simulation program working at the second order of the perturbation theory. The parameters were then optimized by the trial and error method. The best-fit results are represented as dashed lines in Fig. 6. The spectrum of compound **3** (Fig. 6a) is typical for magnetically isolated copper(II) chromophores with nearly axial symmetry. It shows well-resolved $^{63,65}$Cu ($I = 3/2$) hyperfine structure in the low-field region being $A_{||} = 175\cdot 10^{-4}$ $cm^{-1}$ and $g_{||} = 2.271$ (see SI 3). A detailed inspection of the perpendicular band reveals a slight rhombic distortion with g values of 2.064 and 2.061. The sequence $g_{||} > g_{\perp} > 2.04$ indicates a Cu(II) $d_{x^2-y^2}$ ground state in agreement with $Cu^{2+}$ ions with elongated octahedral or square pyramidal environments. The estimated $A_{||}$ and $g_{||}$ values are typical of $Cu^{2+}$ complexes where the four closest donor atoms ligands to the metal are two nitrogen atoms and two oxygen atoms [36].

A pattern giving two roughly equal larger g-values ($g_1 = 2.190$; $g_2 = 2.166$) and one lower g-value ($g_3 = 2.062$) is observed in the spectrum of $[Cu_2(TCC)(H_2O)_2]$ (**4**) at room temperature (Fig. 6b). The observed g values do not reflect the structural characteristics of the axially elongated square-base pyramidal coordination of the copper ions in this compound. It appears that signals in the spectrum have been averaged by extensive magnetic exchange coupling between non-magnetically equivalent $Cu^{2+}$ ions [37].

The Q-band spectrum of the complex with acyclovir and TCC (**5**) shows clear rhombic symmetry with unresolved hyperfine structure in the parallel region (Fig. 6c). The calculated g values are $g_1 = 2.221$, $g_2 = 2.134$ and $g_3 = 2.057$. It should be noted that the average value of $g_1$ and $g_2$ (2.178) is virtually the same as the average value of those components in compound **4**. Thus, it seems that the acyclovir ligand could be blocking a fluxional behavior in the TCC dimer. Moreover, the linewidth in the $[Cu_2(TCC)(acv)_2]\cdot 6H_2O$ spectrum are clearly greater than in $[Cu_2(TCC)(H_2O)_2]$. This fact is consistent with a closer Cu–Cu distance and lower magnetic exchange interaction in the former than in the latter.

Variable-temperature magnetic susceptibility measurements were carried out on powdered samples of the complexes **4** and **5** in the 5–300 K temperature range. No such characterization was performed for compound **3** because the presence of hyperfine structure in its EPR spectrum indicates that $Cu^{2+}$ ions are magnetically isolated in that complex. The thermal variation of the inverse of the magnetic molar susceptibility ($\chi_m^{-1}$) and the $\chi_m T$ product ($\chi_m T = (\mu_{eff})^2/8$) for both compounds are shown in Fig. 7. As can be seen, the $\chi_m T$ magnitude remains practically constant down to 20 K, temperature below which the magnetic effective moment values rapidly decrease towards zero. At room temperature, the $\chi_m T$ values are 0.847 (**4**) and 0.851 $cm^3$ K/mol which are close to the expected values for two uncoupled copper (II) ions with $g = 2.14$ (see EPR results). On the other hand, the Curie–Weiss law is followed over the whole measured temperature range in both cases. The calculated values of $C_m$ and the Weiss temperature ($\theta$) are 0.85 (**2**) and 0.86 (**3**) $cm^3$ K/mol and −2.5 (**4**) and −1.7 (**5**) K, respectively.

The abovementioned aspects are indicative of the occurrence of antiferromagnetic exchange coupling which should take place through the disulfide bridges. A more complete description of the observed magnetic behaviors may be obtained by using the Bleaney–Bowers equation copper dimers [38], derived from the Heisenberg spin Hamiltonian ($H = -2JS_1S_2$) for two coupled S = 1/2 ions:

$$\chi_m = (2Ng^2\beta^2/kT)[3 + \exp(-2J/kT)]^{-1} \quad (1)$$

where $N$ is the Avogadro's number, $\beta$ the Bohr magneton and $k$ the Boltzmann constant. The best least-squares fits (solid lines in Fig. 7) were obtained for the exchange parameters $J/k = -4.7$ and $-2.8$ K with $g = 2.14$ and 2.13 for compounds **4** and **5**, respectively. The good agreement between experimental and calculated data confirms the predominance of the dimeric interactions in both compounds, even if extensive exchange must be operative since the collapse of the hyperfine structure. The observed small J-values implies a poor overlapping between the magnetic orbitals (mainly $d_{x^2-y^2}$) of the two copper(II) ions in these compounds.

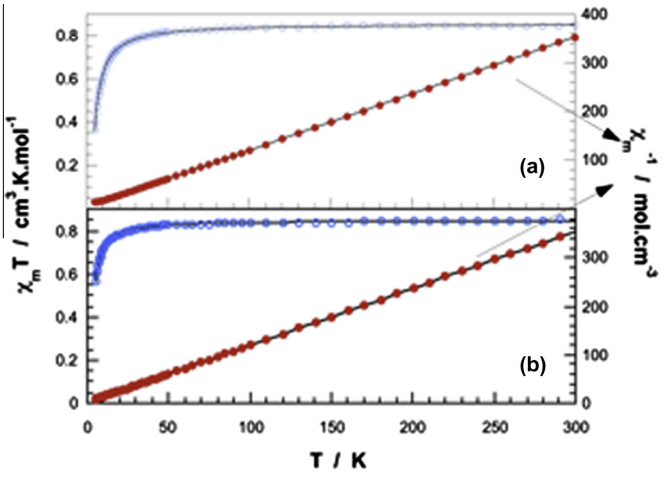


**Fig. 7.** Plots of $\chi_m^{-1}$ and $\chi_m T$ *vs* $T$ for compounds **4** (a) and **5** (b). The solid lines correspond to the best theoretical fits.

*3.4.3. Thermal stability of compounds **1** to **4***

Thermogravimetric analyses for **1** and **2** shows that have onset weight losses within the temperature range of 155–180 °C and 100–170 °C, respectively. This first steps in **1** correspond to the very low weight loss of $CO_2$ and $H_2O$, whereas that in **2** is due to release of most of the crystallization acetone. Almost without pause, between 170–550 °C, the free-of-solvents $H_2$BCBC begin to decomposes continuously with production of $CO_2$, $H_2O$, CO, $H_2C{=}CH_2$, SCNH, $SO_2$, $N_2O$, NO gases, mainly, until a final residue of 1.6% in **1** and of 2.3% in **2**. Complexes **3** and **4** are air-stable and can retain the crystalline integrity at ambient conditions. In **3** (see SI 4) the first steps of TGA curve (50–135 °C) correspond to the release of the $1/2H_2O$ and trace amounts of $CO_2$ (experimental loss weight 1.540%, calc. for $1/2H_2O$ 1.555%). Five additional decomposition steps (135–900 °C) produce $H_2O$, $CO_2$, CO, and methanol as well as N-oxides ($N_2O$, NO and $NO_2$ at 370–585 °C) to yield a final residue of impure CuO (at 900 °C, experimental 15.85%, calc. 13.74%). The formation of $SO_2$ in not observed. Probably, SCNH is gradually evolved as S-containing gas. In **4** (see SI 5) the thermal decomposition starts with a first step at 200–236 °C and almost without pause, in four steps, the complex begin to decompose continuously with production of SCNH (230–470 °C), $SO_2$ (470–775 °C) and N-oxides (470–560 °C). Near 600 °C, a stable residue of non-pure $CuO{\cdot}CuSO_4$ (exp. 43.15%, calc., 44.00%) is obtained, to give the final products CuO at 950 °C (exp. 32.76%, calc. 29.27%).

*3.5. The metal binding pattern of acyclovir and molecular recognition aspects in ternary copper(II) complexes with $NO_2S$-tripodal tetradentate chelators*

In this work we elucidate the MBP of acv in compounds **3** and **5** and discuss related molecular recognition aspects. A related compound was reported by Turel et al. according to the formula trans-$[Cu(acv)_2(H_2O)_2](NO_3)_2$ (HOSQUB in CSD) [12]. However, some relevant differences should be remarked. In the salt HOSQUB, the Cu(II) complex containing acv is a cation while compounds **3** and **5** (in this work) are neutral molecules. The acv-Cu(II) ratio is also different, being 2:1 in the salt and 1:1 in compounds **3** and **5**. Moreover, in HOSQUB the coligands are aqua (with a low steric factor) while the tripodal tetradentate $NO_2$ + S(thioether in **3** or disulfide in **5**) are rather bulky groups. The equimolar mole ratio acv-$H_2O$ in HOSQUB seems appropriate to display the main MBP of this SPN consisting in the Cu–N7(acv) bond assisted by an (aqua)O–H···O6(acv) interaction. Indeed the coordination of O-aqua atoms [Cu–OW 1.953(2) Å) among the four closest donors of copper(II) would favor that fact [22]. Surprisingly the crystal structure determination dictated that the 'unusual' asymmetric chelation mode [Cu–N7 2.004(2) and Cu–O6 2.698(2) Å] is favored, a fact attributed to the use of absolute methanol as solvent [12]. Considering the results reported by our research group [21–25] as well as others authors [16–20], one can agree with the idea that the metal binding of acv is very sensitive to the solvent used. In addition, we think that the neutrality or ionic charge of the complex, and obviously the crystal packing forces, is a relevant factor. As far as concerns the molecular complexes **3** and **5**, all influencing factors (i.e., the polarity of the solvent, the neutrality of the novel ternary complexes, the chelating nature of the coligands…) lead to short Cu-S(apical/distal), with averaged distances of 2.61 and 2.66 Å for **3** and **5**, respectively. This fact determines the shortness of the trans-Cu···O6 distance and therefore the weakness of the coordination bond, which can be considered simply a contact. That increases the asymmetry of the chelation/MBP of acv to a critical limit.

*3.6. State-of-the-art on the role of solvents in the synthesis and crystal growth of aciclovir metal complexes*

A sort discussion about the role of solvent can be instructive. First of all Iztok Turel et al. (1997) [11] has obtained trans-$[Cu(acv)_2(H_2O)_3](NO_3)_2{\cdot}H_2O$ (RUMGAH in CSD) from a solution of reactants in equimolar amounts of water and methanol, which evaporation would easy loss the most volatile solvent. In this compound the metal exhibits an square-base pyramidal coordination (type 4+1) with an apical-distal aqua ligand whereas the MBP simply consist of the Cu–N7(acv). The same reactants in dry methanol yield trans-$[Cu(acv)_2(H_2O)_2](NO_3)_2$ (HOSQUB) [12] with only two aqua ligands per metal ion. The Cu(II) coordination in the centrosymmetric complex cation (build by two O-aqua and two N7-acv donors) was initially referred as square-planar but the Cu–O6 distances (2.698(2) Å) are significantly shorter than the sum of the Van der Waals radii ($r_O + r_{Cu}$ = 1.50 + 1.40 = 2.90 Å). Hence, HOSQUB will be considered as the first reported case where acv display an asymmetrical-N7,O6 chelating role. The structural comparison of these two compounds (having the same counter anion) enhances the influence of the solvent polarity, but does not mean uselessness of the water as a media for the synthesis of acv-metal complexes. Indeed, trans-$[Cu(acv)_2(H_2O)_2Cl_2]$ (ZATJIN in CSD) [10] was obtained from water. In other word the polarity of the solvent (s) is not the unique factor to be kept in mind, but examples are known that emphasizes its relevance. In this context our attempts to obtain a ternary $Cu^{II}$-iminodiacetate-acv complex from water yield colorless $acv{\cdot}0.66H_2O$ and blue crystals of $\{Cu(ida)(H_2O)_2\}_n$. After complete evaporation of water, both reactants were re-dissolved in a large amount of dry methanol to obtain, by low evaporation, the also polymeric compound $\{[Cu(IDA)(acv)]{\cdot}2CH_3OH\}_n$ (IPUXIB in CSD) [21].

## 4. Concluding remarks

The $NO_2S$-tripodal tetradentate copper(II) chelates of N,N-bis (carboxymethyl)-S-benzylcysteaminate(2-) (BCBC) and N,N,N′,N′-tetrakis(carboxymethyl) cysteaminate(4-) (TCC) have proven to be suitable receptors for the synthetic purine nucleoside analog acyclovir. The Cu(BCBC) chelate mimics mononuclear centers with an S-disulfide apical/distal donor atom while TCC ligand simulate a dinuclear $Cu_2$(TCC) receptor with a S-disulfide atom apical/distal donor atom per metal. This idea is well supported by the 'molecular form' of the binary chelate $[Cu_2(TCC)(H_2O)_2]$ also reported herein. The $NO_2S$-tripodal tetradentate role of BCBC as well as each

half of TCC ligands envisions the availability of, at least, one coordination sites among the four closest to the copper(II) atom to bind the borderline N7 donor atom of acyclovir. However the corresponding Cu–N7(acv) bond cannot cooperate with an X–H···O6 (acv) intra-molecular interligand interaction, a rather common MBP in mixed-ligand metal complexes with acv (X being an O or N coordinated atom). Interestingly both novel ternary complexes reported in this work feature the rather uncommon N7,O6-chelating mode, above referred as HOSQUB and early reported by –Turel et al. These compounds have in common the binding of the borderline N7-acv donor among the four closest atoms in the metal surrounding, while the hard O6-acv donor atom occupies an apical/distal coordination site. The main difference between trans-[Cu(acv)$_2$(H$_2$O)$_2$](NO$_3$)$_2$ (HOSQUB) and compounds **3** and **5** is the Cu–O6(acv) bond distance, clearly shorter in the compound reported by Turel et al. (2.698(2) Å) than in the two novel complexes (~3.0 Å). The Cu–O6 distance in **3** or **5** is clearly lengthened as far as possible because the Cu-S(thioether) or Cu-S(disulfide) is shortened to averaged distances of 2.61 or 2.66 Å respectively. Indeed our recent structural results on ternary copper(II) complexes with BCBC or TCC and adenine or 2,6-diaminopurine revealed that if crystal packing elongates the Cu-S bond that shortens the trans-Cu–O bond. That is particularly observed in the structure of the binuclear compound [Cu$_2$(BCBC)$_2$(μ$_2$-N7,N9-H(N3)dap)(H$_2$O)$_2$]·4H$_2$O [4] where the Cu-S(thioether) bonds of 2.658(3) and 2.867(3) Å have in trans sites the Cu–O(aqua) bonds of 2.917(5) and 2.704(6) Å respectively. But that is not featured by the crystal of novel compounds here reported with acyclovir.

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## Appendix A. Supplementary material

CCDC 1441444 to 1441448 contains the supplementary crystallographic data for **3**, **4**, **5**, **2**, and **1**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2016.05.005.

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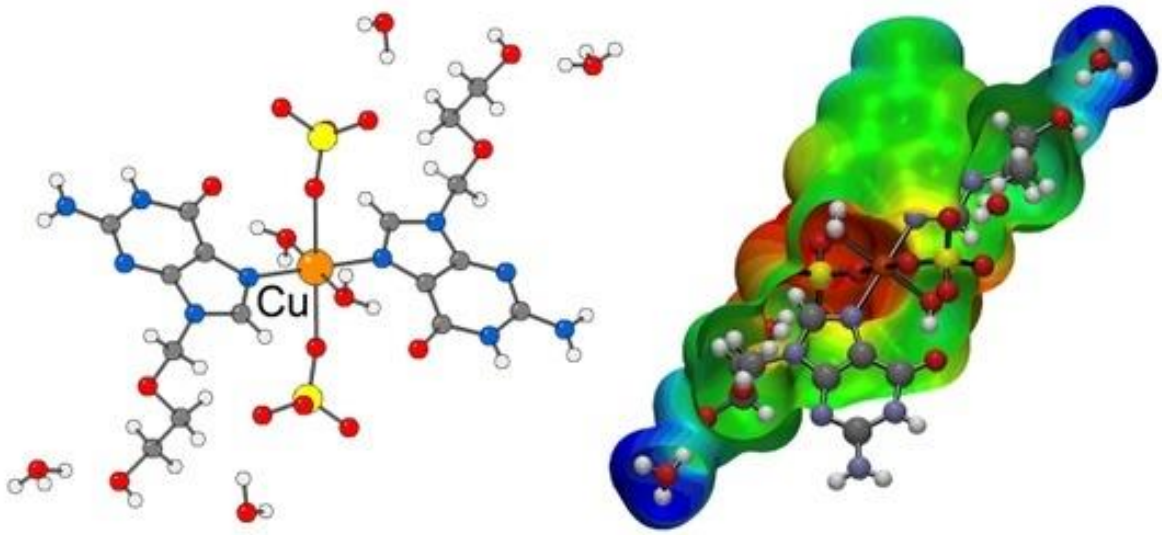
## 5.4. ARTÍCULO 4: STRUCTURAL AND THEORETICAL EVIDENCE OF THE DEPLETED PROTON AFFINITY OF THE N3-ATOM IN ACYCLOVIR





### RESUMEN:

Se ha sintetizado y cristalizado la sal de hidronio $(H_3O)_2[Cu(N7–acv)_2(H_2O)_2(SO_4)_2]\cdot 2H_2O$ (1, acv = acyclovir) . El compuesto ha sido investigado por difracción de rayos X con monocristal y métodos espectrales. La síntesis del compuesto produce $Cu(OH)_2$ solvatado como subproducto. En el anión complejo, centrosimétrico y todo–trans, (a) el entorno de coordinación del átomo de Cu(II) es octaédrico alargado (b) el modo de reconocimiento molecular del nucleósido acv consistente en una cooperación entre el enlace coordinado Cu-N7(acv) y una interacción intra-molecular interligandos (aqua)OH···O6(acv), y (c) la coordinación monodentada de los ligandos aniónicos sulfato es trans-apical/distal. Los ligandos neutros, acv y aqua, ocupan pares de posiciones trans-basales/proximales del entorno de coordinación del metal, propiciando el referido modo de coordinación de nucleósido sintético. Es también interesante observar que en el cristal cada catión hidronio(1+) se implica en la formación de tres enlaces de hidrógeno con aceptores O–sulfato, O6(acv) y O-alcohol(acv), procedentes de tres complejos aniónicos adyacentes. Por consiguiente, el catión hidronio no interacciona mediante enlaces de hidrógeno con átomos de oxígeno de las moléculas de agua no coordinadas ni N3 de acv. Cálculos teóricos de superficies de potencial electrostático molecular y cargas atómicas apoyan que el átomo O-alcohol de la cadena acíclica en N9(acv) es un aceptor de hidrógeno mejor que el átomo N3 heterocíclico o el átomo O-éter del nucleósido acv.

## STRUCTURAL AND THEORETICAL EVIDENCE OF THE DEPLETED PROTON AFFINITY OF THE N3-ATOM IN ACYCLOVIR

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*Communication*

# Structural and Theoretical Evidence of the Depleted Proton Affinity of the N3-Atom in Acyclovir

**Esther Vílchez-Rodríguez [1], Inmaculada Pérez-Toro [1], Antonio Bauzá [2] and Antonio Matilla-Hernández [1,*]**

[1] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain; estervr@correo.ugr.es (E.V.-R.); inptoro@ugr.es (I.P.-T)

[2] Department of Chemistry, Faculty of Science, University of the Balearic Islands, Crta. de Valldemossa km 7.5, 07122 Palma de Mallorca (Baleares), Spain; antonio.bauza@uib.es

* Correspondence: amatilla@ugr.es; Tel.: +34-958-243-854

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**Abstract:** The hydronium salt $(H_3O)_2[Cu(N7–acv)_2(H_2O)_2(SO_4)_2]\cdot 2H_2O$ (1, acv = acyclovir) has been synthesized and characterized by single-crystal X-ray diffraction and spectral methods. Solvated $Cu(OH)_2$ is a by-product of the synthesis. In the all-*trans* centrosymmetric complex anion, (a) the Cu(II) atom exhibits an elongated octahedral coordination; (b) the metal-binding pattern of acyclovir (acv) consists of a Cu–N7(acv) bond plus an (aqua)O–H···O6(acv) interligand interaction; and (c) *trans*-apical/distal sites are occupied by monodentate O–sulfate donor anions. Neutral acyclovir and aqua-proximal ligands occupy the basal positions, stabilizing the metal binding pattern of acv. Each hydronium(1+) ion builds three H-bonds with O-sulfate, O6(acv), and O–alcohol(acv) from three neighboring complex anions. No O atoms of solvent water molecules are involved as acceptors. Theoretical calculations of molecular electrostatic potential surfaces and atomic charges also support that the O-alcohol of the N9(acv) side chain is a better H-acceptor than the N3 or the O-ether atoms of acv.

**Keywords:** copper(II); mixed-ligand; hydronium; crystal structure; DFT calculations; interligand interactions

## 1. Introduction

During the past decades, various contributions on metal ion complexes with acyclovir (acv, Figure 1) have been reported. This acyclic guanine nucleoside analog has proved to bind nucleoside phosphorylases [1] as well as several metal ions. Structural knowledge on mixed-ligand metal–acv complexes (see selected reference [2–12]) supports a variety of metal binding patterns (MBPs) and interesting molecular recognition features. So far, the reported MBPs can be summarized as follows: (a) the formation of the M–N7 bond, with [2–9,12] or without [8,10] the cooperation of an intra-molecular interligand A–H···O6(acv) interaction (A=O or N acceptor); (b) the N7,O6-chelation mode [11]; (c) the $\mu_2$-N7,O(ol) (see Figure 1) bridging role [3]; and finally, (d) a multi-functional role featured by the $\mu_3$-N7,O6,O(e)+O(ol), which comprises the bridging, chelating, and tetradentate modes of acv [12].

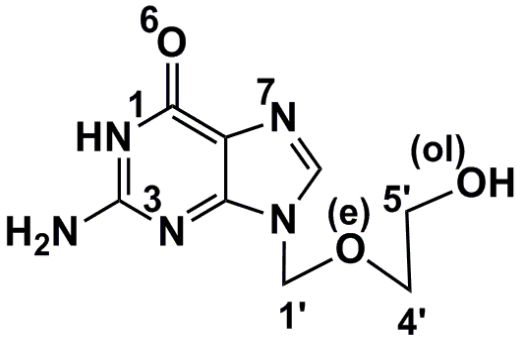



**Figure 1.** Formula of acyclovir and the numbering used in this work (see also Figure A1).

## 2. Results and Discussion

As part of our program expanding the frontiers of acv as a ligand, different reactions between acv and metal chelates were performed, using a large variety of tri- and tetra-dentate chelators. An attempt to obtain the ternary complex Cu(II)–DEA–acv (DEA = diethanolamine) yielded a DEA-free greenish powder with a few well-shaped single crystals corresponding to the formula $(H_3O)_2[Cu(acv)_2(H_2O)_2(SO_4)_2]\cdot 2H_2O$ (**1**, 100 K, monoclinic system, space group $P2_1/c$, final $R_1 = 0.045$. Table A1) along with bluish $Cu(OH)_2$. The *all-trans* centrosymmetric anions (Figures 2 and A2) have symmetry-related pairs of O–aqua, N7–acv, and O–sulfate donor atoms featuring a rather typical elongated-octahedral Cu(II) coordination, type 4 + 2, with bond lengths of Cu–O(aqua) of 1.963(2) Å, of Cu–N7(acv) of 2.018(2) Å, and of Cu–O(sulfate) of 2.427(2) Å, respectively (Table A2). It seems clear that the, shortest strongly-bound Cu–O(aqua) favor the cooperation of each Cu–N7(acv) bond with an intra-molecular interligand (aqua)O1–H1B···O6(acv) interaction (2.615(3) Å, 157.3°) (Table A3), thus leading to the most common MBP of the acv ligand [2–9,12]. This fact imposes the coordination of O–sulfate atoms towards the apical/distal sites of the copper(II) surrounding. In addition, three (hydronium)O–H···O interactions stabilize the structure involving the O6, O(ol), and O(sulfate) atoms from three neighboring complex anions as acceptors, excluding the participation of O-water molecules within the intermolecular network (Table A4, Figures A3 and A4). The novel compound is closely related to the molecular compound all *trans*-$[Cu(acv)_2(H_2O)_2Cl_2]$ [5] where chloride ligands are also moved to the *trans*-apical/distal coordination to favor the cooperation between Cu–N7(acv) bonds and (aqua)O–H···O6(acv) interactions.

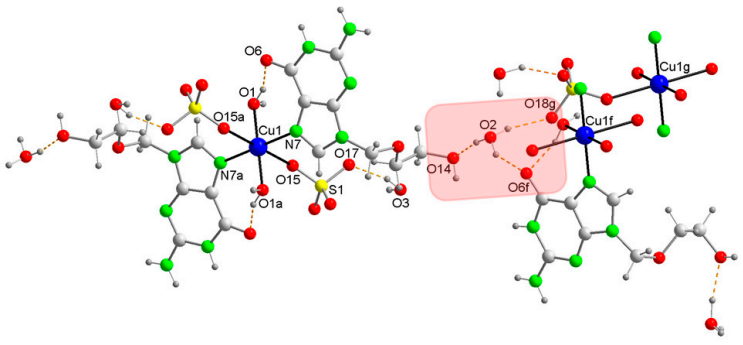
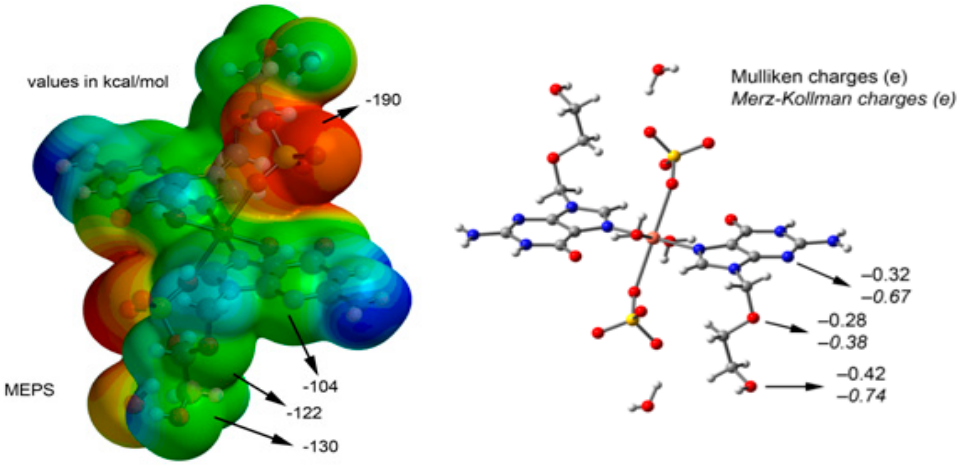



**Figure 2.** Structure and H-bonding interactions (dashed lines) in **1**. The $H_3O^+$ ion is H-bonded to O-acceptors of three neighboring complex anions. Symmetry codes: $a = -x, -y + 1, -z$; $f = x + 1, -y + 1/2, z + 1/2$; $g = -x + 1, y - 1/2, -z + 3/2$.

In the Fourier transform infrared (FT-IR) spectrum of **1** (see also Figure A5 for acv·0.68 $H_2O$ and Figure A6, Table A5), the monodentate sulfate ligands (~$C_{3v}$ symmetry) split the $\nu_3$ mode in two intense bands at 1122 and 1041 $cm^{-1}$, while only one $\nu_3$ band is observed for the free ion at about

1033–1440 $cm^{-1}$. Likewise, the sulfate $\nu_4$ mode consists of two medium intensity bands at 652 and 611 $cm^{-1}$, but only one at 613 $cm^{-1}$ for the free ion [4]. The identification of the hydronium ion by FT-IR spectroscopy is not an easy task. In compound **1**, the $H_3O^+$ ion seems responsible of the broad absorption ($\nu_1$ and/or $\nu_3$) at ~2743 $cm^{-1}$ and the defined band ($\nu_4$) at 1190 $cm^{-1}$ [13]. The electronic spectra of compound 1 (Figure A8) explain its greenish color (see Appendix A.4).

This structure, therefore, exhibits two uncommon features: (a) the apical/distal copper(II) coordination of the divalent sulfate anions versus the basal coordination of neutral aqua and acv ligands, and (b) the unexpected formation of hydronium(1+) cations instead of the protonation of the N3–acv atom. The molecular electrostatic potential surface (MEPS) was computed in the complex anion (Figure 3, Cartesian coordinates in Table A6) in order to better understand the basis of these features. As expected, the most negative region is located around the sulfate ligands, which are the best candidates to participate in H-bonding interactions with the $H_3O^+$ ion. Indeed, this is observed in the crystal packing of compound **1**. A comparison of MEPS values at the N3 and O(ol) atoms of the N9-acyclic chain reveals that the most negative electrostatic potential falls at the O(ol) atom, supporting the observed $(H_3O^+)O–H\cdots O(ol)$ interaction, whereas no interaction with $(H_3O^+)O–H\cdots N3(acv)$ is built. To further discuss the ability of the O(ol) atom and the N3(acv) atom, from the acv N9-side chain and the purine-like moiety, respectively, to participate in H-bonding interactions as acceptors, the atomic charges for $[Cu(acv)_2(H_2O)_2(SO_4)_2]^{2-}\cdot 2H_2O$ were also computed. Results computed using two different methods for deriving atomic charges (see ESI for details) yield a more negative charge on the O(ol) atom than on the O(ether) and N3 atoms (Figure 4), in agreement with the experimental results. Therefore, the N3-acv atom is not protonated in the structure due to the significant depletion of its basicity. The steric hindrance on the N3(acv) atom imposed by the acv N9-side chain and ortho-2-amino group should also be considered.




(**a**) (**b**)

**Figure 3.** Compound **1**: (**a**) molecular electrostatic potential surface (MEPS). The values at selected points of the surface are indicated. Color code: from red to blue, with red being the most negative and blue the most positive values; (**b**) Mulliken and Merz-Kollman charges obtained at the BP86-D3/def2-TZVP level of theory.

We have also evaluated, energetically, the interaction energy of the $H_3O^+$ ion with the O(ol) atom (observed experimentally) and the hypothetical complex with N3(acv), as indicated in Figure 4 (see Cartesian coordinates in Table A7). The interaction energies in both cases are very large (−88.8 and −88.1 kcal/mol, respectively) due to the strong electrostatic attraction between the counter ions. Interestingly, the complexation energy is slightly more favorable with the O(ol) atom than with N3(acv), in agreement with the experimental observation. We have also evaluated the complexation

energy of the solid state assembly commented above in Figure 2 and the theoretical model is depicted in Figure 4c. The interaction energy of this assembly is very large (−100.3 kcal/mol) due to the contribution of both H-bonding interactions and also the pure electrostatic effects.

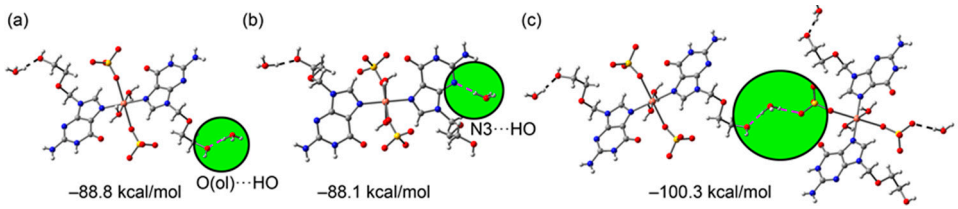



**Figure 4.** Theoretical models used to evaluate the electrostatic assisted H-bonding interactions in the solid state of compound **1**. (**a**): Interaction of $H_3O^+$ with O(ol) atom of acv; (**b**): Interaction of $H_3O^+$ with N3 atom of acv; (**c**): Interaction of $H_3O^+$ with O(ol) of acv and O-Sulfate atom.

## 3. Materials and Methods

### *3.1. Synthesis of Compound **1***

Equimolar amounts (0.5 mmol) of $CuSO_4{\cdot}5H_2O$ and DEA were dissolved in 70 mL of methanol. Acyclovir (acv·$0.66H_2O$, 0.5 mmol) was added in small amounts to yield an apple-greenish solution that was filtered into a crystallizing dish. Slow evaporation yields compound **1** and bluish $Cu(OH)_2$. Compound **1** can easily be collected by filtration and dried on a filter paper. Yield: 65%.

### *3.2. Crystal Structure Determination*

A green plate crystal of $(H_3O)_2[Cu(acv)_2(H_2O)_2(SO_4)_2]{\cdot}2H_2O$ was mounted on a glass fiber and used for data collection. Crystal data were collected at 100(2) K, using a Bruker X8 KappaAPEXII diffractometer. Graphite monochromated MoK(α) radiation (λ = 0.71073 Å) was used throughout. The data were processed with APEX2 [14] and corrected for absorption using SADABS (transmissions factors: 1.000—0.907) [15]. The structure was solved by direct methods using the program SHELXS-2013 [16] and refined by full-matrix least-squares techniques against $F^2$ using SHELXL-2013 [16]. Positional and anisotropic atomic displacement parameters were refined for all non-hydrogen atoms. Hydrogen atoms were located in difference maps and included as fixed contributions riding on attached atoms with isotropic thermal parameters 1.2 times those of their carrier atoms. Criteria of a satisfactory complete analysis were the ratios of the RMS shift to standard deviation less than 0.001 and no significant features in final difference maps. Atomic scattering factors were taken from the International Tables for Crystallography [17]. Molecular graphics were plotted from DIAMOND [18].

### *3.3. Theoretical Calculations*

The energies and atomic charges of the compound included in this study were computed using the BP86-D3 functional [19,20] and def2-TZVP [21] basis set using the crystallographic coordinates within the TURBOMOLE 7.0 program [22]. This level of theory, which includes the latest available dispersion correction (D3) [23], is adequate for studying non-covalent interactions, for which dispersion effects are important. The MEP surfaces were generated using Spartan'10 v. 1.1.0 software [24] using the B3LYP [25–27] method and the 6-31+G* basis set.

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**Author Contributions:** Esther Vílchez-Rodríguez and Inmaculada Pérez-Toro have performed the synthesis of compound and preparation of samples. Antonio Bauzá has performed the MEPS calculations. Data analysis and write manuscript by Antonio Matilla-Hernández. All authors have participated in the discussion of results.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Appendix A

Crystallographic data for **1** has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 1433120. Copies of this information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

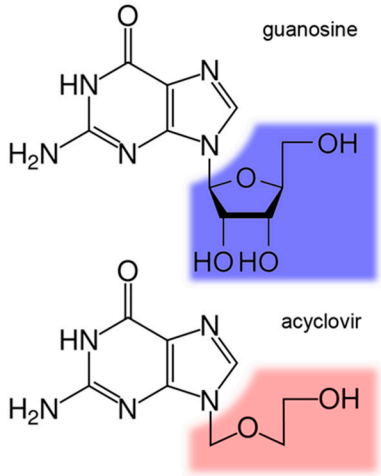


**Figure A1.** Structural correlation between guanosine and acyclovir.

### *Appendix A.1. Structural Data*

**Table A1.** Crystal data, structure solution, and refinement of compound **1**.

| Identification code | 14jnac876 |
|---|---|
| Empirical formula | $C_{16}H_{36}CuN_{10}O_{20}S_2$ |
| Formula weight | 816.21 |
| Crystal system, space group | Monoclinic, $P2_1/c$ |
| Unit cell dimensions | $a$ = 12.1489(4)Å, α = 90° |
| | $b$ = 18.2712(5)Å, β = 102.755(1)° |
| | $c$ = 6.8294(2) Å, γ = 90° |
| Volume | 1478.55(8) Å$^3$ |
| $Z$, Calculated density | 2, 1.833 Mg/m$^3$ |
| Absorption coefficient | 0.987 mm$^{-1}$ |
| $F$(000) | 846 |
| Crystal size | 0.100 × 0.080 × 0.040 mm |
| Theta range for data collection (°) | 2.229 to 29.204 |
| Limiting indices | $-15 \leq h \leq 16$, $-24 \leq k \leq 24$, $-9 \leq l \leq 9$ |
| Reflections collected/unique | 19,513/3985 [$R_{int}$ = 0.0392] |
| Completeness to θ = 25.242 | 99.8% |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 1.0000 and 0.9069 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/parameters | 3985/223 |
| Goodness-of-fit on $F^2$ | 1.092 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1$ = 0.0449, $wR_2$ = 0.1042 |
| $R$ indices (all data) | $R_1$ = 0.0559, $wR_2$ = 0.1099 |
| Largest diff. peak and hole | 1.260 and −0.907 e.Å$^{-3}$ |

**Table A2.** Coordination bond lengths (Å) and angles (°) for compound **1**.

| Bond Lengths (Å) of Compound 1 | |
|---|---|
| Cu(1)–O(1) [a] | 1.9630(18) |
| Cu(1)–O(1) | 1.9630(18) |
| Cu(1)–N(7) [a] | 2.018(2) |
| Cu(1)–N(7) | 2.018(2) |
| Cu(1)–O(15) | 2.4271(17) |
| Cu(1)–O(15) [a] | 2.4271(17) |
| **Angles (°) for Compound 1** | |
| O(1) [a]–Cu(1)–O(1) | 180.0 |
| O(1) [a]–Cu(1)–N(7) [a] | 90.48(8) |
| O(1)–Cu(1)–N(7) [a] | 89.52(8) |
| O(1) [a]–Cu(1)–N(7) | 89.52(8) |
| O(1)–Cu(1)–N(7) | 90.48(8) |
| N(7) [a]–Cu(1)–N(7) | 180.0 |
| O(1) [a]–Cu(1)–O(15) | 88.41(7) |
| O(1)–Cu(1)–O(15) | 91.59(7) |
| N(7) [a]–Cu(1)–O(15) | 86.78(7) |
| N(7)–Cu(1)–O(15) | 93.22(7) |
| O(1) [a]–Cu(1)–O(15) [a] | 91.59(7) |
| O(1)–Cu(1)–O(15) [a] | 88.41(7) |
| N(7) [a]–Cu(1)–O(15) [a] | 93.22(7) |
| N(7)–Cu(1)–O(15) [a] | 86.78(7) |
| O(15)–Cu(1)–O(15) [a] | 180.00(8) |

Symmetry transformation used to generate equivalent atoms, [a]: $-x, -y + 1, -z$.

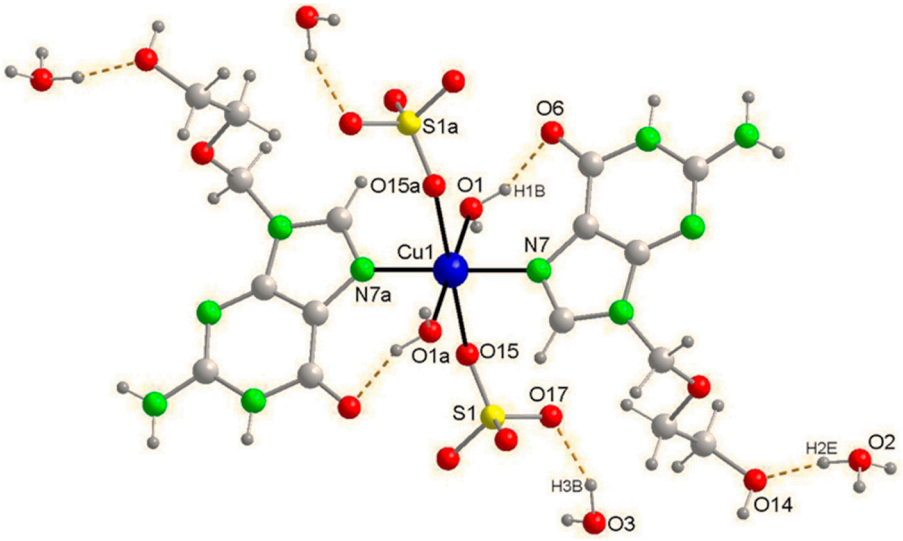


**Figure A2.** Structure of compound **1**, corresponding to two symmetry-related asymmetric units (symmetry transformation, **a**: $-x, -y + 1, -z$).

**Table A3.** Hydrogen bonds for compound **1** (Å, °).

| D–H···A | *d*(D–H) | *d*(H···A) | *d*(D···A) | Z(DHA) |
|---|---|---|---|---|
| O(1)–H(1A)···O(17) | 0.87 | 2.17 | 2.727(3) | 121.3 |
| O(1)–H(1B)···O(6) | 0.87 | 1.79 | 2.615(3) | 157.3 |
| O(14)–H(14)···O(16) [c] | 0.84 | 1.82 | 2.647(3) | 166.2 |
| N(1)–H(1)···O(18) [d] | 0.88 | 1.96 | 2.832(3) | 170.2 |
| N(2)–H(2A)···O(17) [e] | 0.88 | 2.11 | 2.905(3) | 149.4 |
| N(2)–H(2B)···O(15) [d] | 0.88 | 2.08 | 2.859(3) | 147.3 |
| O(2)–H(2C)···O(6) [f] | 0.87 | 2.06 | 2.825(3) | 146.2 |
| O(2)–H(2D)···O(18) [g] | 0.87 | 1.96 | 2.808(3) | 165.5 |
| O(2)–H(2E)···O(14) | 0.98 | 1.82 | 2.786(3) | 170.4 |
| O(3)–H(3A)···O(14) [h] | 0.84 | 2.61 | 3.124(3) | 121.0 |
| O(3)–H(3A)···O(16) [i] | 0.84 | 2.59 | 3.101(3) | 120.2 |
| O(3)–H(3A)···O(2) [j] | 0.84 | 2.48 | 3.053(4) | 125.8 |
| O(3)–H(3B)···O(17) | 0.98 | 1.83 | 2.751(3) | 153.9 |

Symmetry transformations used to generate equivalent atoms, c: −x + 1, −y + 1, −z + 1; d: −x, y − 1/2, −z + 1/2; e: x, −y + 1/2, z − 1/2; f: x + 1, −y + 1/2, z + 1/2; g: −x + 1, y − 1/2, −z + 3/2; h: −x + 1, −y + 1, −z + 2; i: x, y, z + 1; j: −x + 1,y + 1/2, −z + 3/2.

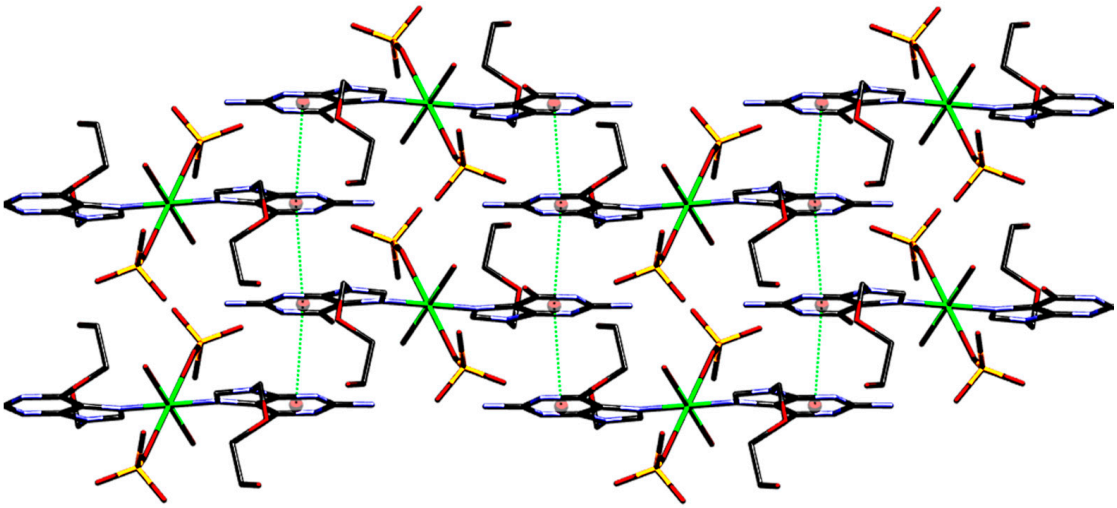

**Figure A3.** π,π-interactions between the six-membered rings of guanine moieties building 2D frameworks parallel to the bc plane of the crystal.

**Table A4.** π,π-Staking interaction parameters in the crystal of compound **1** (Å, °).

| π···π interactions | Cg(I)···Cg(J) | α |
|---|---|---|
| Cg(1)···Cg(1) [e] | 3.4235 | 3.00 |
| Cg(1)···Cg(1) [k] | 3.4235 | 3.00 |

Cg(1): ring [N(1)/C(2)/N(3)/C(4)/C(5)/C(6)]. Symmetry transformations used to generate equivalent atoms, e: x, −y + 1/2, z − 1/2; k: x, −y + 1/2, z + $\frac{1}{2}$; Cg(I)···Cg(J): distance between ring centroids; α: dihedral angle between planes I and J.

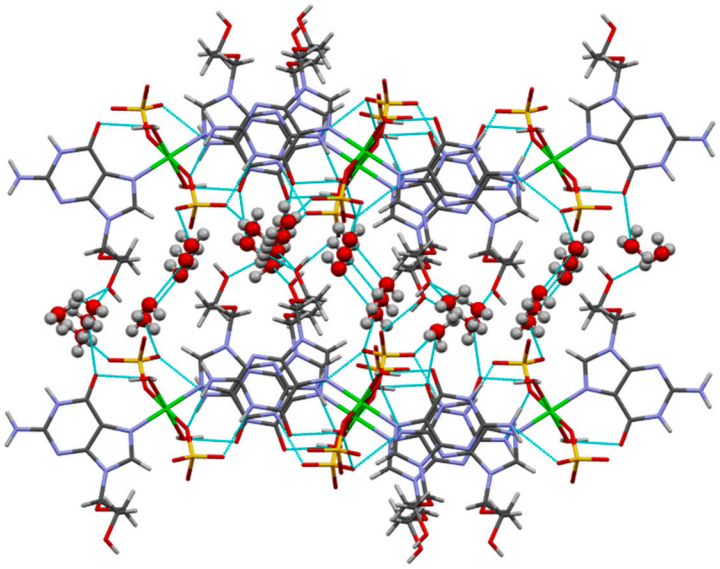

**Figure A4.** Many H-bonds, some of them involving $H_3O$+ ions, $H_2O$ molecules, and acv-O(ol)H groups as H-donors, linking the π,π-stacked 2D-layers in a 3D array in the crystal of compound **1**.

## *Appendix A.2. FT-IR Spectrum*

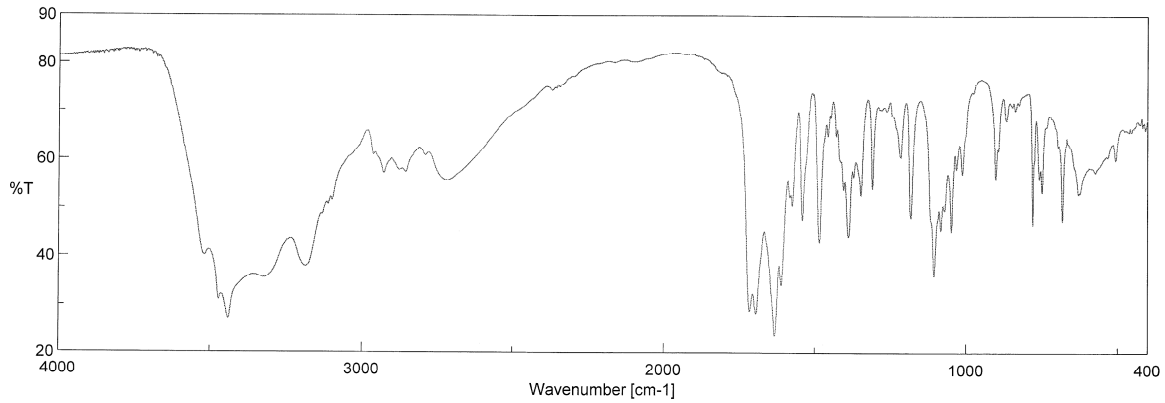


**Figure A5.** FT-IR spectrum of a commercial sample of acv·0.66 $H_2O$ (KBr disks).

The absorption band of the stretching mode ν(C=O) in various spectra recorded for commercial samples of acv·0.66$H_2O$ splits into two partially-overlapped bands at 1720(3) and 1695(2) $cm^{-1}$.

In the FT-IR spectra of copper(II) complexes having solvate and/or coordinated acv, this band is located very close to 1695 $cm^{-1}$. However, this is not the case of compound **1** (see Figure A6), where this ν(C=O) band appears at 1683 $cm^{-1}$ because the exocyclic O6 atom of acv acts twice as an H-acceptor for an intra-molecular and an inter-molecular H-bonding interaction.

An additional band with good diagnostic value is that of the out-of-plane deformation mode δ(O–H) for the terminal alcohol functional group of the N9-side chain, –O(ol)–H, that appears as a more or less defined band near 1387(3) $cm^{-1}$ (see band 33 at 1387 $cm^{-1}$).

However, attention must be paid if the studied copper(II) complexes contain nitrate or carboxylate anions, which produce stretching bands near to 1385 $cm^{-1}$.

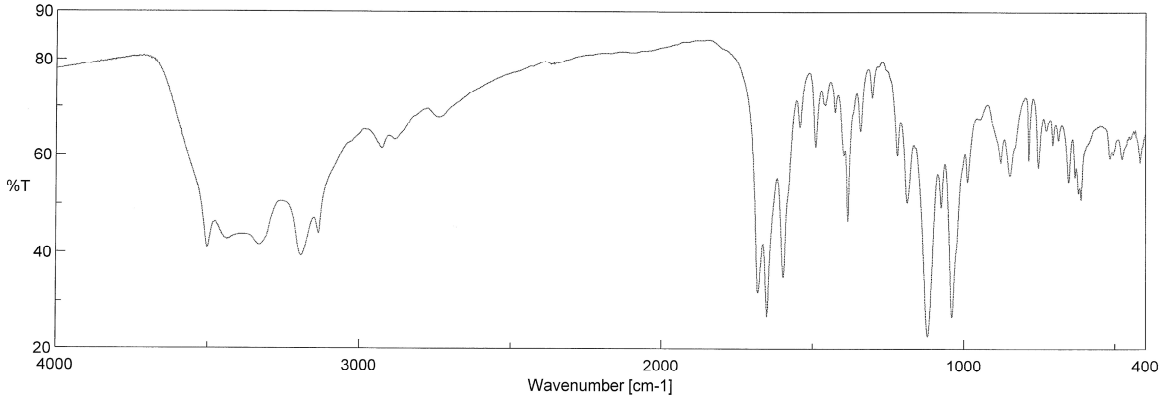


**Figure A6.** FT-IR spectrum of compound **1**.

**Table A5.** Assignation peaks of compound **1**.

| Ligand or Solvent | Chromophore | Mode | Wavenumber ($cm^{-1}$) | Band Number in the Read Spectrum |
|---|---|---|---|---|
| $H_3O^+$ ion | $H_3O^+$ | $\nu_1(A_1)$ and $\nu_3(E)$ | 2743 (broad) | 9 |
| | | $\nu_2(A_1)$ | 1190 | 24 |
| $H_2O$ | $H_2O$ | $\nu_{as}$ | 3430 | 2 |
| | | $\nu_s$ | ~3450 | N/M * |
| | | $\delta$ | 1652 | 11 |
| acv | O(ol)–H | $\nu$ | 3502 | 1 |
| | | $\delta$ | 1385 | 20 |
| | $–N(2)H_2$ | $\nu_{as}$ | 3327 | 3 |
| | | $\nu_s$ | 3195 | 4 |
| | | $\delta$ | 1598 | 12 |
| | –N(1)–H | $\nu$ | 3139 | 5 |
| | | $\delta$ | 1541 | 14 |
| | –C=O(6) | $\nu$ | 1683 | 10 ** |
| | C–O(e)–C | $\nu_{as}$ | 1178 | 26 |
| sulfate | $SO_4^{2-}$ | $\nu_3$ | 1122 | 25 |
| | | | 1041 | 27 |
| | | $\nu_1$ | 989 | 28 |
| | | $\nu_4$ | 652 | 36 |
| | | | 611 | 39 |
| | | $\nu_2$ | 448 | 44 |

* N/M = not measured. ** This band usually splits in two at 1720(3) and 1695(3) $cm^{-1}$ in the spectra of acv·0.66$H_2O$ samples, and appear at about 1695 $cm^{-1}$ in the spectra of Cu(II)-acv complexes with monodentate acv ligands. Note that, in compound **1**, the O6 atom of acv is involved as an acceptor in two H-bonds.

### *Appendix A.3. ESR Spectrum and Magnetic Properties of Compound **1***

X-band ESR (Electronic Spin Resonance) measurements were carried out on a Bruker ELEXSYS 500 spectrometer equipped with a super-high-Q resonator ER-4123-SHQ. For Q-band studies, ESR spectra were recorded on a Bruker EMX system equipped with an ER-510-QT resonator. The room temperature X-band powder spectra are not well resolved due to a rather large line width. However at the Q-band (Figure A7) the signal is clearly characteristic of an axial g tensor with the following main values: $g\| = 2.339$, and $g\perp = 2.086$ (computer simulation: WINEPR-Simfonia, version 1.5, Bruker Analytische Messtechnik GmbH.

The g values are typical of Cu(II) ions in distorted octahedral environments in good agreement with the structural characteristics of the $CuN_2O_4$ chromophore. Moreover, the lowest g deviates appreciably from the free electron value ($g_0 = 2.0023$) indicating a dx2-y2 ground state, as corresponds to an axially-elongated octahedral environment for Cu(II) ions. The absence of well-resolved hyperfine

lines contrasts with the structurally monomeric nature of the compound. The collapse of the hyperfine structure usually indicates the presence of long-range exchange coupling. The hydrogen bonding and/or the π,π-stacking of the acyclovir rings can provide the necessary exchange pathway.

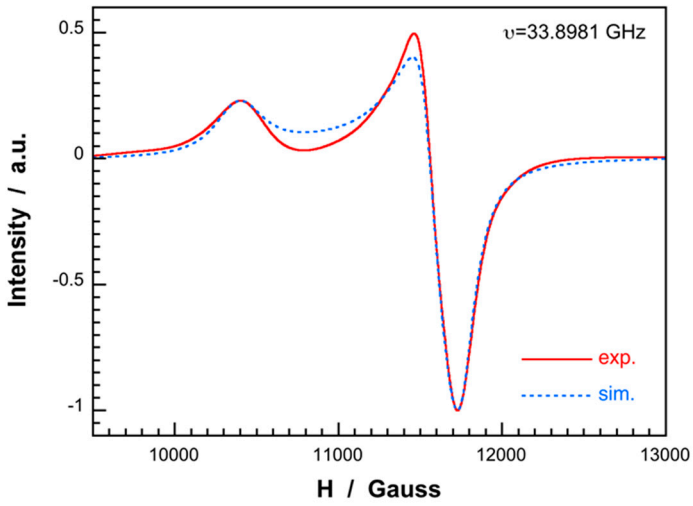


**Figure A7.** Q-band ESR powder spectrum of compound **1** registered at room temperature. Dotted line is the best fit; see text for the fitting parameters.

Variable temperature (5–300 K) magnetic susceptibility measurements on polycrystalline samples were carried out with a Quantum Design MPMS-7 SQUID magnetometer under a magnetic field of 0.1 T. The experimental susceptibilities were corrected for the diamagnetism of the constituent atoms by using Pascal's tables. Magnetic susceptibility data show typical Curie–Weiss behavior. The calculated Curie constant (Cm = 0.44 $cm^3 \cdot K/mol$) is in good agreement with the *g*-values obtained from ESR experiments ($g$ = 2.170; Cm = 0.442). The Weiss temperature intercept is close to zero indicating that magnetic interactions between Cu(II) centers are very weak.

*Appendix A.4. Electronic Spectrum of Compound* ***1***

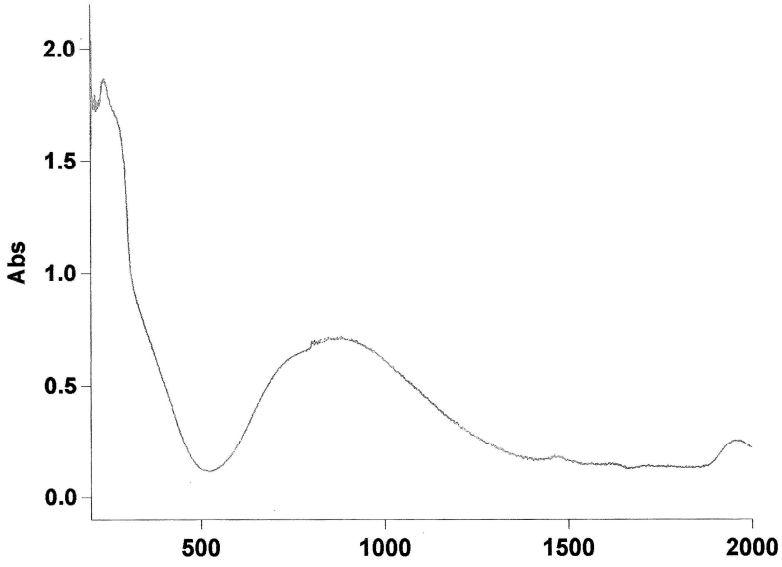


**Figure A8.** Electronic spectrum (diffuse reflectance) of compound **1** (Abs. vs: wavelength, nm.).

The asymmetric *d-d* band spectrum exhibits a maximum of absorption at 881 nm (11,350 $cm^{-1}$) with an intensity barycenter at 950 nm (10,525 $cm^{-1}$) according to the apple-greenish color of compound **1**.

For comparison, the electronic spectrum for a blue solution of the aqua-complex ion, $[Cu(H_2O)_6]^{2+}$, shows a $\nu_{max}$ near 800 nm (~12,500 $cm^{-1}$).

*Appendix A.5. Cartesian Coordinates*

**Table A6.** Model in Figure 3

| Cu | 0.00000055 | 9.13598209 | −0.00000659 |
|---|---|---|---|
| S | 1.95000055 | 10.31898209 | 2.88599341 |
| O | −1.55199945 | 8.26798209 | 0.83299341 |
| H | −1.60699945 | 8.50198209 | 1.67299341 |
| H | −1.46399945 | 7.39998209 | 0.78199341 |
| O | −1.59299945 | 5.76898209 | 0.06499341 |
| O | 4.64200055 | 5.81798209 | 2.09099341 |
| O | 5.76400055 | 6.14698209 | 4.77399341 |
| H | 6.38900055 | 6.69498209 | 4.64399341 |
| O | 0.71900055 | 10.04798209 | 2.13099341 |
| O | 3.14500055 | 10.12898209 | 2.04599341 |
| O | 2.01700055 | 9.38598209 | 4.04799341 |
| O | 1.90700000 | 11.71500000 | 3.40000000 |
| N | −0.21299945 | 3.97698209 | 0.19599341 |
| H | −0.92299945 | 3.45898209 | 0.14899341 |
| N | 1.00800055 | 2.02198209 | 0.31099341 |
| H | 1.76200055 | 1.57498209 | 0.37999341 |
| H | 0.24400055 | 1.58798209 | 0.24399341 |
| N | 2.16200055 | 4.02698209 | 0.40799341 |
| N | 1.08500055 | 7.44998209 | 0.22599341 |
| N | 2.97700055 | 6.29598209 | 0.45999341 |
| C | 1.02000055 | 3.35598209 | 0.30799341 |
| C | 1.97600055 | 5.35998209 | 0.36699341 |
| C | 0.79600055 | 6.08098209 | 0.22499341 |
| C | −0.42199945 | 5.34098209 | 0.15099341 |
| C | 2.38500055 | 7.52198209 | 0.37599341 |
| H | 2.86300055 | 8.34098209 | 0.42199341 |
| C | 4.39300055 | 6.03698209 | 0.72299341 |
| H | 4.68000055 | 5.24198209 | 0.20799341 |
| H | 4.92900055 | 6.80998209 | 0.41299341 |
| C | 4.54000055 | 7.03898209 | 2.85799341 |
| H | 3.70400055 | 7.51498209 | 2.61799341 |
| −H | 5.30400055 | 7.63198209 | 2.64799341 |
| C | 4.53600055 | 6.71398209 | 4.32899341 |
| H | 4.35800055 | 7.54198209 | 4.84099341 |
| H | 3.80100055 | 6.07898209 | 4.51699341 |
| S | −1.94999945 | 7.95198209 | −2.88600659 |
| O | 1.55200055 | 10.00298209 | −0.83300659 |
| H | 1.60700055 | 9.76998209 | −1.67300659 |
| H | 1.46400055 | 10.87098209 | −0.78200659 |
| O | 1.59300055 | 12.50198209 | −0.06500659 |
| O | −4.64199945 | 12.45298209 | −2.09100659 |
| O | −5.76399945 | 12.12398209 | −4.77400659 |
| H | −6.38899945 | 11.57698209 | −4.64400659 |
| O | −0.71899945 | 8.22298209 | −2.13100659 |
| O | −3.14499945 | 8.14198209 | −2.04600659 |
| O | −2.01699945 | 8.88498209 | −4.04800659 |
| O | −1.90699945 | 6.55698209 | −3.40000659 |

**Table A6.** *Cont.*

| | | | |
|---|---|---|---|
| N | 0.21300055 | 14.29398209 | −0.19600659 |
| H | 0.92300055 | 14.81198209 | −0.14900659 |
| N | −1.00799945 | 16.24898209 | −0.31100659 |
| H | −1.76199945 | 16.69598209 | −0.38000659 |
| H | −0.24399945 | 16.68298209 | −0.24400659 |
| N | −2.16199945 | 14.24398209 | −0.40800659 |
| N | −1.08499945 | 10.82198209 | −0.22600659 |
| N | −2.97699945 | 11.97498209 | −0.46000659 |
| C | −1.01999945 | 14.91498209 | −0.30800659 |
| C | −1.97599945 | 12.91198209 | −0.36700659 |
| C | −0.79599945 | 12.18998209 | −0.22500659 |
| C | 0.42200055 | 12.92998209 | −0.15100659 |
| C | −2.38499945 | 10.74898209 | −0.37600659 |
| H | −2.86299945 | 9.92998209 | −0.42200659 |
| C | −4.39299945 | 12.23398209 | −0.72300659 |
| H | −4.67999945 | 13.02898209 | −0.20800659 |
| H | −4.92899945 | 11.46198209 | −0.41300659 |
| C | −4.53999945 | 11.23198209 | −2.85800659 |
| H | −3.70399945 | 10.75598209 | −2.61800659 |
| H | −5.30399945 | 10.63898209 | −2.64800659 |
| C | −4.53599945 | 11.55698209 | −4.32900659 |
| H | −4.35799945 | 10.72898209 | −4.84100659 |
| H | −3.80099945 | 12.19198209 | −4.51700659 |
| O | 3.53500000 | 10.00600000 | 6.25700000 |
| H | 2.95000000 | 10.55300000 | 6.51100000 |
| H | 3.16700000 | 9.55200000 | 5.46800000 |
| O | −3.53500000 | 8.26500000 | −6.25700000 |
| H | −2.95000000 | 7.71800000 | −6.51100000 |
| H | −3.16700000 | 8.71900000 | −5.46800000 |

**Table A7.** Models in Figure 4

| (a) | | | |
|---|---|---|---|
| Cu | 0.000 | 9.136 | 0.000 |
| S | 1.950 | 10.319 | 2.886 |
| O | −1.552 | 8.268 | 0.833 |
| H | −1.607 | 8.502 | 1.673 |
| H | −1.464 | 7.400 | 0.782 |
| O | −1.593 | 5.769 | 0.065 |
| O | 4.642 | 5.818 | 2.091 |
| O | 5.764 | 6.147 | 4.774 |
| H | 6.389 | 6.695 | 4.644 |
| O | 0.719 | 10.048 | 2.131 |
| O | 3.145 | 10.129 | 2.046 |
| O | 2.017 | 9.386 | 4.048 |
| O | 1.907 | 11.715 | 3.400 |
| N | −0.213 | 3.977 | 0.196 |
| H | −0.923 | 3.459 | 0.149 |
| N | 1.008 | 2.022 | 0.311 |
| H | 1.762 | 1.575 | 0.380 |
| H | 0.244 | 1.588 | 0.244 |
| N | 2.162 | 4.027 | 0.408 |
| N | 1.085 | 7.450 | 0.226 |
| N | 2.977 | 6.296 | 0.460 |
| C | 1.020 | 3.356 | 0.308 |
| C | 1.976 | 5.360 | 0.367 |
| C | 0.796 | 6.081 | 0.225 |
| C | −0.422 | 5.341 | 0.151 |

**Table A7.** *Cont.*

| | | | |
|---|---|---|---|
| C | 2.385 | 7.522 | 0.376 |
| H | 2.863 | 8.341 | 0.422 |
| C | 4.393 | 6.037 | 0.723 |
| H | 4.680 | 5.242 | 0.208 |
| H | 4.929 | 6.810 | 0.413 |
| C | 4.540 | 7.039 | 2.858 |
| H | 3.704 | 7.515 | 2.618 |
| H | 5.304 | 7.632 | 2.648 |
| C | 4.536 | 6.714 | 4.329 |
| H | 4.358 | 7.542 | 4.841 |
| H | 3.801 | 6.079 | 4.517 |
| S | −1.950 | 7.952 | −2.886 |
| O | 1.552 | 10.003 | −0.833 |
| H | 1.607 | 9.770 | −1.673 |
| H | 1.464 | 10.871 | −0.782 |
| O | 1.593 | 12.502 | −0.065 |
| O | −4.642 | 12.453 | −2.091 |
| O | −5.764 | 12.124 | −4.774 |
| H | −6.389 | 11.577 | −4.644 |
| O | −0.719 | 8.223 | −2.131 |
| O | −3.145 | 8.142 | −2.046 |
| O | −2.017 | 8.885 | −4.048 |
| O | −1.906 | 6.556 | −3.400 |
| N | 0.213 | 14.294 | −0.196 |
| H | 0.923 | 14.812 | −0.149 |
| N | −1.008 | 16.249 | −0.311 |
| H | −1.762 | 16.696 | −0.380 |
| H | −0.244 | 16.683 | −0.244 |
| N | −2.162 | 14.244 | −0.408 |
| N | −1.085 | 10.822 | −0.226 |
| N | −2.977 | 11.975 | −0.460 |
| C | −1.020 | 14.915 | −0.308 |
| C | −1.976 | 12.912 | −0.367 |
| C | −0.796 | 12.190 | −0.225 |
| C | 0.422 | 12.930 | −0.151 |
| C | −2.385 | 10.749 | −0.376 |
| H | −2.863 | 9.930 | −0.422 |
| C | −4.393 | 12.234 | −0.723 |
| H | −4.680 | 13.029 | −0.208 |
| H | −4.929 | 11.462 | −0.413 |
| C | −4.540 | 11.232 | −2.858 |
| H | −3.704 | 10.756 | −2.618 |
| H | −5.304 | 10.639 | −2.648 |
| C | −4.536 | 11.557 | −4.329 |
| H | −4.358 | 10.729 | −4.841 |
| H | −3.801 | 12.192 | −4.517 |
| H | 7.901 | 4.003 | 3.867 |
| H | 7.245 | 3.409 | 4.980 |
| H | 6.560 | 4.557 | 4.397 |
| O | −7.129 | 14.485 | −4.204 |
| H | −7.901 | 14.268 | −3.867 |
| H | −7.245 | 14.862 | −4.980 |
| H | −6.560 | 13.714 | −4.397 |
| | (b) | | |
| Cu | 0.00000000 | 9.13600000 | 0.00000000 |
| S | 1.95000000 | 10.31900000 | 2.88600000 |
| O | −1.55200000 | 8.26800000 | 0.83300000 |
| H | −1.60700000 | 8.50200000 | 1.67300000 |
| H | −1.46400000 | 7.40000000 | 0.78200000 |
| O | −1.59300000 | 5.76900000 | 0.06500000 |
| O | 4.64200000 | 5.81800000 | 2.09100000 |

**Table A7.** *Cont.*

| | | | |
|---|---|---|---|
| O | 5.76400000 | 6.14700000 | 4.77400000 |
| H | 6.38900000 | 6.69500000 | 4.64400000 |
| O | 0.71900000 | 10.04800000 | 2.13100000 |
| O | 3.14500000 | 10.12900000 | 2.04600000 |
| O | 2.01700000 | 9.38600000 | 4.04800000 |
| O | 1.90699945 | 11.71501791 | 3.40000659 |
| N | −0.21300000 | 3.97700000 | 0.19600000 |
| H | −0.92300000 | 3.45900000 | 0.14900000 |
| N | 1.00800000 | 2.02200000 | 0.31100000 |
| H | 1.76200000 | 1.57500000 | 0.38000000 |
| H | 0.24400000 | 1.58800000 | 0.24400000 |
| N | 2.16200000 | 4.02700000 | 0.40800000 |
| N | 1.08500000 | 7.45000000 | 0.22600000 |
| N | 2.97700000 | 6.29600000 | 0.46000000 |
| C | 1.02000000 | 3.35600000 | 0.30800000 |
| C | 1.97600000 | 5.36000000 | 0.36700000 |
| C | 0.79600000 | 6.08100000 | 0.22500000 |
| C | −0.42200000 | 5.34100000 | 0.15100000 |
| C | 2.38500000 | 7.52200000 | 0.37600000 |
| H | 2.86300000 | 8.34100000 | 0.42200000 |
| C | 4.39300000 | 6.03700000 | 0.72300000 |
| H | 4.68000000 | 5.24200000 | 0.20800000 |
| H | 4.92900000 | 6.81000000 | 0.41300000 |
| C | 4.54000000 | 7.03900000 | 2.85800000 |
| H | 3.70400000 | 7.51500000 | 2.61800000 |
| H | 5.30400000 | 7.63200000 | 2.64800000 |
| C | 4.53600000 | 6.71400000 | 4.32900000 |
| H | 4.35800000 | 7.54200000 | 4.84100000 |
| H | 3.80100000 | 6.07900000 | 4.51700000 |
| S | −1.95000000 | 7.95200000 | −2.88600000 |
| O | 1.55200000 | 10.00300000 | −0.83300000 |
| H | 1.60700000 | 9.77000000 | −1.67300000 |
| H | 1.46400000 | 10.87100000 | −0.78200000 |
| O | 1.59300000 | 12.50200000 | −0.06500000 |
| O | −4.64200000 | 12.45300000 | −2.09100000 |
| O | −5.76400000 | 12.12400000 | −4.77400000 |
| H | −6.38900000 | 11.57700000 | −4.64400000 |
| O | −0.71900000 | 8.22300000 | −2.13100000 |
| O | −3.14500000 | 8.14200000 | −2.04600000 |
| O | −2.01700000 | 8.88500000 | −4.04800000 |
| O | −1.90700000 | 6.55700000 | −3.40000000 |
| N | 0.21300000 | 14.29400000 | −0.19600000 |
| H | 0.92300000 | 14.81200000 | −0.14900000 |
| N | −1.00800000 | 16.24900000 | −0.31100000 |
| H | −1.76200000 | 16.69600000 | −0.38000000 |
| H | −0.24400000 | 16.68300000 | −0.24400000 |
| N | −2.16200000 | 14.24400000 | −0.40800000 |
| N | −1.08500000 | 10.82200000 | −0.22600000 |
| N | −2.97700000 | 11.97500000 | −0.46000000 |
| C | −1.02000000 | 14.91500000 | −0.30800000 |
| C | −1.97600000 | 12.91200000 | −0.36700000 |
| C | −0.79600000 | 12.19000000 | −0.22500000 |
| C | 0.42200000 | 12.93000000 | −0.15100000 |
| C | −2.38500000 | 10.74900000 | −0.37600000 |
| H | −2.86300000 | 9.93000000 | −0.42200000 |
| C | −4.39300000 | 12.23400000 | −0.72300000 |
| H | −4.68000000 | 13.02900000 | −0.20800000 |
| H | −4.92900000 | 11.46200000 | −0.41300000 |
| C | −4.54000000 | 11.23200000 | −2.85800000 |
| H | −3.70400000 | 10.75600000 | −2.61800000 |

**Table A7.** *Cont.*

| | | | |
|---|---|---|---|
| H | −5.30400000 | 10.63900000 | −2.64800000 |
| C | −4.53600000 | 11.55700000 | −4.32900000 |
| H | −4.35800000 | 10.72900000 | −4.84100000 |
| H | −3.80100000 | 12.19200000 | −4.51700000 |
| O | 7.12900000 | 3.78600000 | 4.20400000 |
| H | 7.90100000 | 4.00300000 | 3.86700000 |
| H | 7.24500000 | 3.40900000 | 4.98000000 |
| H | 6.56000000 | 4.55700000 | 4.39700000 |
| O | −4.65114130 | 15.47000153 | −0.72450806 |
| H | −4.64493571 | 15.98253054 | −1.42730071 |
| H | −4.75966993 | 15.95560247 | −0.01024322 |
| H | −3.80193352 | 15.01038869 | −0.57267532 |
| | (c) | | |
| Cu | 0.000 | 9.136 | 0.000 |
| S | 1.950 | 10.319 | 2.886 |
| O | −1.552 | 8.268 | 0.833 |
| H | −1.607 | 8.502 | 1.673 |
| H | −1.464 | 7.400 | 0.782 |
| O | −1.593 | 5.769 | 0.065 |
| O | 4.642 | 5.818 | 2.091 |
| O | 5.764 | 6.147 | 4.774 |
| H | 6.389 | 6.695 | 4.644 |
| O | 0.719 | 10.048 | 2.131 |
| O | 3.145 | 10.129 | 2.046 |
| O | 2.017 | 9.386 | 4.048 |
| O | 1.907 | 11.715 | 3.400 |
| N | −0.213 | 3.977 | 0.196 |
| H | −0.923 | 3.459 | 0.149 |
| N | 1.008 | 2.022 | 0.311 |
| H | 1.762 | 1.575 | 0.380 |
| H | 0.244 | 1.588 | 0.244 |
| N | 2.162 | 4.027 | 0.408 |
| N | 1.085 | 7.450 | 0.226 |
| N | 2.977 | 6.296 | 0.460 |
| C | 1.020 | 3.356 | 0.308 |
| C | 1.976 | 5.360 | 0.367 |
| C | 0.796 | 6.081 | 0.225 |
| C | −0.422 | 5.341 | 0.151 |
| C | 2.385 | 7.522 | 0.376 |
| H | 2.863 | 8.341 | 0.422 |
| C | 4.393 | 6.037 | 0.723 |
| H | 4.680 | 5.242 | 0.208 |
| H | 4.929 | 6.810 | 0.413 |
| C | 4.540 | 7.039 | 2.858 |
| H | 3.704 | 7.515 | 2.618 |
| H | 5.304 | 7.632 | 2.648 |
| C | 4.536 | 6.714 | 4.329 |
| H | 4.358 | 7.542 | 4.841 |
| H | 3.801 | 6.079 | 4.517 |
| S | −1.950 | 7.952 | −2.886 |
| O | 1.552 | 10.003 | −0.833 |
| H | 1.607 | 9.770 | −1.673 |
| H | 1.464 | 10.871 | −0.782 |
| O | 1.593 | 12.502 | −0.065 |
| O | −4.642 | 12.453 | −2.091 |
| O | −5.764 | 12.124 | −4.774 |
| H | −6.389 | 11.577 | −4.644 |
| O | −0.719 | 8.223 | −2.131 |
| O | −3.145 | 8.142 | −2.046 |

**Table A7.** *Cont.*

| | | | |
|---|---|---|---|
| O | −2.017 | 8.885 | −4.048 |
| O | −1.906 | 6.556 | −3.400 |
| N | 0.213 | 14.294 | −0.196 |
| H | 0.923 | 14.812 | −0.149 |
| N | −1.008 | 16.249 | −0.311 |
| H | −1.762 | 16.696 | −0.380 |
| H | −0.244 | 16.683 | −0.244 |
| N | −2.162 | 14.244 | −0.408 |
| N | −1.085 | 10.822 | −0.226 |
| N | −2.977 | 11.975 | −0.460 |
| C | −1.020 | 14.915 | −0.308 |
| C | −1.976 | 12.912 | −0.367 |
| C | −0.796 | 12.190 | −0.225 |
| C | 0.422 | 12.930 | −0.151 |
| C | −2.385 | 10.749 | −0.376 |
| H | −2.863 | 9.930 | −0.422 |
| C | −4.393 | 12.234 | −0.723 |
| H | −4.680 | 13.029 | −0.208 |
| H | −4.929 | 11.462 | −0.413 |
| C | −4.540 | 11.232 | −2.858 |
| H | −3.704 | 10.756 | −2.618 |
| H | −5.304 | 10.639 | −2.648 |
| C | −4.536 | 11.557 | −4.329 |
| H | −4.358 | 10.729 | −4.841 |
| H | −3.801 | 12.192 | −4.517 |
| O | 7.129 | 3.786 | 4.204 |
| H | 7.901 | 4.003 | 3.867 |
| H | 7.245 | 3.409 | 4.980 |
| H | 6.560 | 4.557 | 4.397 |
| O | −7.129 | 14.485 | −4.204 |
| H | −7.901 | 14.268 | −3.867 |
| H | −7.245 | 14.862 | −4.980 |
| H | −6.560 | 13.714 | −4.397 |
| C | 9.887 | 0.000 | 9.991 |
| S | 7.937 | 1.183 | 7.106 |
| O | 11.439 | −0.867 | 9.159 |
| H | 11.494 | −0.634 | 8.318 |
| H | 11.351 | −1.736 | 9.209 |
| O | 11.480 | −3.366 | 9.927 |
| O | 5.245 | −3.317 | 7.900 |
| O | 4.123 | −2.988 | 5.217 |
| H | 3.498 | −2.441 | 5.347 |
| O | 9.168 | 0.912 | 7.860 |
| O | 6.742 | 0.993 | 7.946 |
| O | 7.870 | 0.250 | 5.943 |
| O | 7.980 | 2.579 | 6.592 |
| N | 10.100 | −5.158 | 9.795 |
| H | 10.810 | −5.677 | 9.842 |
| N | 8.880 | −7.114 | 9.680 |
| H | 8.125 | −7.561 | 9.612 |
| H | 9.644 | −7.548 | 9.747 |
| N | 7.725 | −5.108 | 9.583 |
| N | 8.802 | −1.686 | 9.765 |
| N | 6.910 | −2.839 | 9.532 |
| C | 8.867 | −5.780 | 9.683 |
| C | 7.911 | −3.776 | 9.624 |
| C | 9.091 | −3.054 | 9.766 |
| C | 10.309 | −3.795 | 9.841 |
| C | 7.503 | −1.613 | 9.615 |

**Table A7.** *Cont.*

| | | | |
|---|---|---|---|
| H | 7.024 | −0.795 | 9.570 |
| C | 5.494 | −3.099 | 9.269 |
| H | 5.207 | −3.894 | 9.783 |
| H | 4.958 | −2.326 | 9.578 |
| C | 5.348 | −2.097 | 7.134 |
| H | 6.183 | −1.621 | 7.374 |
| H | 4.583 | −1.504 | 7.344 |
| C | 5.352 | −2.421 | 5.662 |
| H | 5.529 | −1.593 | 5.150 |
| H | 6.087 | −3.057 | 5.475 |
| S | 11.837 | −1.183 | 12.877 |
| O | 8.335 | 0.867 | 10.824 |
| H | 8.280 | 0.634 | 11.665 |
| H | 8.424 | 1.736 | 10.773 |
| O | 8.295 | 3.366 | 10.056 |
| O | 14.529 | 3.317 | 12.082 |
| O | 15.651 | 2.988 | 14.765 |
| H | 16.276 | 2.441 | 14.635 |
| O | 10.606 | −0.912 | 12.122 |
| O | 13.032 | −0.993 | 12.037 |
| O | 11.904 | −0.250 | 14.040 |
| O | 11.794 | −2.579 | 13.391 |
| N | 9.674 | 5.158 | 10.187 |
| H | 8.964 | 5.677 | 10.141 |
| N | 10.895 | 7.114 | 10.302 |
| H | 11.649 | 7.561 | 10.371 |
| H | 10.131 | 7.548 | 10.236 |
| N | 12.049 | 5.108 | 10.400 |
| N | 10.972 | 1.686 | 10.218 |
| N | 12.865 | 2.839 | 10.451 |
| C | 10.907 | 5.780 | 10.300 |
| C | 11.863 | 3.776 | 10.358 |
| C | 10.683 | 3.054 | 10.216 |
| C | 9.466 | 3.795 | 10.142 |
| C | 12.272 | 1.613 | 10.368 |
| H | 12.750 | 0.795 | 10.413 |
| C | 14.281 | 3.099 | 10.714 |
| H | 14.567 | 3.894 | 10.200 |
| H | 14.816 | 2.326 | 10.404 |
| C | 14.427 | 2.097 | 12.849 |
| H | 13.592 | 1.621 | 12.609 |
| H | 15.191 | 1.504 | 12.639 |
| C | 14.423 | 2.421 | 14.320 |
| H | 14.245 | 1.593 | 14.832 |
| H | 13.688 | 3.057 | 14.508 |
| O | 12.646 | −3.786 | 15.779 |
| H | 11.873 | −4.003 | 16.115 |
| H | 12.530 | −3.409 | 15.003 |
| H | 13.214 | −4.557 | 15.586 |
| O | 2.759 | −5.350 | 5.788 |
| H | 1.986 | −5.132 | 6.124 |
| H | 2.643 | −5.726 | 5.012 |
| H | 3.327 | −4.579 | 5.594 |

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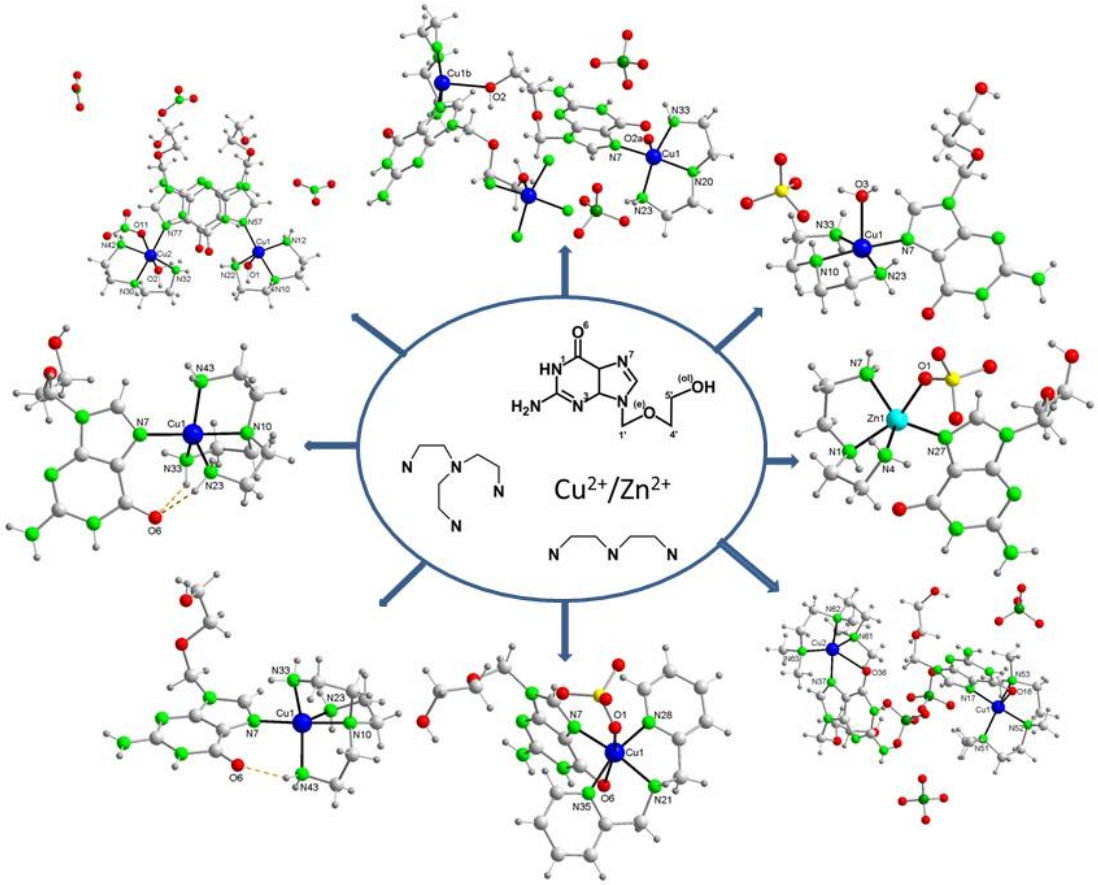
## 5.5. MANUSCRIPT: COPPER(II) CHELATES WITH DIEN, TREN OR RELATED POLYAMINES AS EFFICIENT RECEPTORS FOR ACYCLOVIR.

### SYNOPSYS ENTRY

Crystal structures of seven $Cu^{II}$-polyamine-acv and a $Zn^{II}$-dien-acv complexes emphasize the cooperation of the metal-N7(acv) bond and one or two N-H···O6 interligand interaction. Hindering such interaction acv plays an asymmetric N7,O6-chelator role.




### RESEARCH HIGHLIGHTS

- Cu(II) or Zn(II) chelates with dien or trien are suitable receptors for acyclovir (acv).
- Cu-N7(acv) bond is assisted by a (primary)N-H···O6(acv) interaction.
- N(terminal)-blocked dien-Cu chelates bind acv as a N7,O6- asymmetric chelator.
- But (dien)Zn-N7(acv) bond cooperates with the (secondary)N-H···O6 interaction.

## RESUMEN

Con la finalidad de comprender mejor el modo de reconocimiento molecular de aciclovir (acv), se hicieron reaccionar diferentes oxosales de cobre(II) y zinc(II) (nitrato, sulfato o perclorato), poliaminas quelantes tridentadas (dien, bpa, pmdta) o tetradentadas trípode (trien) y acv para obtener los siguientes compuestos:

$[Cu(dien)(N7\text{-}acv)(H_2O)]SO_4\cdot 1.25MeOH\cdot 0.5H_2O$ (1)

$[Cu(dien)(N7\text{-}acv)(H_2O)\cdot Cu(dien)(N7\text{-}acv)(H_2O)(NO_3)](NO_3)_3\cdot 3H_2O$ (2)

$\{[Cu(dien)(\mu_2\text{-}N7,O(N9\text{-side chain})\text{-}acv)](ClO_4)_3\}_n$ (3)

$[Zn(dien)(N7\text{-}acv)(SO_4)]$ (4)

$[Cu(pmdta)(N7,O6\text{-}acv)](ClO_4)_2\cdot H_2O$ (5)

$[Cu(bpa)(N7,O6\text{-}acv)(SO_4)]\cdot 6H_2O$ (6)

$[Cu(tren)(N7\text{-}acv)](NO_3)_2$ (7)

$[Cu(tren)(N7\text{-}acv)](ClO_4)_2$ (8)

(dien = dietilentriamina, tren = tris(2-aminoetil)amina, pmdta = bis-(2-(dimetilamino)-etil)metilamina), bpa = bis-(2-picolil)amina, pmdta = *N*,*N*′,*N*′′,*N*′′-pentametildietile-notriamina).

Todos los compuestos fueron estudiados por métodos de difracción de rayos X de cristales únicos. Siete de estos compuestos ternarios exhiben un enlace de coordinación Cu-N7 o Zn-N7 mientras que en el compuesto 3 se encontró el inusual modo puente $\mu_2$-N7, O (ol, N9-cadena lateral). El modo de reconocimiento molecular de los compuestos 1-3, 7 y 8 consiste en la cooperación del enlace Cu-N7(acv) con una interacción intra-molecular (primario/terminal)N-H···O6(acv) (el cual es "bifurcado" en el compuesto 8). En el compuesto 4, el enlace Zn-N7(acv) presenta un refuerzo mediante una interacción intra-molecular (secundario)N-H···O6(acv). Esta última interacción, aunque no ocurre, sería posible en los compuestos 5 y 6, los cuales presentan un modo de reconocimiento molecular quelante asimétrico N7,O6-acv con el O6 actuando como átomo dador de Cu(II) apical/distal.

## COPPER(II) CHELATES WITH DIEN, TREN OR RELATED POLYAMINES AS EFFICIENT RECEPTORS FOR ACYCLOVIR.

*Inmaculada Pérez-Toro[a], Alicia Domínguez-Martín[a,b,*], Duane Choquesillo-Lazarte[b], M. Eugenia García-Rubiño[a], Josefa M. González-Pérez[a], Alfonso Castiñeiras[d], Juan Niclós-Gutiérrez[a]*

[a] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain. Email: adominguez@ugr.es
[b, †] Department of Chemistry, University of Zurich, Winterthurestrasse 190, CH-8057, Zurich, Switzerland.
[c] Laboratorio de Estudios Cristalográficos, IACT, CSIC-Universidad de Granada, Av. de las Palmeras 4, E-18100 Armilla, Granada, Spain
[d] Department of Inorganic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

ABSTRACT

In order to further understand the metal-binding patterns (MBP) of acyclovir (acv), copper(II) and zinc(II) oxysalts (nitrate, sulfate or perchlorate), tridentate (dien, bpa, pmdta) or tripodal-tetradentate (trien) chelating-polyamines and acyclovir (acv) were reacted to obtain the following compounds: [Cu(dien)(N7-acv)($H_2O$)]$SO_4$·1.25MeOH·0.5$H_2O$ (1), [Cu(dien)(N7-acv)($H_2O$)·Cu(dien)(N7-acv)($H_2O$)($NO_3$)]($NO_3$)$_3$·3$H_2O$ (2), {[Cu(dien)($\mu_2$-N7,O(N9-side chain)-acv)]($ClO_4$)$_3$}$_n$ (3), [Zn(dien)(N7-acv)($SO_4$)] (4), [Cu(pmdta)(N7,O6-acv)]($ClO_4$)$_2$·$H_2O$ (5), [Cu(bpa)(N7,O6-acv)($SO_4$)]·6$H_2O$ (6) [Cu(tren)(N7-acv)]($NO_3$)$_2$ (7), [Cu(tren)(N7-acv)]($ClO_4$)$_2$ (8), (dien = diethylenetriamine, tren = tris(2-aminoethyl)amine, pmdta = bis-(2-(dimethylamino)ethyl)methylamine), bpa = bis-(2-picolyl)amine, and pmdta =*N*,*N*,*N*′,*N*′,*N*″-pentamethyl-diethylenetriamine). All compounds were studied by single-crystal X-ray diffraction methods. Seven ternary complexes exhibit a Cu-N7 or Zn-N7 coordination bond while the unusual bridging $\mu_2$-N7,O(ol, N9-side chain) mode is found in compound 3. The metal binding pattern of compounds 1-3, 7 and 8 consists in the cooperation of the Cu-N7(acv) bond with an intra-molecular (primary/terminal)N-H···O6(acv) interaction (which is 'bifurcated' in 8). In 4, the Zn-N7(acv) bond is reinforced with the intra-molecular (secondary)N-H···O6(acv) interaction. This latest interaction is possible but not found in 5 or 6, which exhibit an asymmetric chelating-N7,O6-acv MBP with O6 acting as apical/distal Cu(II) donor atom.

## Introduction

Acyclovir (also called acycloguanosine, hereafter acv) is one of the most relevant antiviral drugs used worldwide for the treatment of *Herpesviridae* infections. The similarities of this molecule to the natural nucleobase guanine (Scheme 1), besides the chemical nature of the acv-N9 pendant arm, encourage the study of the metal binding abilities of this antiviral agent. To date, the available structural information reveals that the N7 atom is by far the preferred donor atom of acv to bind metal ions. For instance, with the sole exception of the outer-sphere complex (H(N7)acv)trans-[$Ru^{II}Cl_4$(O-dmso)(NO)] [1], the metal binding patterns (MBP) of acv can be summarized as follows: *(MBP-1)* Formation of a single M-N7 bond, reported in the compounds cis-[$Pt(NH_3)_2(acv)_2]Cl_2\cdot 2H_2O$ [2], trans-[$Cu(acv)_2(H_2O)_3](NO_3)_2\cdot H_2O$ [3] and $\{[Cu(IDA)(acv)]\cdot 2CH_3OH\}_n$ [4] (IDA = iminodiacetate anion). *(MPB-2)* Cooperation between a M-N7(acv) bond and an intra-molecular interligand H-bonding interaction such as A-H···O6(acv) with A = N or O [4-13]. This latter mode is featured, among others, in the square-planar molecular complex $[Cu(glygly)(acv)]\cdot H_2O$ [4] where the terminal primary amino group of the glycylglycinate chelator participates in the interligand N-H···O6(acv) interaction. Note that the reinforcement of the coordination bond was not possible in the above referred polymer with IDA, since the chelator did not provide appropriate H-donors [4]. MBP-2 has also been observed in metal complexes with the $[Cu(trien)]^{2+}$ chelate. In these compounds the N7(acv) is located at the apical/distal site within the 4+1 coordination polyhedron, assisted by an intra-molecular H-bonding interaction [11]. The cooperation of the Cu-N7(acv) bond with an (aqua)O-H···O6(acv) has been also reported by our research group for the oxonium derivative $(H_3O)_2[Cu(acv)_2(H_2O)_2(SO_4)_2]\cdot 2H_2O$ [12]. Here, the sulfate anions were driven to the trans-apical/distal sites in the centrosymmetric 4+2 coordination

polyhedron of the complex anion. A peculiar case is found in the structure of $[Pt(en)(acv)_2]SO_4 \cdot 2.5H_2O$ [13] where MBP-1 and MBP-2 modes are featured in the complex cation. *(MBP-3)* I. Turel et al. reported the compound *trans*-$[Cu(acv)_2(H_2O)_2](NO_3)_2$ [14] where acyclovir exhibits the asymmetrical chelating-N7,O6 mode. The O-aqua and N7-acv atoms, from both acv ligands, are the four closest donors of the Cu(II) center. In addition, both O6-acv donors occupy the *trans*-apical/distal coordination sites in the elongated octahedral coordination polyhedron, type 4+2. Relevant bond distances are Cu-N7 2.004(2) Å and Cu-O6 2.698(2) Å. In this compound, the Cu-O6 distance is shorter than the sum of Van der Waals radii of Cu (1.40 Å) and O (1.50 Å) atoms. In 2016, our research group reported a series of ternary Cu(II) complexes with $NO_2$+S(thioether or disulfide) chelators where this MBP was also found for acv [15]. Nevertheless, the Cu···O6 contacts here were quite longer, thus being considered as a very weak inter-atomic interaction or just a simple contact. *(MBP-4)* In the polymer $\{Cd(\mu_2\text{-}Cl)_2(\mu_2\text{-}N7,O(ol)\text{-}acv)] \cdot H_2O\}_n$ [6] the synthetic nucleoside displays a bridging mode that involves the Cd-N7 bond (2.402(2) Å) and the Cd-O(ol) bond (2.305(1) Å). The Cd-N7 bond of one Cd center cooperates with an acv-O(ol)-H···O6-acv H-bond (2.635 Å, 175.0º), with the acceptor being an acv ligand from the adjacent unit in the polymeric chain. This interligand interaction is intermolecular and therefore different from that above referred as MBP-2.

Taken together previous works remark the suitability of N7-acv as the preferred donor atom for metal binding and the possibility of cooperation of this M-N7 coordination bond with an appropriate intra-molecular interligand H-bonding interaction, using O6-acv as acceptor [4-12]. Our research group has been recently devoted to provide a clear picture of acv metal binding abilities [4, 11]. Thus, the main

aim of this work is to deepen on the role of copper(II) chelates with tridentate and tripodal tetradentate amines as potential acv receptors.

**Experimental Section**

*Materials.* Metal oxysalts ($Cu(NO_3)_2 \cdot 3H_2O$, $Cu(ClO_4) \cdot 6H_2O$, $CuSO_4 \cdot 5H_2O$ and $ZnSO_4 \cdot 7H_2O$) and acv were purchased already purified from various commercial sources, e.g. Merk (former Sigma-Aldrich) and used as received.

*Synthesis and crystallization of metal complexes.* The reported compounds were crystallized in aqueous-methanol solutions. First, 1 mmol of the metal oxysalt was dissolved in 70 ml of MeOH. While stirring, 1 mmol of the corresponding polyamine dissolved in 10 ml of MeOH was drop-wise added. To the resulting solution, 1 mmol of acv (225 mg) was added, either as small powder fractions or dissolved in 80 mL MeOH. The reaction mixture (in some cases with certain turbidity) was carefully filtered without vacuum on a crystallization flask, which is placed for diethyl ether diffusion, used as anti-solvent.

Regardless of the small amounts of water introduced by the hydrated metal oxysalts during the synthesis, methanol was selected as the preferred solvent for crystallization due to its polarity [4]. Eventually, the formation of colorless crystal was observed. When appearing, these crystals were removed by filtration without vacuum and the mother liquors were placed in a new crystallization flask, again for diethyl ether diffusion. Colorless crystals were identified as acv by FT-IR spectroscopy. A sharp absorption band observed at 1390 $cm^{-1}$ was used for identification linked to the ν(C-O) stretching mode and the contribution of the δ(O-H) in-plane-deformation of the primary alcohol moiety in the acyclic N9-side-chain. Note that this band is rather sensitive to coupling effects. Well-shaped deep-blue or purple crystals of the novel compounds (1-

7) and colorless crystals of the Zn compound (8) were formed with the diffusion of diethyl ether. However, these compounds can be re-dissolved in methanol or 10:90 water-methanol mixture and recrystallized by diffusion of $Et_2O$. In such case, the FT-IR spectra of the compounds shows the above referred band, related to acv, slightly shifted towards 1385 $cm^{-1}$ (e.g. 1384 $cm^{-1}$ in the spectrum of the colorless Zn derivative, 8).

*Crystallography.* Diffraction data were obtained at 100(1) K, using Bruker X8 Kappa APEXII (compounds **1**, **2** and **6**), Bruker Smart CCD-1000 (compounds **3**, **4**, and **5**) or Bruker D8 Venture (compounds **7** and **8**) diffractometers from crystals mounted on glass fibers. Data were corrected for Lorentz and polarization effects and for absorption following multi-scan [16] types. The structures were solved by direct methods using the program SHELXS-97, [17] which revealed the positions of all non-hydrogen atoms. These were refined on F2 by a full-matrix least-squares procedure using anisotropic displacement parameters [17]. All hydrogen atoms were located in difference maps, and the positions of O-H and N-H hydrogen atoms were refined (others were included as riders); the isotropic displacement parameters of H atoms were constrained to 1.2 Ueq of the carrier atoms. Molecular graphics were generated with PLATON [18] and DIAMOND [19]. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 1544627-1544634. This information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44 1223 336 033; email: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

## Results and discussion

### M(II)-dien-acv complexes (M = Cu or Zn)

*[Cu(dien)(N7-acv)($H_2O$)]$SO_4$·1.25MeOH·0.5$H_2O$ (**1**)*

The crystal structure of this compound belongs to the monoclinic system, space group I2/a. The solution was refined to a final $R_1$ value = 0.066. The copper(II) atom exhibits a distorted square-base pyramidal coordination (type 4+1) in the complex cation [Cu(dien)(N7-acv)($H_2O$)]$^{2+}$. The Cu-O(aqua) apical/distal bond is moderately long (2.259(3) Å). The trans-basal coordination angles lead to an Addison-Reedijk parameter of $\tau = 0.18$. The Cu-N7(acv) coordination bond (1.994(4) Å) is reinforced by the intra-molecular interligand interaction (dien)N23-H(23A9···O6(acv) (2.990(5) Å, 144.4º), involving a primary amino N-H group from the chelating triamine dien (Fig. 1).

In the crystal, additional H-bonds connect complex cations and sulfate anions in a 3D array, building hydrophobic channels parallel to the *a* axis with disordered solvents (methanol and water) inside, which are H-bonded between them and weakly lodge. Furthermore, pairs of five-membered rings of acv ligands build π,π-stacking interactions (inter-centroid distance $d_{c-c}$ = 3.48 Å, interplanar distance $d_{\pi-\pi}$ 3.40 Å, $\alpha$ = 4.54º, slipping angles $\beta$ or $\gamma$ = 12.92º or 12.00º).

*[Cu(dien)(N7-acv)($H_2O$)·Cu(dien)(N7-acv)($H_2O$)($NO_3$)]($NO_3$)$_3$·3$H_2O$ (**2**).*

This compound crystallizes in the triclinic system, space group P-1 (final $R_1$ 0.041). In the asymmetric unit, two non-equivalent Cu(II) complex units are present: [Cu(dien)(N7-acv)($H_2O$)] (2-A) and [Cu(dien)(N7-acv)($H_2O$)($NO_3$)] (2-B), differing in the coordination number of the metal atoms (Fig. 2). Complex 2-A exhibits a typical elongated square-base pyramidal geometry (type 4+1). Trans-basal coordination angles $\theta$(N10-Cu1-N57) > $\varphi$(N12-Cu1-N22) yield a value of the Addison-Reedijk parameter $\tau$

= (θ-φ)/60 = 0.169. On the other hand, complex 2-B shows an asymmetric elongated octahedral coordination polyhedron (type 4+1+1), with a rather long Cu-O(nitrate) bond distance (2.850(2) Å). This value is close to the sum of the Van der Waals radii (2.90 Å), being 1.40 Å for Cu and 1.50 Å for O atoms. According to the influence of the coordination number in the bond lengths, the Cu-O(aqua apical/distal) bond length is longer for Cu2 (Cu2-O2, 2.310(2) Å) than for Cu1 (Cu1-O1 2.230(2) Å).

In both complex units, the tridentate chelator dien adopts a *mer*-conformation. The Cu-N7(acv) bonds show almost identical bond length distances, within the experimental error (Cu1-N57 2.060(2) and Cu2-N77 2.059(2) Å). Likewise, both non-equivalent complex cations (2-A and 2-B) reinforce the Cu-N7(acv) bond with an intra-molecular interligand interaction (dien)N-H···O6(acv), namely N22-H22D···O56 (2.785(3) Å,148.1º) in 2-A and N32-H32D···O76 (2.839(3) Å, 139.4º) in 2-B. For these complexes, with unidentate N7-acv ligands, the dihedral angle between the mean plane defined by the four closest N-donors and the corresponding guanine moiety of the acv ligand is 26.77º for 2-A and 33.75º for 2-B.

Many other inter-molecular H-bonds contribute to the stability of the crystal. Additional multi-π,π-staking interactions are present along the *a* axis and connect alternating six-membered heterocyclic ring of acv ligands from 2-A and 2-B complexes (inter-centroid distance $d_{c-c}$ = 3.50 Å, inter-planar distance $d_{\pi-\pi}$ ~3.40 Å, α 4.66º, slipping angles β or γ = 16.12º or 16.48º, symmetry code -1+x,y,z and $d_{c-c}$ = 3.62 Å, inter-planar distance $d_{\pi-\pi}$ ~3.50 Å, α 4.66º, slipping angles β or γ = 16.48º or 11.90º, symmetry code x,y,z, respectively).

*{[Cu(dien)(μ$_2$-N7,O(ol)-acv)](ClO$_4$)$_2$}$_n$* ***(3)***

This polymeric compound crystallizes in the monoclinic system, space group $P2_1/c$ (final R1 0.039). The copper(II) center shows a square-base pyramidal geometry (Fig. 3), where the *mer*-dien tridentate chelator and the N7-acv donor atom provide the four shortest Cu-N bonds (~2.00 Å). The apical/distal donor is an O(ol) atom from the acv-N9-pendant arm that belongs to the adjacent complex unit within the polymeric chain (Cu-O(ol) 2.295(2) Å). The trans-basal coordination angles lead to an Addison- Reedijk parameter of $\sigma = 0.175$. The bridging role of acv ligands in the polymer as well as the *mer*-conformation of dien ligand does not preclude the cooperation of the Cu-N7(acv) bond with a (dien)N33-H33B···O6(acv) H-bonding interaction (2.898(3) Å, 148.1º). Note that, in this case, an open dihedral angle (55.77º) between the mean basal plane of copper(II) coordination and the purine moiety of acv is observed.

Compound **3** consist of zigzag polymeric chains of μ-N7,O(ol)-acv ligands running parallel to the *b* axis and perchlorate counter-anions. No π,π-stacking interaction is observed in the crystal, built by many N-H···O and some O(ol)-H···O H-bonding interactions that connect the polymeric acv chains with the perchlorate anions in a 3D network.

*[Zn(dien)(N7-acv)(SO$_4$)]* ***(4)***

In contrast to the previously reported Cu(II)-dien-acv compounds (**1**-**3**), this zinc(II) complex has a molecular nature. It crystallizes in the monoclinic system, space group Cc (final $R_1$ 0.032). The filled $3d^{10}$ electronic structure of Zn(II) determine the coordination polyhedron to be a distorted trigonal bipyramide (Fig. 4). The metal binding pattern of acv in this compound consist of a coordination bond Zn1-N27(acv) in cooperation with the intra-molecular interligand interaction (dien)N1-H1···O26(acv).

The two primary amino N atoms of dien, N4 and N7, and the N27(acv) atom show M-N bond distances close to 2 Å while the secondary N1-dien atom and an O-sulfate atom occupy the trans-apical sites with unequal bond distances (Zn-N1(dien) 2.195(4) Å > Zn-O1(sulfate) 2.098(3) Å, O1-Zn-N1 158.73º). The Zn-O(sulfate) bond is shorter than the Zn-N1(dien) bond due to the anionic nature of the trans-sulfate anion and the implication of the N1(secondary amino) in the above referred intra-molecular H-bonding interaction.

The crystal consists of a 3D H-bonded network. It should be noted that the O(ol)-H group of acv is disordered in two positions. Among the H-bonding network, there is a rather unusual inter-molecular interaction (amino primary dien)N7-H7A···O31(ether-acv) (3.010(5) Å, 167.6º). No π,π-stacking interactions contribute to the crystal packing of this compound.

**Cu(II)-acv complexes with N-blocked-dien analogs.**

*[Cu(pmdta)(N7-O6-acv)]$(ClO_4)_2$·$H_2O$ (**5**)*

The methylation of all amino groups in diethylenetriamine affords the ligand *N*,*N*,*N*′,*N*′,*N*″-pentamethyl-diethylenetriamine. Interestingly, the pmdta ligand cannot build intra-molecular interligand interaction type (chelating amine)N-H···O6(acv), as reported in the previous metal complexes. Single crystals of compound [Cu(pmdta)(N7-O6-acv)]$(ClO_4)_2$·$H_2O$ (**5**) were isolated and its structure solved in the triclinic system, space group P-1 (final $R_1$ = 0.060). The asymmetric unit contains twice the formula of the compound, with two non-equivalent but very similar complex cations $[Cu(pmdta)(N7\text{-}O6\text{-}acv)]^{2+}$. The copper(II) atom exhibits a distorted square-base pyramidal coordination, where pmda fulfill three of the four closest Cu(II) basal sites. The remaining basal coordination site is occupied by the N7 atom of acv while the O6-

acv exocyclic atom satisfies the apical/distal position of the 4+1 coordination polyhedron (Fig. 5). The metal binding pattern of acv in this compound can be described as an asymmetric N7,O6-acv chelating mode, due to the marked difference in bond lengths: Cu-N7(acv) 1.994(3) Å << Cu-O6(acv) 2.663(3) or 2.695(3) Å. The distal coordination of the hard Pearson O6-acv donor yields interatomic distances shorter than the sum of Van der Waals radii of Cu and O (2.9 Å). To display such chelating role, the guanine moiety of acv lies perpendicular to the mean basal coordination plane, P[4N], being the corresponding dihedral angles of 88.69 or 87.98º.

*[Cu(bpa)(N7,O6-acv)($SO_4$)]·6$H_2O$ (**6**)*

The crystal of [Cu(bpa)(N7,O6-acv)($SO_4$)]·6$H_2O$ (**6**) crystallizes in the monoclinic system, space group $P2_1/n$ (final $R_1$ = 0.039). In the complex molecule, the metal exhibits an asymmetrical elongated octahedral coordination, type 4+1+1 (Fig. 6). The tridentate ligand bis-(2-picolyl)amine adopts an expected *mer*-conformation, occupying three of the four closest coordination sites to the metal center. The Cu-N7(acv) coordination bond completes the coordination plane. As described in compound **5**, the guanine moiety of the acv ligand falls nearly perpendicular to the mean plane P[N4] (dihedral angle of 88.84º). That favors the asymmetrical N7,O6-chelating role of the acv and precludes the cooperation of the Cu-N7(acv) bond with an intra-molecular (bpa)N-H···O6(acv) interaction. Interestingly, the sulfate anion is displaced to the other apical/distal coordination site. In this case, the relatively short Cu-O(sulfate) bond enlarge the trans-distal Cu-O(6) to a value of 2.828(2) Å, close to the sum (2.90 Å) of Van der Waals radii of Cu (1.40 Å) and O (1.50 Å) atoms. This is in contrast to compound **5** where the asymmetrical chelating role N7,O6-acv shows Cu-O6(acv) distances of about 2.7 Å. The structure of the novel compound **6** can be compared to

that of recently reported with formula $[Cu(bpa)(H_3CCN)(ClO_4)]ClO_4$ [20] where N-acetonitrile and perchlorate ligands play the roles of N7-acv and sulfate in compound **6**. The crystal of **6** shows a 1D intermolecular multi-π,π-stacking system involving the pyridine moieties of bpa ligands with the six-membered rings of adjacent molecules. These interactions build chains of complex molecules running parallel to the *b* axis, with the following parameters: inter-centroid distance $d_{c\text{-}c}$ 3.47 Å, inter-planar dihedral angle α 8.7º, slipping angles β or γ 12.6 or 16.6º, averaged inter-planar distance $d_{\pi\text{-}\pi}$ 3.35 Å. Additional H-bonds help to build the 3D network.

**Cu(II)-tren-acv complexes**

Two closely related ternary Cu(II)-tren-acv complexes have been structurally characterized with the tripodal-tetradentate tris(2-aminoethyl)amine ligand:

*[Cu(tren)(N7-acv)]$(NO_3)_2$ (7)*

Compound **7** crystallizes in the monoclinic system, space group $P2_1/c$ (final $R_1$ = 0.078). In the complex cation, the copper(II) atom is $N_5$-five coordinated. The tren ligand form three rather similar Cu-N bonds of ~ 2.05 Å and one long Cu1-N23 (2.15 Å) bond. The shortest coordination bond is Cu1-N7(acv) (Fig. 7). This coordination bond is reinforced by an intra-molecular interligand interaction (amino primary tren)N-H···O6(acv). The trans-basal angles N7-Cu1-N10 and N33-Cu1-N43 yield an Addison-Reedijk parameter τ = 0.75, consistent with a distorted trigonal bipyramidal coordination, with the amino tertiary N10(tren) and the N7(acv) atoms acting as trans-apical donors.

In the crystal of **7**, pairs of symmetry related complex cations stack the guanine moieties of their acv ligands in an antiparallel manner. This π,π-interaction is featured according to the following parameters: inter-centroid distance $d_{c\text{-}c}$ 3.48 Å, inter-planar

dihedral angle α 0.78º, slipping angles β or γ 14.03º or 14.57º, averaged inter-planar distance $d_{\pi-\pi}$ 3.37 Å. Many H-bonding interactions link these pairs of staked cations in a 3D network.

*[Cu(tren)(N7-acv)]($ClO_4$)$_2$ (**8**)*

Compound **8** was also crystallized in the monoclinic system, space group $P2_1/c$ (final $R_1$ = 0.037). The coordination center of this compound resembles to compound **7**. Again, in the complex cation $[Cu(tren)(N7\text{-}acv)]^{2+}$ (Fig. 8), the Cu1-N23(tren) (2.126(2) Å) bond is significantly longer than the other three Cu-N(tren) bonds (~2.06 Å) and the Cu1-N7(acv) bond is the shortest (1.987(2) Å). The Cu-N7 bond is peculiarly assisted by two intra-molecular interligand H-bonding interactions: N23(distal)-H23B···O6 (2.995(2) Å, 142.2º) and N33-H33A···O6 (3. 085(2) Å, 125.5º). The estimated Adisson-Reedijk parameter, calculated from the trans-coordination angle values N7-Cu1-N10 and N33-Cu1-N43, is τ = 0.68. This indicates that the Cu(II) coordination polyhedron is also defined with a distorted trigonal bipyramidal geometry.

The crystal packing of compound **8** consists of 2D H-bonded frameworks that extend parallel to the *bc* plane. In these layers, tren ligands fall oriented towards the external faces. However, no π,π-stacking interactions between the guanine moieties of acv ligands.

**Metal(II) chelates as acyclovir receptors.**

The three Cu-dien-acv complexes are salts with nitrate, perchlorate or sulfate as counter-anions (compounds **1**-**3**). In the complex cations, dien adopts its most common *mer*-conformation. This fact enables the coordination of the N7-acv atom amongst the four closest copper(II) coordination sites. The Cu(II) center is strongly influenced by the

Jahn-Teller effect ($3d^9$), featuring, in most of the cases, an elongated square-planar pyramidal geometry (type 4+1). In these complexes, the observed metal binding pattern consist of a Cu(II)-N7 coordination bond in cooperation with an intra-molecular interligand interaction (primary amino dien)N-H···O6(acv). This is indeed the most common MBP reported for acv. In contrast, the molecular Zn(II) compound (**4**) exhibits a distorted trigonal bipyramidal geometry, with a *fac*-dien conformation. This is certainly promoted by the $3d^{10}$ configuration of the metal center, free of Jahn-Teller influences and ligand field influences. The Zn-N7(acv) bond is also reinforced by an intra-molecular (secondary dien)N-H···O6(acv) interligand interaction. The two Cu-tren-acv complexes are also salts with nitrate or perchlorate as counter-anions (compounds **7**-**8**). The metal center in the complex cations exhibits a distorted trigonal bipyramidal coordination, where the Cu-N7(acv) bond shows the shortest bond length within the metal surrounding. In the presence of tren, the metal binding pattern also consist of the cooperation of a coordination bond plus an intra-molecular interligand interaction. One striking feature is observed in compound **8** where two, instead of one, H-bonds participate in the reinforcement.

The complete methylation of the N-H bonds or the blockage of the amino primary groups in dien (i.e. the pmda and bpa ligands, respectively) efficiently prevents the cooperation of the Cu-N7(acv) bond with an intra-molecular N-H···O6 interligand interaction. On the other hand, enables the chelation of $Cu(pmda)^{2+}$ or $Cu(bpa)^{2+}$ moieties by acyclovir in an asymmetric chelating N7,O6-acv mode, with a short Cu-N7(acv) bond and a rather long Cu-O6(acv) bond. It should be noted the sensitivity of the apical/distal Cu-O6(acv) bond to the nature of the *trans*-ligands. In the complex cation $[Cu(pmdta)(N7\text{-}O6\text{-}acv)]^{2+}$ (**5**), the Cu-O6(acv) bond length approaches to 2.7 Å

while in [Cu(bpa)(N7,O6-acv)($SO_4$)] (**6**) the bond distance is as long as 2.86 Å, with the sum of Van der Waals radii of Cu(II) and O being 2.9 Å.

## Conclusions

Tridentate or tripodal-tetradentate polyamine copper(II) chelates are suitable receptors for acyclovir. The Cu-N7(acv) bond can be efficiently reinforced by one or two appropriate intra-molecular interligand (primary amino)N-H···O6 interactions, with the tridentate dien being in *mer*-conformation. This molecular recognition patterns includes the compound {[Cu(dien)($\mu_2$-N7,O(ol)-acv)]($ClO_4$)$_2$}$_n$ in spite of the bridging role of the μ-acv ligand (being it responsible to its zigzag 1D-polymeric dimensionality). In contrast, the Zn(II) compound exhibits a *fac*-dien conformation and assist the Zn-N7 coordination bond by the (secondary amino)N-H···O6 interaction. Likewise, the tripodal-tetradentate tren ligand binds acyclovir reinforcing the Cu-N7(acv) bond with one or two N-H···O6 interactions. This metal binding pattern is the most commonly reported for acv and is in clear contrast to what was previously reported for copper(II) chelates with tripodal tetradentate $NO_2$+S chelators. These latter complexes are unable to contribute with an intra-molecular interligand N-H···O6 interaction, such as the here studied N-blocked dien analogs (pmda, bpa), and promote the asymmetric chelating N7,O6-acv mode.

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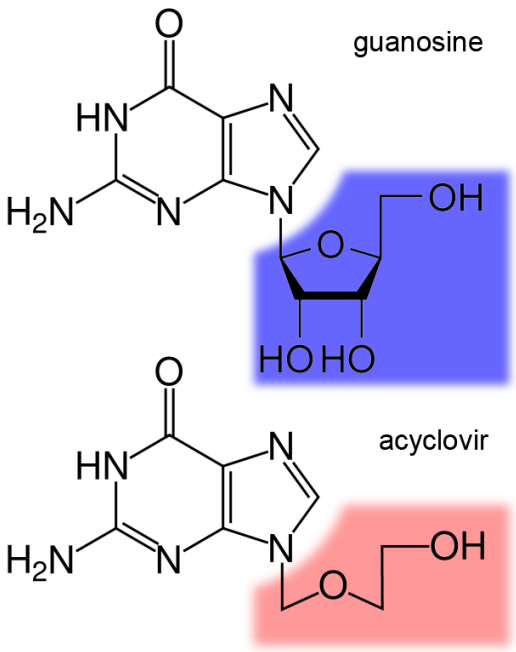
## Figures and captions




Scheme 1. Chemical formulas of acv and guanosine.

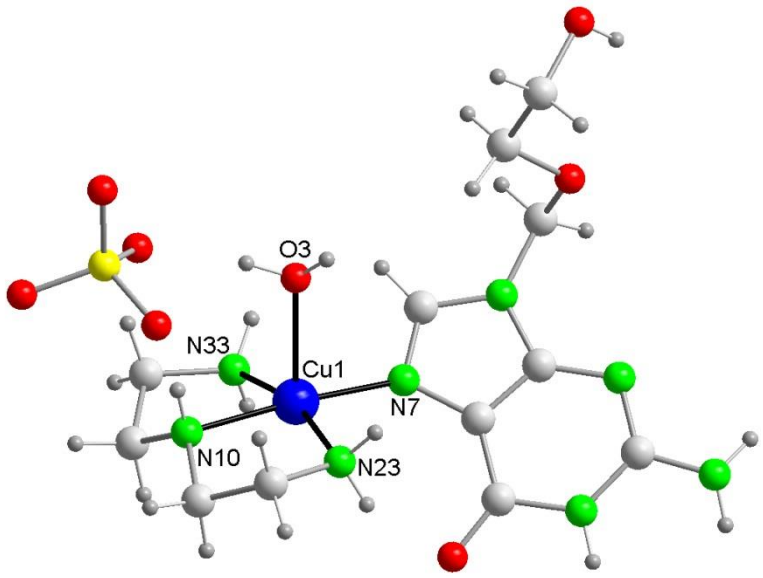



Fig. 1. Structure of the complex cation in the crystal of [Cu(dien)(N7-acv)($H_2O$)] $SO_4$·1.25MeOH·0.5$H_2O$ (**1**). The molecular recognition of acv consist of the formation of the Cu-N7 bond and the interligand interaction N23-H23A···O6(acv) (2.990(5) Å, 144.1º).

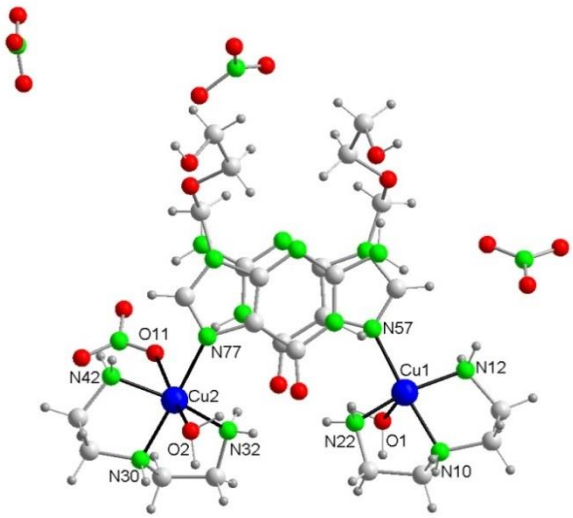



Fig. 2.a Asymmetric unit of the compound [Cu(dien)(N7-acv)($H_2O$)·Cu(dien)(N7-acv)($H_2O$)($NO_3$)]($NO_3$)$_3$·3$H_2O$ (**2**, non-coordinated water omitted for clarity). In both non-equivalent complex units, the Cu-N7(acv) bond cooperates with an intra-molecular interligand interaction (primary amino-dien)N-H···O6(acv).

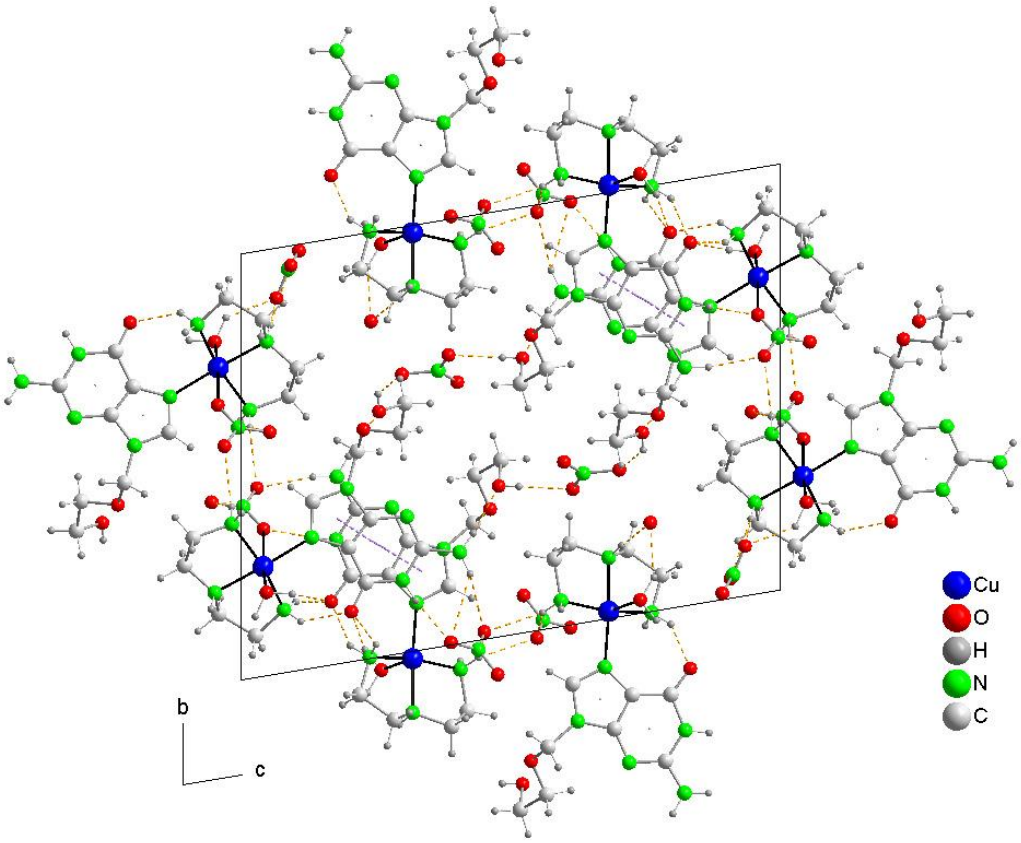



Fig. 2. b. Packing view of 1 along "a" axis, showing part of the hydrogen bonds (orange dashed lines) and pi-pi stacking interactions (violet dashed lines).

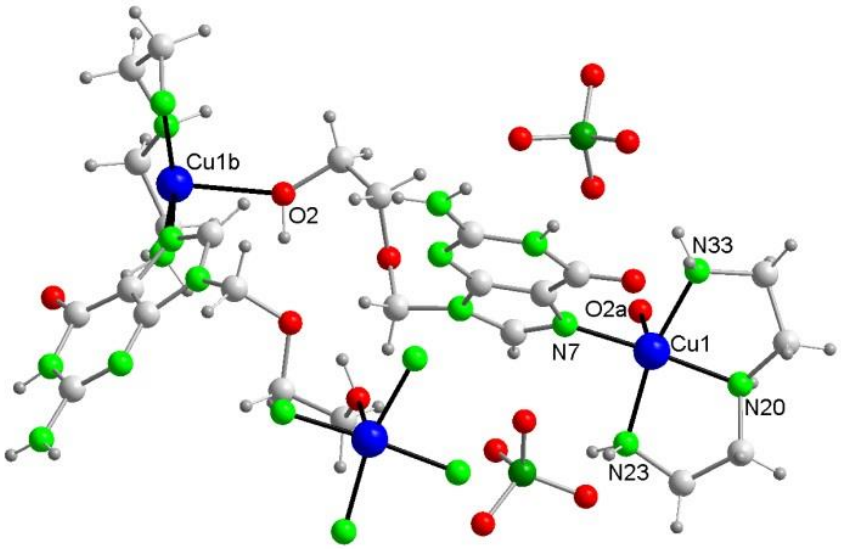



Fig. 3. Polymeric structure of {[Cu(dien)($\mu_2$-N7,O(ol)-acv)]($ClO_4$)$_2$}$_n$ (**3**). Each complex unit shows the Cu-N7(acv) bond cooperating with the (dien)N33-H33B···O6(acv) interligand interaction (2.898(3), 148.1º). The ribbon polymer extends along the *b* axis linking alternating molecules by μ-acv ligands (Cu1b-O2(ol, acv) 2.295(2) Å).

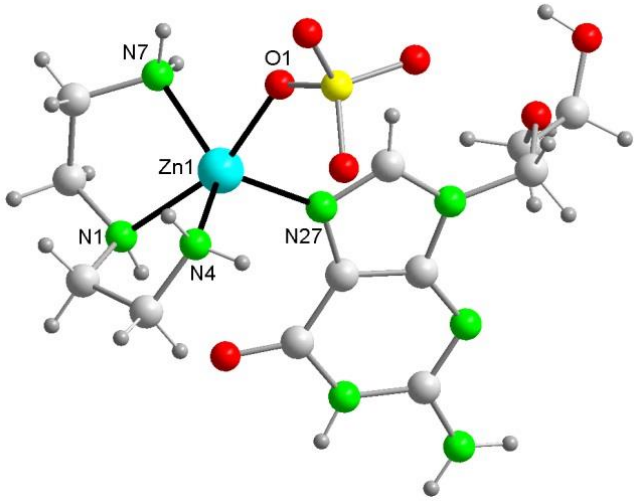



Fig. 4. Structure of the molecular complex [Zn(dien)(N7-acv)($SO_4$)] (**4**). The trigonal bipyramidal coordination involves two rather distinct trans-apical Zn1-N1(secondary dien) and Zn1-O1(sulphate) bonds (2.195(4) and 2.098(3) Å, respectively. The Zn-N7(acv) bond is reinforced by the intra-molecular interligand (secondary amino)N1-H···O(acv) interaction (2.896(2) Å, 149.2º).

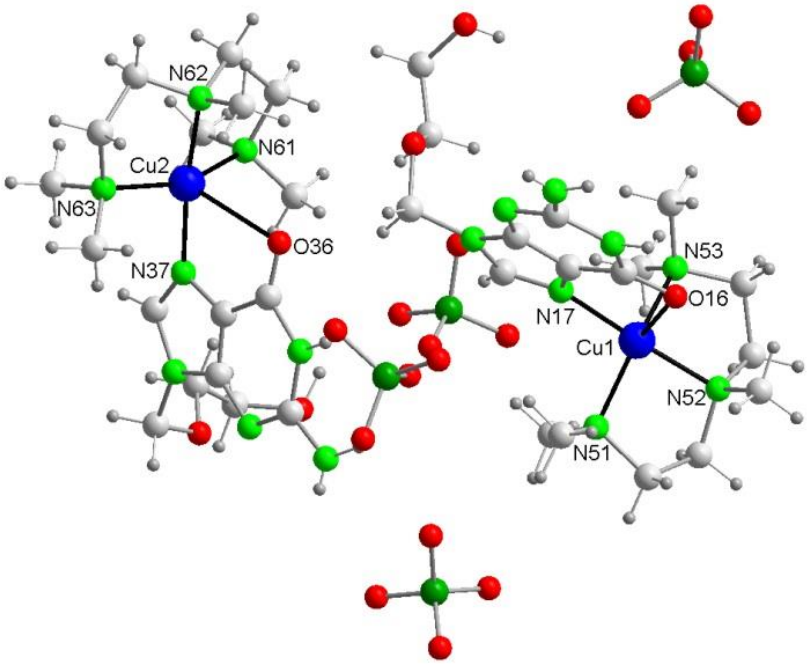



Fig. 5. In the complex cation of [Cu(pmdta)(N7,O6-acv)]$(ClO_4)_2 \cdot H_2O$ (**5**), the acv ligand displays an asymmetric N7,O6-chelationg mode, with the Cu-N7(acv) bonds (1.994(3) Å) and close similar Cu1-O16(3) and Cu2-O36 bonds (2.663(3) and 2.695(3) Å respectively). The distal coordination of the hard O6-acv donor yields interatomic distances shorter than the sum of van der Waals radii of Cu and O (2.9 Å).

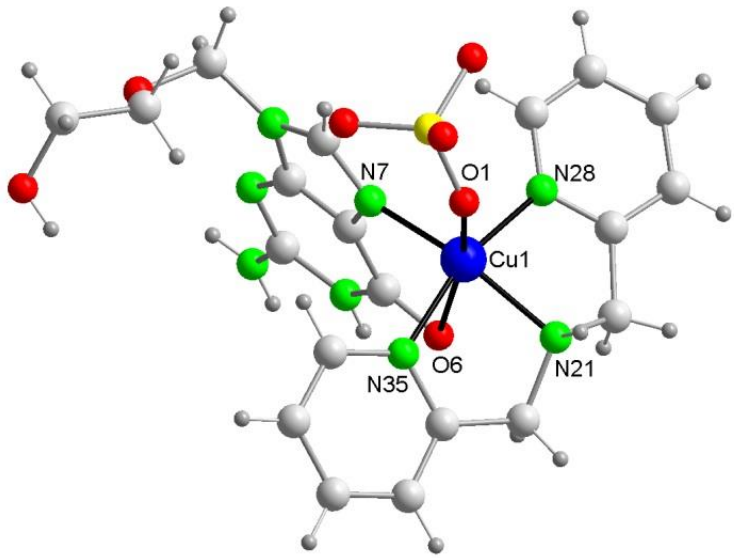



Fig. 6. In the molecular complex of [Cu(bpa)(N7,O6-acv)$(SO_4)] \cdot 6H_2O$ (**6**) the acv ligand exhibits a markedly asymmetric N7,O6-chelationg mode (Cu1-N7 1.999(2) Å and Cu1-O6 2.861(2) Å). This longest Cu1···O6(acv) distance is favored by shortest trans-distal bond Cu1-O1(sulfate) (2.253(2) Å, Cu1-Cu1-O6 171.85º).

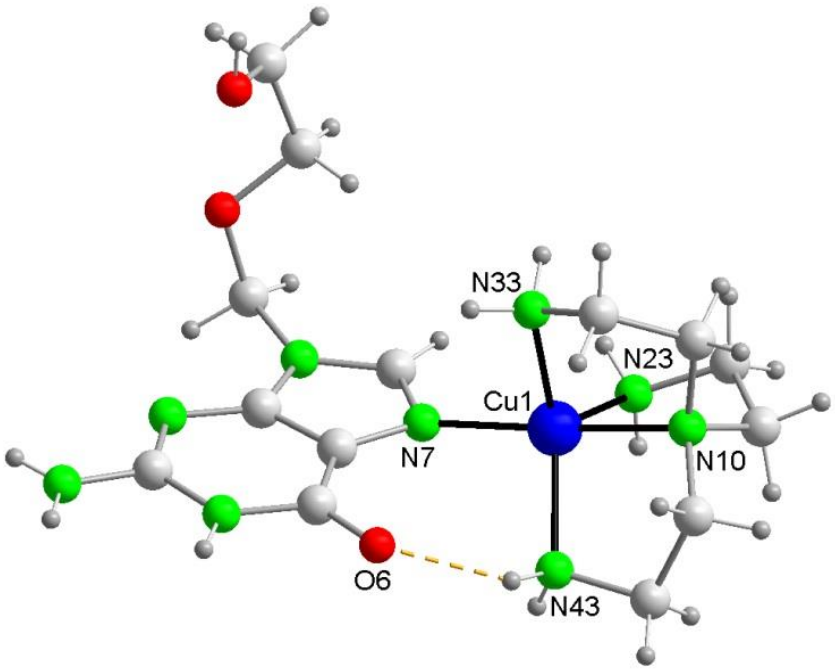



Fig. 7. The complex cation of compound $[Cu(tren)(N7\text{-}acv)](NO_3)_2$ (**7**) shows the Cu1-N7(acv) bond (2.007(4) Å) reinforced with a single N43(distal)-H43A···O6 interaction (2.828(2) Å, 134.1º). The N43(tren) atom is among the four closest N atoms of the Cu(II).

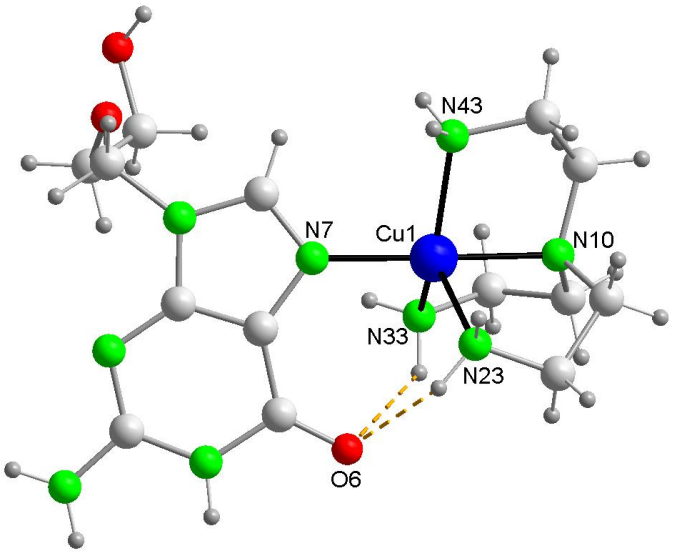



Fig. 8. In the complex cation of compound $[Cu(tren)(N7\text{-}acv)](ClO_4)_2$ (**8**) the Cu1-N7(acv) bond (1.987(2) Å) cooperates with two intra-molecular interligand H-bonding interactions. Hence the exocyclic O6(acv) atom acts twice H-acceptor for two different amino primary groups of tren.

AUTHOR INFORMATION

**Corresponding Author**

Alicia Domínguez Martín

Department of Inorganic Chemistry, Faculty of Pharmacy, University of Granada,

18071 Granada, Spain

Phone +34 958243855

Fax +34 958246219

E-mail address: adominguez@ugr.es

**Present Addresses**

† Department of Chemistry, University of Zurich, Winterthurestrasse 190, CH-8057,

Zurich, Switzerland.

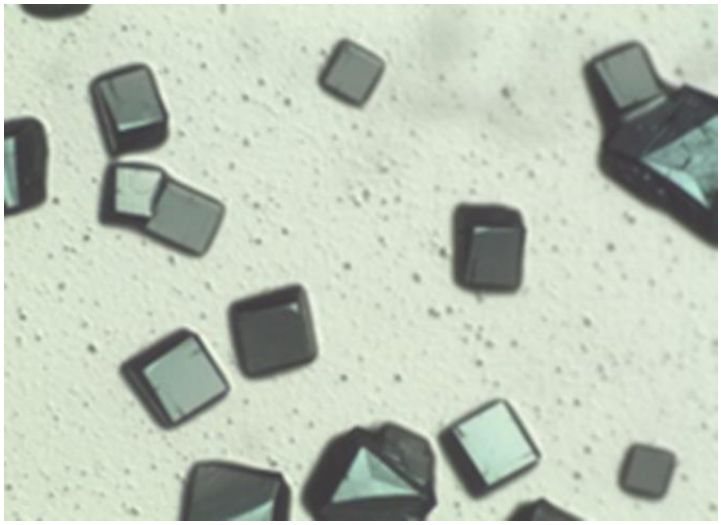
## 5. 6. AVANCES RECIENTES

Durante el tiempo de elaboración de la Memoria de esta Tesis Doctoral se han producido avances relativos a nuevos modos de coordinación de aciclovir, que están siendo objeto de estudios adicionales, al margen de su caracterización cristalográfica.

Estos resultados serán remitidos, con posterioridad a la Defensa de la Tesis Doctoral, para su publicación en revistas de prestigio, como **artículos adicionales a los incluidos en la Memoria.** Por su notable interés, se describen a continuación, en formato breve, pero con suficiente detalle.

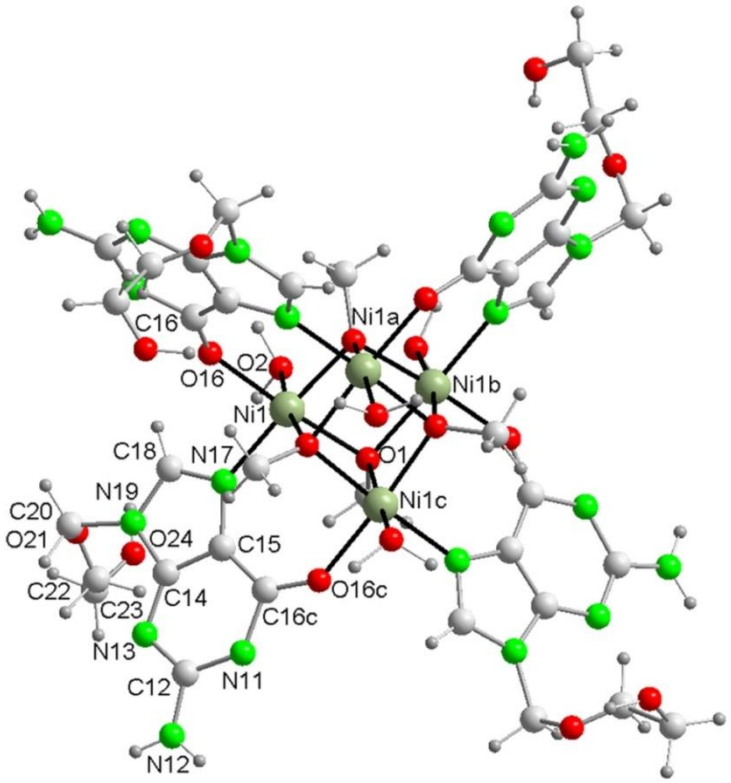
**1. Modo de coordinación puente $\mu_2$-N7,O6 para aciclovir aniónico (acv-H$^-$) en un complejo molecular y tetranuclear de niquel(II), conteniendo el agregado $[Ni^{II}_4(\mu_3\text{-metanolato})_4]^{4-}$: Estructura de $[Ni(\mu_2\text{-N7,O6-acv-H})(MeO)(H_2O)]_4\cdot 8H_2O$.**

El compuesto resultó como producto inesperado de la reacción de las sales $NiCl_2\cdot 6H_2O$ o $Ni(NO_3)_2\cdot 6H_2O$ (0.5 mmol) con 2-(2-aminoetoxi)etanol (2aee, 0.5 mmol) en 50 ml de MeOH, seguida de la adición equimolar de acv (0.5 mmol), hasta su total disolución. La evaporación controlada del disolvente produjo abundancia de cristales bien formados, muchos de ellos apropiados para estudios cristalográficos.

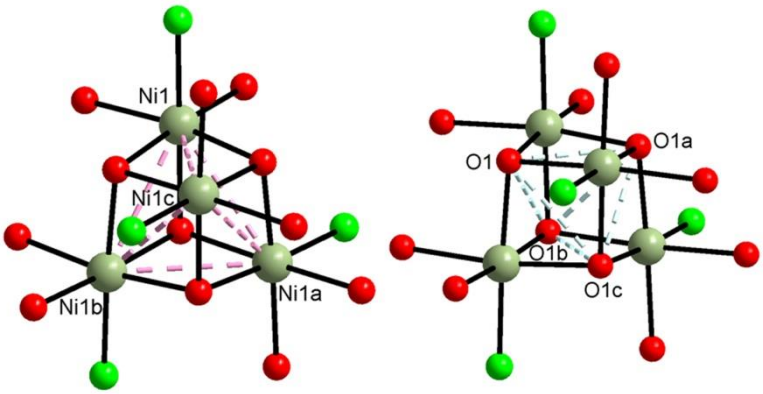


El estudio cristalográfico (100(2) K) revelo que se trataba del compuesto $[Ni(\mu_2\text{-N7,O6-acv-H})(MeO)(H_2O)]_4\cdot 8H_2O$, en cuya composición no había el potencial quelante tridentado 2aee ni los aniones (cloruro o nitrato) de las sales de niquel(II) usados en las síntesis. La estructura se resolvió en el grupo espacial Fd-3c del sistema cúbico, afinándose hasta un valor de $R_1 = 0.097$. El afinamiento logrado está limitado en buena parte al tratamiento del desorden en moléculas de disolvente y al desorden en los N9-sustituyentes de los ligandos acv-H aniónicos.

La molécula tetranuclear contiene cuatro centros de Ni(II) en vértices opuestos del esqueleto tipo cubano, cuatro ligandos $\mu_3$-metanolato(1-) (con sus O-dadores ocupando los restantes vértices del esqueleto tipo cubano), cuatro ligandos aqua (unidos a sendos centros metálicos) y cuatro ligandos aniónicos $\mu_2$-N7,O6-(acv-H), cada uno de ellos coordinado a dos centros de Ni(II) dispuestos en vértices opuestos del esqueleto tipo cubano:




El esqueleto tipo cubano de esta molécula compleja consiste en dos tetraedros inter-penetrados de iones Ni(II) y de átomos O-metanolato:

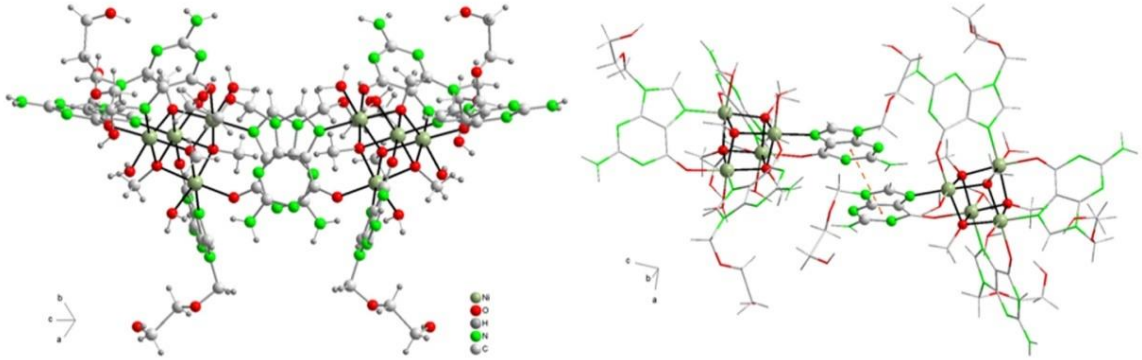


La estructura de esta molécula compleja aporta dos aspectos por completo novedosos:

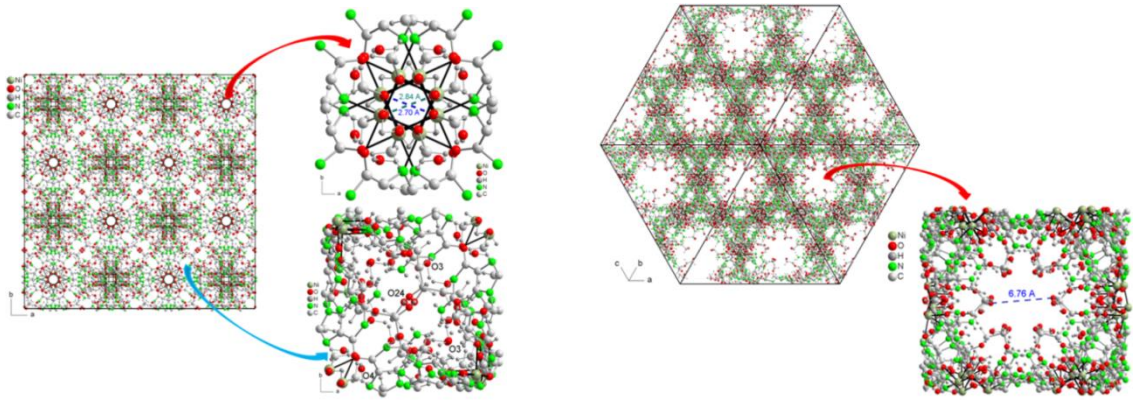
(a) La coordinación de aciclovir (acv) en forma aniónica, acv-H(1-), carente del átomo de hidrógeno presente en el átomo N1 de la molécula acv.

(b) El novedoso modo puente $\mu_2$-N7,O6-(acv-H) con el anión de aciclovir aportando sus dadores N7 y O6 de su parte guanina a dos centros de Ni(II). Este modo de coordinación del nucleósido sintético es distinto del modo puente $\mu_2$-N7,O(ol)-acv reportado para el polímero de coordinación ({Cd($\mu_2$-Cl)$_2$($\mu_2$-N7,O(ol)-acv)]·$H_2O$}$_n$ (HOPCAQ, [1]) y también del modo quelante, inicialmente establecido para el ligando molecular acv en *trans*-[Cu($\mu_2$-N6,O6-acv)$_2$($H_2O$)$_2$]($NO_3$)$_2$ (HOSQUB, [2]), además de los complejos de Cu(II) con acv y quelantes tetradentados trípode-$NO_2$+S, [Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**1**) y [$Cu_2$(TCC)(acv)$_2$]·6$H_2O$ (**2**) descritos en el ARTICULO 3 (Punto 5.3) de esta Tesis Doctoral.

En el cristal del nuevo compuesto de Ni(II) y acv-H(1-) se establecen interacciones-π,π entre anillos de seis miembros de ligandos acv-H adyacentes (distancia inter-centroides $d_{c\text{-}c}$ 3.76 Å e inter-planar $d_{\pi\text{-}\pi}$ 3.39 Å):

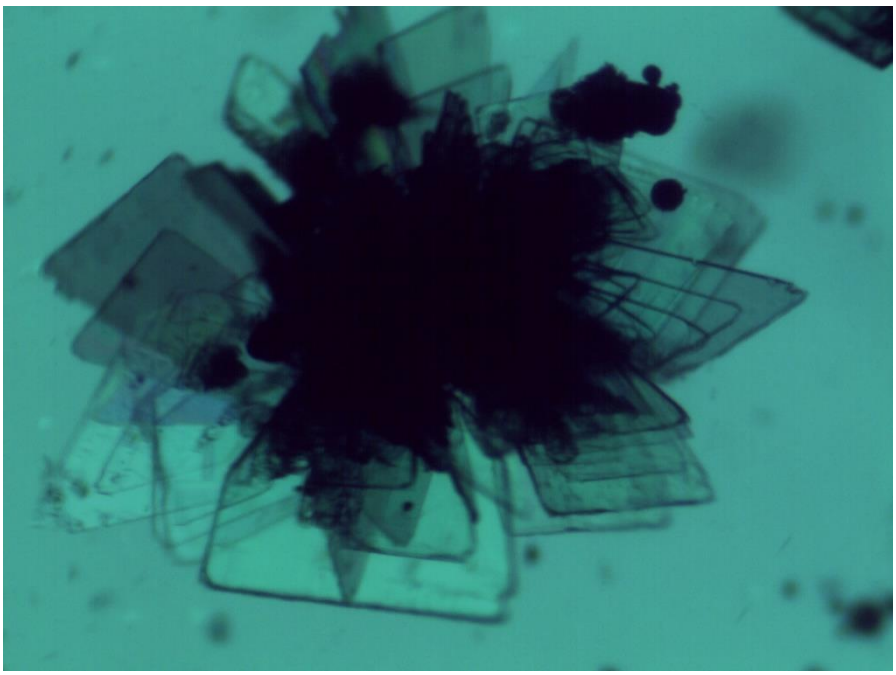


Además, abundantes enlaces de hidrógeno contribuyen a la estabilidad del edificio cristalino, generando distintas cavidades, con diferente dimensión y orientación, donde pueden albergarse desordenadas moléculas de disolventes:



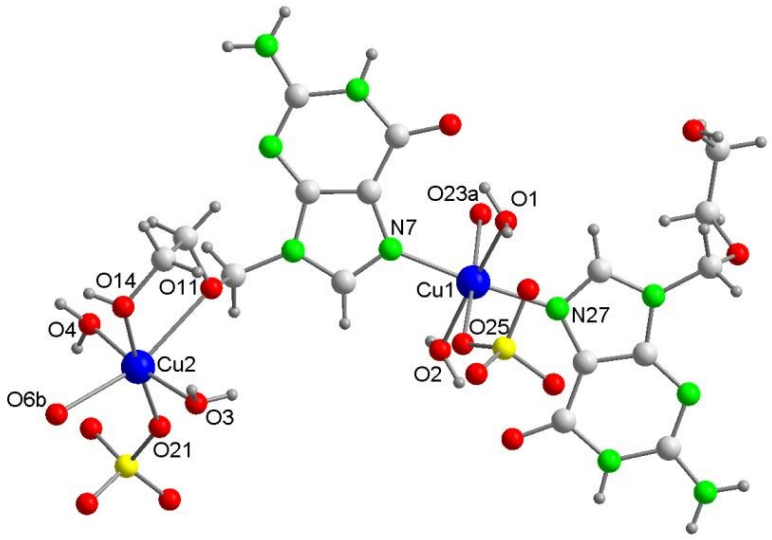
**2. Modo de coordinación multi-funcional (tetradentado, puente y quelante) en {[$Cu_2(SO_4)(\mu_2\text{-}SO_4)$(N7-acv)($\mu_3$-N7,O6,O(e),O(ol)(acv) $(H_2O)_4$]· MeOH·$H_2O$}$_n$.**

Este nuevo compuesto se obtuvo, de manera inesperada, por reacción equimolar (0.5 mmol) de $CuSO_4 \cdot 5H_2O$ y dietanolamina (dienol) en MeOH:DMF (40:15), que produce una disolución azul, a la que se adiciona, con agitación, acv (0.5 mmol), cambiando el color a verde manzana. La formación de un muy fino precipitado (verde claro) exigió repetidas filtraciones hasta disponer de una disolución clara. Por difusión de éter, se obtuvieron cristales de tamaño y calidad apropiados para su estudio cristalográfico, además de muestra para la caracterización por estrectroscopía FT-IR, UV-vis (reflectancia difusa) y análisis termogravimétrico.



Por razones de brevedad, se describen sólo los resultados estructurales más relevantes de este compuesto (referencia cristalográfica interna: 15jnac877). La estructura (100(2) K) se resolvió en el grupo espacial $P2_1$, del sistema monoclínico, afinándose hasta un valor de $R_1 = 0.048$. El cristal consiste en cadenas poliméricas, que se extienden a lo largo del eje c, además de moléculas de disolventes (metanol y agua) en la proporción que refleja la fórmula del compuesto. El polímero contiene (a) dos centros metálicos no equivalentes, Cu1 y Cu2, (b) dos tipos de ligandos acv, uno N7-monodentado y otro multifuncional, que es $\mu_3$-puente (entre un centro Cu1 y dos centros Cu2), (c) dos tipos de ligandos sulfato, uno monodentado y otro puente entre dos centros, uno Cu1 y otro Cu2, y además (d) cuatro ligandos aqua, dos de ellos para cada tipo de centro metálico, actuando todos éstos como ligandos proximales (esto es, satisfaciendo dos de las cuatro posiciones de coordinación más próximas de Cu1 o de Cu2).

La unidad asimétrica se muestra a continuación:



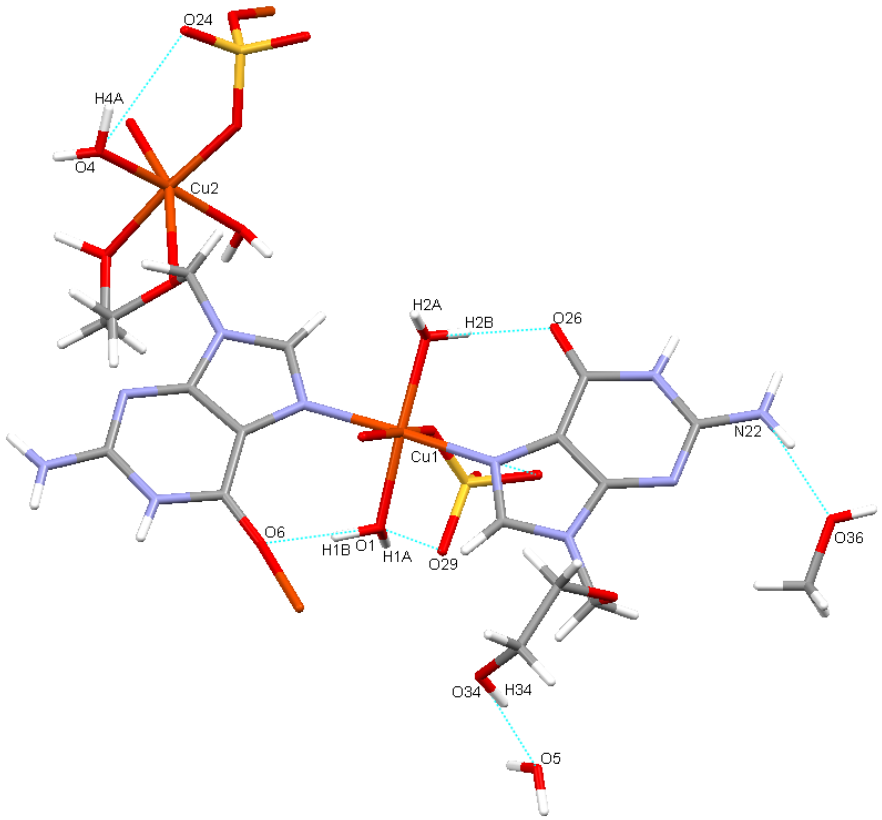

a) *Coordinación en los centros metálicos*. Ambos centros metálicos muestran entornos de coordinación octaédricos, asimétricamente alargados, tipo 4+1+1, con las posiciones distales en disposición trans y distancias de enlace algo diferentes.

El entorno de Cu1 es todo-trans, generando un cromóforo $CuN(acv)_2O(aqua)_2+O(sulfato)_2$, algo alargado, que implican los enlaces Cu1-O1 (1.952(5) Å) y Cu1-O2 (1.951(6) Å) a sendos ligandos aqua, los enlaces Cu1-N27 (2.027(7) Å) y Cu-N7 (2.035(7) Å) a dadores N7 de acv-monodentado y $\mu_3$-acv, respectivamente, así como los enlaces Cu1-O25 (2.416(7) Å) y Cu1-O23#1 (2.476/6) Å, # = a, b; #1 = x,y,z+1) que aportan el sulfato monodentado y el sulfato puente, respectivamente.

El entorno del Cu2 está más asimétricamente alargado que el del centro de Cu1 y, además, todos sus dadores son átomos de oxígeno: Cu2-O21 (1.929(6) Å) del ligando $\mu$-$SO_4^{2-}$, Cu2-O3 (1.957(6) Å) y Cu2-O4 (1.970(7) de sendos ligandos aqua, Cu2-O14 (1.983(6) Å) con el dador O(ol) de $\mu_3$-acv, Cu-O6#2 (2.363(5) Å, b (en la figura) = #2 = x,y,z-1) implicando al dador O6 exocíclico de otro $\mu_3$-acv y Cu2-O11 (2.489(6) Å) con el dador O(e) de $\mu_3$-acv. Es decir, que los centros Cu2 son quelados por un ligando $\mu_3$-acv, usando los dadores O(e) y O(ol) del sustituyente N9-acíclico – algo por completo novedoso – y coordinados también por el dador exocíclico O6 de guanina, procedente de un segundo ligando $\mu_3$-acv (además de por dos ligandos aqua y un O-sulfato).

b) Interacciones interligandos que desempeñan una función relevante.

La figura insertada a continuación indica la unidad asimétrica del cristal que ahora nos ocupa, resaltando los átomos implicados en los enlaces de hidrógeno relevantes, en lo referente al modo de coordinación de los dos tipos de ligandos aciclovir (acv monodentado y $\mu_3$-acv multifuncional).




1. De una parte, el ligando aqua con O2 del centro Cu1 da lugar a la interacción interligandos O2-H2A···O26(acv) (2.620(8) Å, 159.7º), revelando que el ligando acv monodentado actúa en el modo a2, por cooperación del enlace Cu-N27 y la referida interacción.

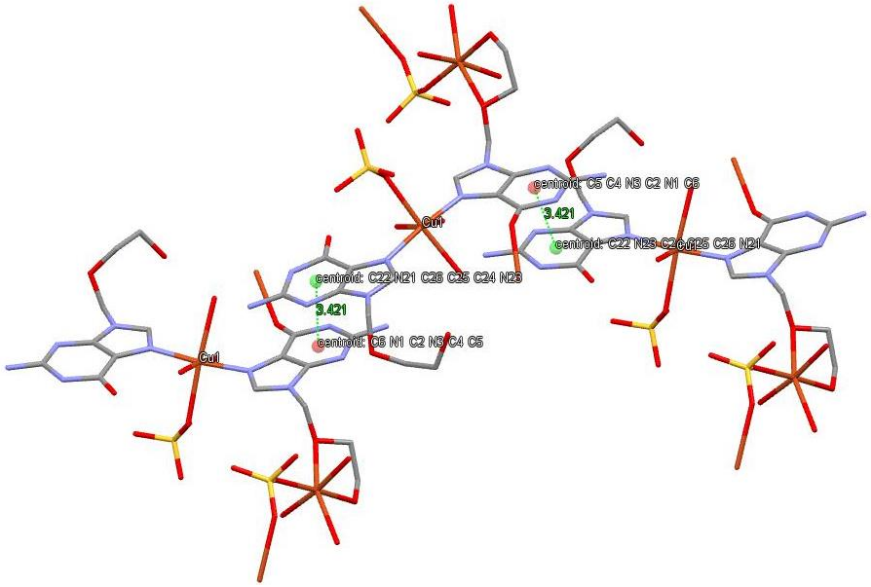
2. De otra parte, el ligando aqua-O1 del centro Cu1 se implica en dos interacciones: O1-H1A···O27(sulfato, monodentado) (2.764(8)Å, 149.2º) y O1-H1B···O6($\mu_3$-acv) (2.622(8) Å, 162.2º). Esta última interacción revela, también, la cooperación del enlace Cu1-N7($\mu_3$-acv) con un enlace de hidrógeno interligandos, permitiendo así matizar que el 'papel multifuncional' del ligando $\mu_3$-N7,O6,O(e),O(ol)-acv supone la función coordinante tipo a2 (propia, entre otros casos, del acv monodentado en este mismo compuesto, más las funciones quelante-O(e),O(ol) y $\mu_3$-puente (conectando un centro Cu1 y dos centros Cu2 relacionados por simetría).

3. El ligando aqua-O4 del centro Cu2 genera la interacción O4-H4A···O24(μ-sulfato) (2.991(9) Å, 148.5º).

4. Las moléculas de disolvente (agua y metanol) están retenidas por los enlaces de hidrógeno (acv)O34(ol)-H34···O5(agua) (2.624(9) Å , 168.0º) y (acv)N22-H22A···O36(MeOH) (2.967(10) Å , 160.4º), respectivamente.

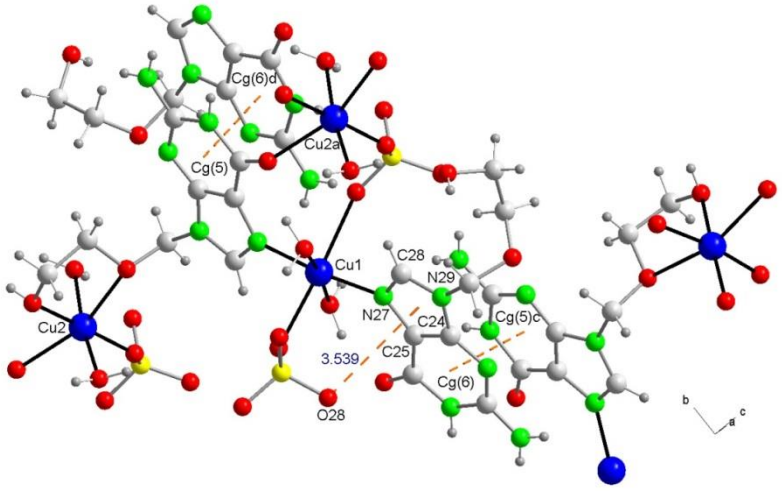
5. Interacciones-π,π entre anillos aromáticos.

En este cristal, los anillos de seis átomos de cada ligando acv (monodentado) y de cada ligando $\mu_3$-acv, de cadenas poliméricas adyacentes, generan una multi-interacción-π,π, con los siguientes parámetros: distancia inter-centroides $d_{c\text{-}c}$ 3.42 Å, distancia inter-planar d $_{\pi\text{-}\pi}$ 3.29 Å, ángulo diedro inter-planar α 2.78º, ángulos de deslizamiento entre anillos β o γ 16.5 o 15.01º. Estas interacciones conectan, por pares, ligandos acv monodentados de una cadena y ligandos $\mu_3$-acv de otra adyacente, de manera que las cadenas poliméricas generan capas 2D paralelas al plano bc del cristal.




6. Interacción anión-π.

Además de las interaccione-π,π entre anillos aromáticos, se contempla una interacción anión-π que relaciona el átomo O28 del sulfato monodentado con el anillo de 5 átomos en la guanina del ligando $\mu_3$-acv, con una distancia O18-centroide de 3.54 Å y un ángulo S2-O28···centroide de 106º.

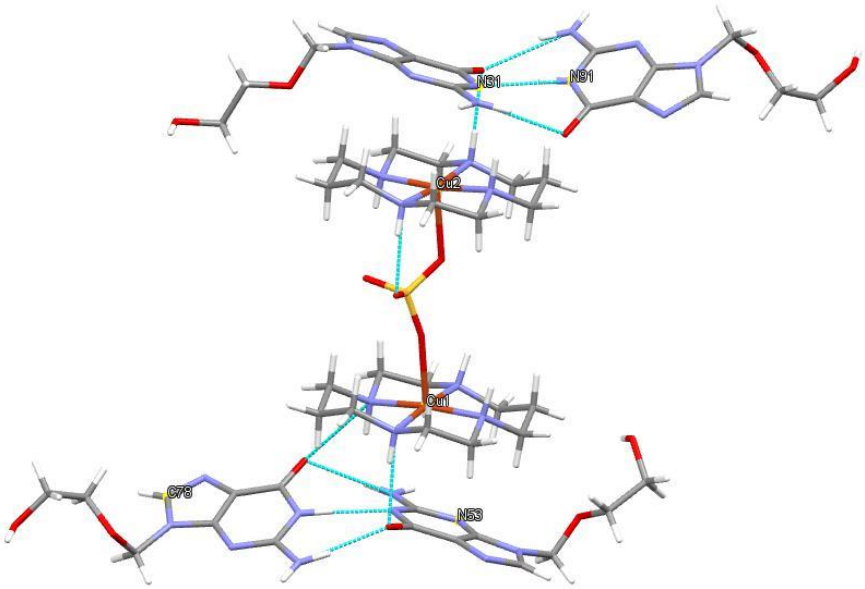


## 3. Nuevas estrategias para investigar la potencial coordinación de nucleósidos o nucleobases purínicos a la posición apical/distal del macroquelato Cu(cyclam)$^{2+}$. Compuestos relacionados conteniendo el anion aciclovir(1-) o adeninato(1-).

### 3.1) Estructura de $[Cu_2(cyclam)_2(\mu\text{-}SO_4)](acv\text{-}H)_2 \cdot acv \cdot 7H_2O$, conteniendo complejo de esfera externa con aciclovir anionico (acv-H$^-$).

Se trata de un compuesto donde el catión $[Cu_2(cyclam)_2(\mu\text{-}SO_4)]^{2+}$ tiene compensada sus cargas con dos aniones acv-H$^-$, que también contiene acv molecular (solvato) y moléculas de agua. El cristal se midió a 100(2)K. Pertenece al grupo espacial $P2_1/n$, del sistema monoclínico y la estructura se afinó hasta $R_1$ 0.044.

Omitiendo las moléculas de disolvente (agua) la siguiente figura trata de resaltar los aspectos más interesantes de este cristal, que se comentan más abajo:



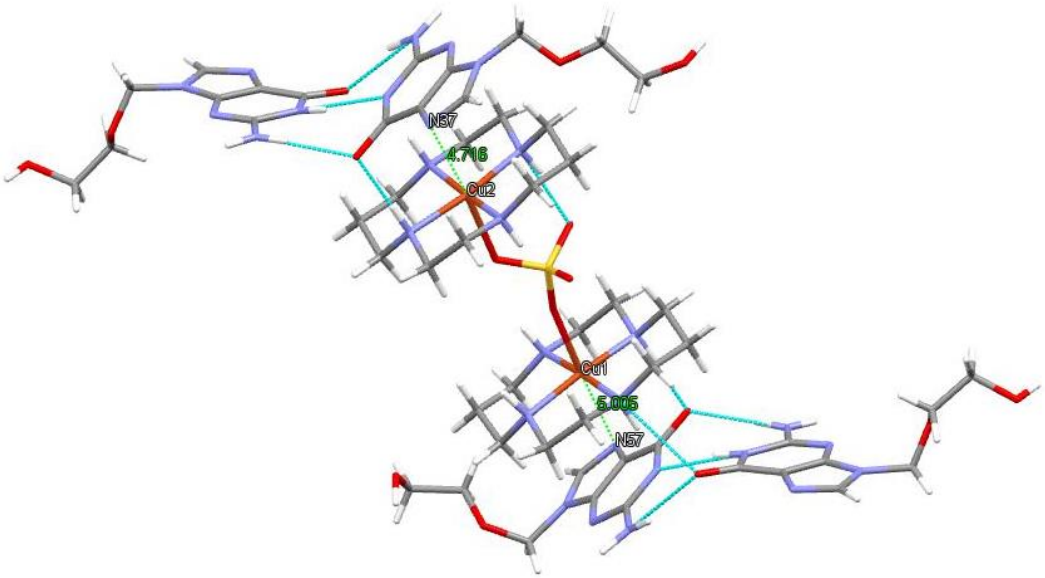

El examen de la figura pone de manifiesto, en mayor o menor grado, lo siguiente:

a) El compuesto debe contemplarse como un "complejo de esfera externa, constituido por el catión dinuclear $[Cu_2(cyclam)_2(\mu\text{-}SO_4)]^{2+}$ y dos aniones acv-H$^-$, que co-cristalizan con dos moléculas acv y siete de agua. El ligando μ-sulfato aporta dos dadores-O a posiciones apicales/distales de sendos macroquelatos Cu(cyclam)$^{2+}$.

b) En el cristal existen un muy elevado número de enlaces de hidrógeno, de tipo N-H···O, N-H···N, O-H···O y, O-H···N (y también algunas interacciones C-H···O, con distancia C···O < 3.2 Å) de los cuales la figura sólo muestra aquellas interacciones O-H···N y N-H···N que resultan más interesantes.

c) Los centros metálicos, Cu1 y Cu2, no son equivalentes. Entre otras razones, porque el centro Cu1 se une a O11(sulfato) sólo por el correspondiente enlace coordinado (2.287(2) Å) mientras en el centro Cu2 el enlace Cu2-O12 (2.328(2) Å ) coopera con la interacción interligandos (cyclam)N23-H23A⋯O12(sulfato) (2.871(3) Å, 167.9º).

d) Los centros metálicos, Cu1 y Cu2 están pentacoordinados. Las distancias interatómicas Cu⋯N7 más cortas son Cu1⋯N57(acv-H) 5.00 Å y Cu2⋯N37(acv-H) 4.72 Å, ambas mucho más largas que la suma de radios de Van der Waals ($r_{Cu}$ 1.40+ $r_N$ 1.55 = 2.95 Å):




Queda pues claro que el anión acv-$H^-$ no se coordina al quelato Cu(cyclam)$^{2+}$ en el compuesto investigado.

No obstante, debe tenerse en cuenta que la coordinación del anión sulfato a una posición apical/distal de cada centro de Cu(cyclam) reduce las posibilidades de coordinación a la correspondiente posición trans-apicales distales.

Nuevos intentos pueden hacerse considerando la conveniencia de las siguientes circunstancias:

- Usar cyclen como macrociclo del Cu(II), ya que tiende a dar complejos Cu(cyclen)L pentacoordinados.

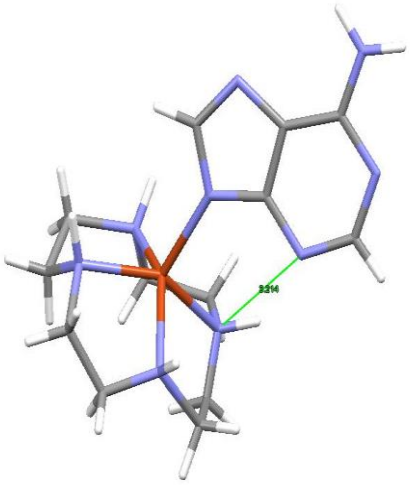
- Usar un anión menos coordinante que sulfato (p. ej. $ClO_4^-$, $BF_4^-$, $PF_6^-$).

-Usar el anión de 9-Meguanina, como modelo de acv.

-Usar aniones de bases púricas no sustituidas en N9 (adeninato, guaninato, etc).

### 3.2) Estructura del complejo de esfera externa trans-[Cu(cyclam)($H_2O$)$_2$](ade)$_2$.

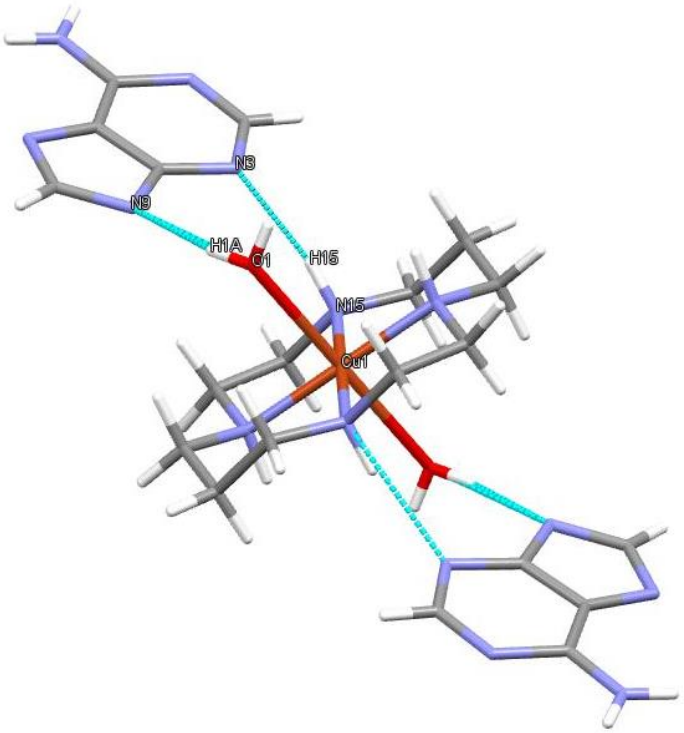
Las anteriores propuestas han sido, en parte, exploradas recientemente por K. Aoki y cols. [3] demostrando que los aniones adeninato(1-), hipoxantinato(1-), teofilinato(1-) o xantinato(1-) son capaces de coordinarse al macroquelato Cu(cyclen)$^{2+}$. Así, por ejemplo, la estructura del cation complejo de [Cu(cyclen)(N9-ade)$ClO_4$·2$H_2O$ (PUNRAS en CSD) la distancia promedio de los cuatro enlaces Cu-N(cyclem) es de 2.04 Å, mientras que la coordinación apical/distal por el dador N9-ade genera un enlace algo más largo (2.06 Å) levemente reforzado por una interacción interligandos (cyclen)N-H···N3(ade), de 3.24 Å y 135.3º:



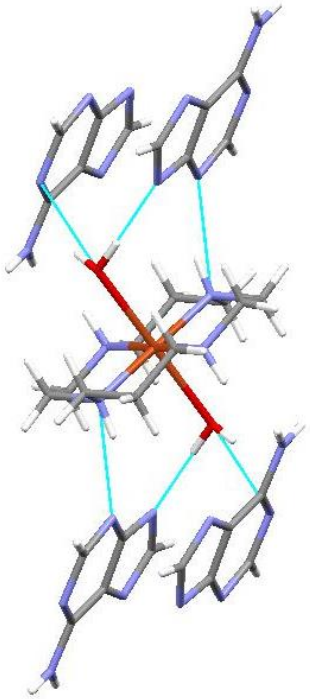
En este complejo, la relativamente corta distancia del enlace Cu-N9(ade) no puede justificarse por la cooperación con el bastante débil enlace de hidrógeno interligandos, debiendo relacionarse con la basicidad incrementada de N9 en el anión adeninato(1-), frente al ligando neutro macrocíclico cyclen. Para la adenina (neutra) se admite, con carácter general, la secuencia de basicidad N9 > N1 > N7 > N3 >> N6-exocíclico.

Nosotros hemos preparado y caracterizado, por cristalografía, el compuesto trans-[Cu(cyclam)($H_2O$)$_2$](ade)$_2$, medido a 100(2) K y resuelto en el grupo espacial P2$_1$/n del sistema monoclínico, afinándose hasta $R_1$ = 0.028.

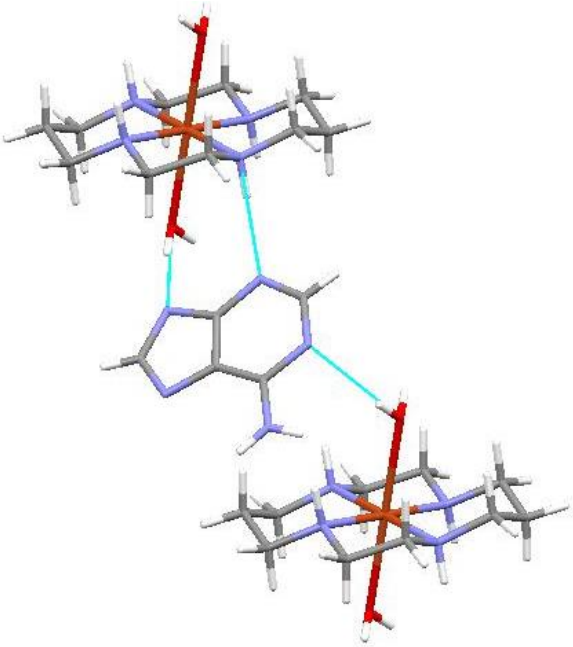
Se trata de un complejo de esfera externa, donde cada catión trans-[Cu(cyclam)($H_2O$)$_2$]$^{2+}$ (con coordinación del cobre(II) octaédrica alargada, tipo 4+2) se asocia a dos aniones adeninato(1-) por un par de enlaces de hidrógeno: (aqua)O1-H1···N9(ade) (2.757(2) Å, 172.7º) y (cyclam)N15-H···N3(ade) (2.945(2) Å, 158.3º.



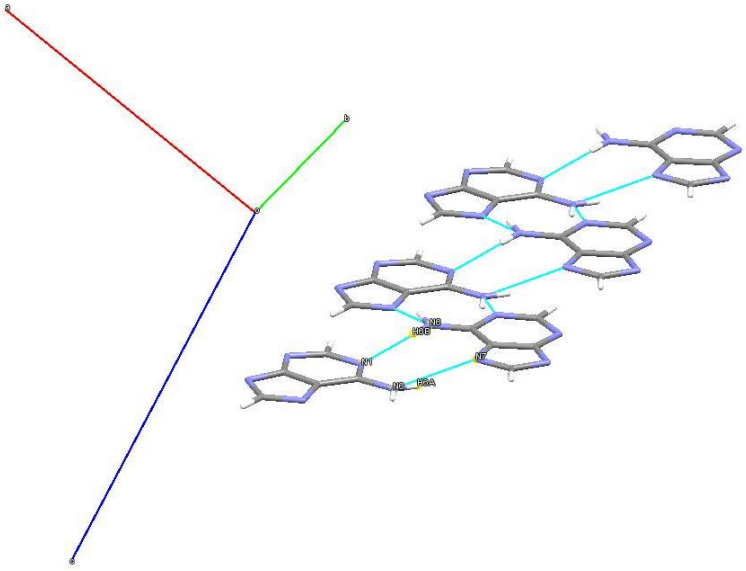

El cristal consiste en una red 3D de enlaces de hidrógeno donde cada catión trans-$[Cu(cyclam)(H_2O)_2]^{2+}$ resulta finalmente unido a cuatro aniones adeninato(1-):



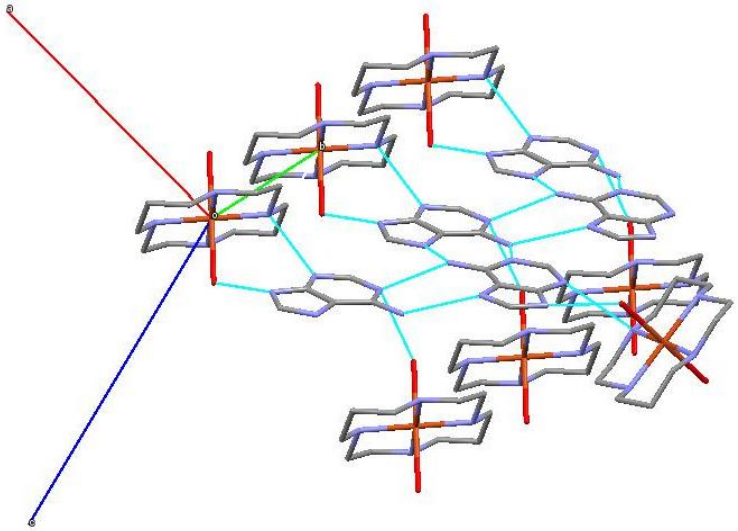
Y cada anión adeninato(1-) se asocia a cuatro cationes trans-$[Cu(cyclam)(H_2O)_2]^{2+}$:



Los aniones adeninato(1-) de asocian entre sí, formando cintas que se extienden en paralelo al eje b del cristal:



Cada cinta de aniones adeninato(1-) se asocia a cuatro secuencias de cationes macroquelato, que se suceden en paralelo al eje b del cristal.



En cualquier caso, el aspecto más notable de este cristal es que el macroquelato $[Cu(cyclam)]^{2+}$ prefiere unirse a dos ligandos aqua trans-apicales/distales (bases duras de Pearson), dando enlaces Cu-O(aqua) relativamente largos (y por tanto débiles), de 2.517(4) Å, antes que hacerlo a los dadores N9 de dos ligandos adeninato(1-) (bases blandas de Pearson). Parece claro que enlaces trans-apicales/distales Cu-N9(ade), en un hipotético compuesto neutro $[Cu(cyclam)(ade)_2]$ (octaédrico) no serían tan cortos como el registrado para el cation complejo pentacoordinado $[Cu(cyclen)(N9\text{-}ade)]^{+}$ (2.06 Å).

## RERERENCIAS

[1] HOPCAQ: A. García-Raso, J.J. Fiol, F. Badenas, R. Cons, A. Terrón, M. Quirós, J. Chem. Soc., Dalton Trans. (1999) 167-174.

[2] HOSQUB: I. Turel, B. Andersen, E. Sletten, A.J.P. White, D.J. Williams, Polyhedron 17 (1998) 4195-4202.

[3] Md. Shahindur Rahman, H. Q. Yuan, T. Kikuchi, I. Fujisawa, K. Aoki, J. Mol. Struct. 966 (2010) 92-101.

# 6. CONCLUSIONES/CONCLUSIONS

## CONCLUSIONES

De los resultados experimentales de esta Tesis Doctoral y la consideración de los antecedentes bibliográficos se deducen las siguientes conclusiones (la numeración ahora usada para los compuestos no se corresponde con la usada en las distintas aportaciones o resultados recogidos en esta Memoria):

1. Una disolución de cantidades equimolares de nitrato de cobre(II) trihidrato, tris(2-aminoetil)amina (tren) y aciclovir (acv) en etanol absoluto, con una pequeña proporción de agua, produjo por difusión de éter el compuesto $[\{Cu(tren)\}_3(\mu_3\text{-tren})]_2(NO_3)_{12}\cdot 3H_2O$ (**1**), sin acv y con alto contenido en nitrógeno. Su estudio termo-gravimétrico (en corriente de aire) revela la descomposición solapada de aniones nitrato y ligandos tren, hasta dejar un residuo de CuO.

2. La amina dietilentriamina (dien) forma compuestos ternarios cobre(II)-dien-acv con nitrato, sulfato o perclorato, oxoaniones que, en general adoptan el papel como contra-aniones: $[Cu(dien)(acv)(H_2O)\cdot Cu(dien)(acv)(H_2O)(NO_3)](NO_3)_3\cdot 3H_2O$ (**2**), $[Cu(dien)(acv)(H_2O)]SO_4\cdot 1.25MeOH\cdot 0.5H_2O$ (**3**), $\{[Cu(dien)(\mu\text{-N7,O(ol)-acv})](ClO_4)_3\}_n$ (**4**). En estos compuestos, el átomo de Cu(II) presenta una **coordinación tipo 4+1** (o **4+1+1**, como excepción). Además, dien adopta la conformación *mer*-tridentada, dejando una de sus cuatro posiciones de coordinación más próximas al metal accesible al átomo dador N7-acv. El enlace Cu-N7(acv) coopera con un enlace intra-molecular interligandos tipo **(dien, amino primario)N-H···O6(acv)** (2 ó 3), incluso en el compuesto **(4)** donde acv ejerce la función de **ligando puente μ-N7,O(ol)**.

3. El sistema Zn(II)-dien-acv produce el compuesto $[Zn(dien)(N7\text{-}acv)(SO_4)]$ (**5**) donde el metal, con configuración electrónica $[Ar]3d^{10}$, muestra una coordinación tipo **bipirámide trigonal**, algo distorsionada, y la conformación de dien es *fac*-tridentada. En este caso, el reconocimiento molecular quelato metálico-acv consiste en la cooperación del enlace Zn-N7(acv) y la interacción interligandos **(dien, amino secundario)N-H···O6(acv)**, revelando hasta qué punto el tipo de entorno del ion metálico y/o la conformación de la amina quelante dien influyen en el referido reconocimiento molecular.

4. El bloqueo (total o parcial) de los grupos amino de dien, en la forma de las aminas 1,1,4,7,7-pentametildietilentriamina (pmdta) y bis(picolil)amina (bpa) produce los compuestos $[Cu(pmdta)(acv)](ClO_4)_2\cdot H_2O$ (**6**) y $[Cu(bpa)(acv)(SO_4)]\cdot 6H_2O$ **(7)**, donde el nucleósido se comporta en **el modo N7,O6-quelante**, muy asimétrico, dando una distancia interatómica Cu···O6 significativamente más larga que la del enlace Cu-N7.

5. El uso de ligandos con funcionalidad quelante-$NO_2S$ tretradentada-trípode, N,N-bis(carboximetil)-S-bencilcisteaminato(2-) (BCBC) y N,N,N',N',-tetrakis(carboximetil)cisteaminato(4-) (TCC) con S-tioéter o S-disulfuro, respectivamente, conduce a los compuestos $[Cu(BCBC)(acv)]\cdot 2.5MeOH\cdot 0.5H_2O$ (**8**) y $[Cu_2(TCC)(acv)_2]\cdot 6H_2O$ (**9**). En sus complejos moleculares, el entorno de coordinación del metal es tipo **4+1+1***, donde el *asterisco* indica que la distancia interatómica Cu···O6(acv) (~3 Å) del acv quelante-N7,O6 (asimétrico) es propia de una muy débil interacción o de un mero contacto.

6. El acv se muestra incapaz de coordinarse a una posición apical-distal del cobre(II) quelado por las tetraaminas macrocíclicas cyclen y cyclam, habiéndose determinado las estructuras de los compuestos (sin acv): $[Cu(cyclam)(ClO_4)_2]$ (**10**), $\{[Cu(cyclam)(\mu_2\text{-}NO_3)](NO_3)\}_n$ (**11**), $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot MeOH\}_n$ (**12**), $\{[Cu(cyclam)(\mu_2\text{-}SO_4)]\cdot 5H_2O\}_n$ (**13**), $[Cu(cyclen)(H_2O)]SO_4\cdot 2H_2O$ (**14**) y $[Cu(cyclen)(H_2O)]SO_4\cdot 3H_2O$ (**15**). En claro contraste, las estructuras de $[Cu(trien)(acv)](NO_3)_2\cdot acv$ (**16**) y $[Cu(trien)(acv)]SO_4\cdot 0.71H_2O$ (**17**) revelan que el reconocimiento molecular entre el quelato $Cu(trien)^{2+}$ y acv consiste en la cooperación del novedoso enlace coordinado **Cu-N7(apical/distal)** y una interacción intra-molecular interligandos **(trien)N-H···O6(acv)**, lo que se atribuye fundamentalmente a la flexibilidad de la tetraamina acíclica trien, frente a la rigidez conformacional de las poliaminas macrocíclicas utilizadas.

7. La reacción de cantidades equimolares de sulfato de cobre(II), dietanolamina (DEA) y acv en metanol produce la sal de oxonio $(H_3O)_2[Cu(acv)_2(H_2O)_2(SO_4)_2]\cdot 2H_2O$ (**18**) carente de DEA e hidróxido del metal. Su estructura cristalina, sustentada por cálculos de modelización-DFT, revela la capacidad de cooperación entre el enlace **Cu-N7(acv)** y la interacción intra-molecular interligandos **(aqua, proximal)O-H···O6(acv)**, promoviendo los aniones sulfato hasta las posiciones trans-apicales/distales del entorno **4+2** del metal, así como la muy reducida basicidad del átomo **N3-acv**, que **no** actúa como **aceptor de hidrógeno** en la interacción N3···H-O(oxonio o aqua).

8. La reacción de cantidades equimolares de nitrato o de cloruro de níquel(II) hidratados, 2-(2-aminoetoxi)etanol (2aee) y acv en metanol produce abundantes cristales del compuesto tetranuclear $[Ni(\mu_2\text{-N7,O6-acv-H})(\mu_3\text{-MeO})(H_2O)]_4\cdot 8H_2O$ (**19**), donde los conta-aniones de la sal metálica utilizada (nitrato o cloruro) y 2aee no están presentes en su composición. El complejo molecular contiene la novedosa implicación de aciclovir aniónico ($acv\text{-}H^-$) actuando como ligando y su función puente **$\mu_2$-N7,O6**, no descrita con anterioridad.

9. En un intento de coordinar aciclovir aniónico ($acv\text{-}H^-$) en una posición apical/distal del macroquelato $Cu(cyclam)^{2+}$, se obtuvieron cristales de $[Cu_2(cyclam)_2(\mu\text{-}SO_4)](acv\text{-}H)_2\cdot 2acv\cdot 7H_2O$ (**20**), que contiene **acv-$H^-$** como **contra-anión**, pero no coordinado al cobre(II). Este comportamiento restringe

de forma notable las esperanzas de coordinar aciclovir a $Cu(cyclam)^{2+}$, con apreciable tendencia a dar complejos octaédricos, al tiempo que revela la eficiente competencia del anión sulfato frente a acv-$H^-$ como ligando apical/distal del cobre(II).

10. Tampoco el anión adeninato(1-) (ade) se coordina al cobre(II) en el compuesto trans-$[Cu(cyclam)(H_2O)_2](ade)_2$ (**21**), donde el catión macroquelato, centro-simétrico, tiene coordinación **4+2**, con sendos ligandos aqua en posiciones trans-apicales/distales. Dada la ausencia de un contra-anión distinto de adeninato(1-), este compuesto debe contemplarse como un ***complejo de esfera externa***. En el cristal, cada catión se asocia a dos aniones $ade^-$, por pares de enlaces de hidrógeno **(cyclam)N-H···N3(ade)** y **(aqua)O-H···N9(ade)**, y a otros dos aniones $ade^-$ más, por el enlace de hidrógeno **(aqua)O-H···N1 (ade)**.

## CONCLUSIONS

Considering the experimental results of this Doctoral Thesis, and the bibliographic background, the following conclusions are derived:

1. An equimolar reaction of copper(II) nitrate trihydrate in solution with tris(2-aminoethyl)amine (tren) and acyclovir (acv) in absolute ethanol, with a small part of aqua, yielded the acv-free and N-rich compound $[\{Cu(tren)\}_3(\mu_3\text{-}tren)]_2(NO_3)_{12}\cdot 3H_2O$ (**1**). Ether diffusion and high nitrogen content were needed for crystallization. The thermogravimetric study (under dry-air flow) shows the overlapped decomposition of the nitrare ligands and the anions, yielding a CuO residue.

2. The diethylenetriamine (dien) ligand takes part of copper(II)-dien-acv ternary complexes, with nitrate, sulfate or perchlorate oxoanions being counter-anions: $[Cu(dien)(acv)(H_2O)\cdot Cu(dien)(acv)(H_2O)(NO_3)](NO_3)_3\cdot 3H_2O$ (**2**), $[Cu(dien)(acv)(H_2O)]SO_4\cdot 1.25MeOH\cdot 0.5H_2O$ (**3**), $\{[Cu(dien)(\mu\text{-}N7,O(ol)\text{-}acv)](ClO_4)_3\}_n$ (**4**). In these compounds, the Cu(II) atom exhibits a **4+1 coordination**, or **4+1+1**, exceptionally. The dien ligand adopts the *mer*-tridentate conformation, leaving one of its four closest metal coordination sites accessible to the N7-acv donor atom. The Cu-N7(acv) bond cooperates with an intra-molecular interligand interaction **(dien, primary amine)N-H···O6(acv)** (**2**,**3**), even in compound (**4**) where acv shows a **bridging μ-N7,O(ol) mode**.

3. The system Zn(II)-dien-acv lead the compound $[Zn(dien)(N7\text{-}acv)(SO_4)]$ (**5**) where the metal, with $[Ar]3d^{10}$ electronic configuration, shows a **trigonal bipyramid coordination**, mildly distorted and the conformation of dien is *fac*-tridentate. Here, the molecular recognition pattern consist of the cooperation between the Zn-N7(acv) coordination bond and the interligand interaction **(dien, secondary amine)N-H···O6(acv)**. This fact highlights till what extent molecular recognition can be influenced by the environment of the metal ion and the conformation of the chelating amine.

4. The partial or total block of the dien amino groups in the amines 1,1,4,7,7-pentamethyldiethylenetriamine (pmdta) and bis-(2-picolyl)amine (bpa) yield the compounds $[Cu(pmdta)(acv)](ClO_4)_2\cdot H_2O$ (**6**) and $[Cu(bpa)(acv)(SO_4)]\cdot 6H_2O$ (**7**), in which the synthetic nucleoside exhibit the **N7,O6-chelating mode**. This peculiar mode is highly asymmetric, since the Cu···O6 interatomic distance is significantly longer than the Cu-N7 bond.

5. The use of chelating-$NO_2S$ tripodal-tretradentate ligands such as N,N-bis(carboxymethyl)-S-benzylcisteaminate(2-) (BCBC) and N,N,N',N',-tetrakis(carboxymethyl)cisteaminate(4-) (TCC), with S-thioether or S-disulfure functionality respectively, leads to the compounds

[Cu(BCBC)(acv)]·2.5MeOH·0.5$H_2O$ (**8**) and [$Cu_2$(TCC)(acv)$_2$]·6$H_2O$ (**9**). In these molecular complexes, the metal coordination environment is type **4+1+1***. The asterisk indicates that the Cu···O6(acv) interatomic distance, of the acv chelating-N7,O6 mode, is close to 3 Å, indicating the nature of a very weak interaction or even a mere contact.

6. Acyclovir was unable to coordinate an apical/distal site of a copper(II) center when chelated by the macrocyclic tetraamines cyclen and cyclam. After several attempts, the structures of the following compounds were determined instead, without acv: [Cu(cyclam)($ClO_4$)$_2$] (**10**), {[Cu(cyclam)($\mu_2$-$NO_3$)]($NO_3$)}$_n$ (**11**), {[Cu(cyclam)($\mu_2$-$SO_4$)]·MeOH}$_n$ (**12**), {[Cu(cyclam)($\mu_2$-$SO_4$)]·5$H_2O$}$_n$ (**13**), [Cu(cyclen)($H_2O$)]$SO_4$·2$H_2O$ (**14**) on [Cu(cyclen)($H_2O$)]$SO_4$·3$H_2O$ (**15**). In contrast, the compounds [Cu(trien)(acv)]($NO_3$)$_2$·acv (**16**) and [Cu(trien)(acv)]$SO_4$·0.71$H_2O$ (**17**) do reveal the intended **apical/distal coordination**. The molecular recognition between the Cu(trien)$^{2+}$ chelate and acv consists of the cooperation of the novel **Cu-N7(apical/distal)** coordination bond and an inter-molecular interligand interaction **(trien)N-H···O6(acv)**. This fact can be mainly attributed to the flexibility of the acyclic tetraamine trien, against the conformational rigidity of the macrocyclic polyamines used before.

7. The equimolar reaction of copper(II) sulfate, diethanolamine (DEA) and acv in methanol produces the oxonium salt ($H_3O$)$_2$[Cu(acv)$_2$($H_2O$)$_2$($SO_4$)$_2$]·2$H_2O$ (**18**), without DEA and metal hydroxide. The crystalline structure, supported by DFT-modeling calculations, shows the ability of cooperation between the **Cu-N7(acv)** bond and the intra-molecular interligand interaction (aqua, proximal)O-H···O6(acv). This fact, together with the reduced basicity of the N3-acv atom, promotes the sulfate anions to occupy the trans-apical/distal position in the **4+2** metal environment. Thus, **the N3-acv** atom does **not act as hydrogen acceptor** in an N3···H-O(oxonio or aqua) interaction.

8. The equimolar reaction of hydrated nickel(II) nitrate or chloride, 2-(2-aminoethoxy)ethanol (2aee) and acv in methanol leads to a large number of crystals of the tetranuclear compound [Ni($\mu_2$-N7,O6-acv-H)($\mu_3$-MeO)($H_2O$)]$_4$· 8$H_2O$ (**19**). The counter-anions of the metal salt used (nitrate or chloride) and 2aee are not involved in the formula. The molecular complex comprises the implication of the newly described **anionic acv (acv-H$^-$)** acting as **bridging $\mu_2$-N7,O6 ligand**.

9. Provided neutral acv was unable to coordinate an apical/distal site within a copper(II) center, a similar macrochelate strategy was designed but using anionic acv (acv-H$^-$) instead. However, in this case we could not succeed either. The resulting crystals with formula [$Cu_2$(cyclam)$_2$($\mu$-$SO_4$)](acv-H)$_2$·2acv·7$H_2O$ (**20**) contained **acv-H$^-$ as counter-anion**. This behaviour notably limits the possibilities of coordinating acv to Cu(cyclam)$^{2+}$, with a considerable tendency

to give octahedral compounds, while reveals the efficient competence of the sulfate anion against acv-$H^-$ as apical/distal ligand for copper(II).

10. The adeninate(1-) (ade) anion is not coordinated either to the copper(II) center in the compound trans-[Cu(cyclam)$(H_2O)_2$](ade)$_2$ (**21**). Here the macrochelate cation, centrosymmetric, exhibits a **4+2** coordination, with each aqua ligand being in trans-apical/distal position. Due to the absence of a counter-anion different to adeninate(1-), this compound should be considered as an ***external sphere complex*.** In the crystal, each cation is associated with two $ade^-$ anions by pairs of hydrogen bonds **(cyclam)N-H···N3(ade)** and **(aqua)O-H···N9(ade)** hydrogen bonds, and with two other $ade^-$ anions by the hydrogen bond **(aqua)O-H···N1 (ade)**.

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