Synthesis, crystal structure and properties of two acetazolamide (5-acetamido-1,3,4-thiadiazole-2-sulfonamide) complexes: bis(5-acetamidato-1,3,4-thiadiazole-2-sulfonamide-*O*)bis(1,2-ethanediamine)copper(II) and bis(5-acetamidato-1,3,4-thiadiazole-2-sulfonamide-*N*)bis(1,3-propanediamine)copper(II); an unusually weak ambidentate anionic ligand

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Abstract

The diverse coordination chemistry exhibited by acetazolamide (H_2acm), a potent inhibitor of the carbonic anhydrase metalloenzyme, is highlighted in two new copper(II) complexes of this ligand: $[Cu(Hacm)_2(en)_2]$ (**I**) and $[Cu(Hacm)_2(tn)_2]$ (**II**). The synthesis, crystal structure and spectroscopic properties of both compounds are reported in this paper. The structures of both compounds consist of discrete units of $[Cu(Hacm)_2(en)_2]$ (**I**) and $[Cu(Hacm)_2(tn)_2]$ (**II**), respectively, interacting through van der Waals contacts and hydrogen bonds only. Hacm, however, binds differently in each compound. In both cases, the Cu(II) ions, lying on the symmetry centers, show an elongated octahedral geometry with the four 1,2-ethanediamine or 1,3-propanediamine N atoms in an approximately square coplanar arrangement (Cu–N distances of 2.00 and 2.01 Å for **I**; 2.04 and 2.05 Å for **II**); two sulfonamido O atoms in I and two thiadiazole N atoms in **II**, from two *trans* Hacm ligands, complete the distorted octahedron at the longer distance of 2.65 and 2.46 Å, respectively. Although the ligand is deprotonated at the acetamido group, in neither case is the interaction with the copper produced via the donor atoms of that group. Furthermore, in **I**, unexpectedly, in spite of its four potentially chelating N atoms, and in spite of the deprotonation of the acetamido group, acetazolamide acts as a monodentate ligand coordinating through one of the O atoms of the sulfonamido moiety. This behavior is completely different from that observed in **II** and in all acetazolamide complexes described up to now, and it must be related to hydrogen bonding and to the copper(II) Jahn–Teller effect. Stabilization of the negative charge at the deprotonated group takes place through 'pairing' of the Hacm ions in the packing system. These results further emphasize the many coordinating possibilities of the ligand, which could be of relevance to a proper understanding of the mechanism of inhibition in the enzyme. Crystallographic data: $[Cu(C_4N_4S_2O_3H_5)_2(C_2N_2H_8)_2]$ (**I**) (MW = 626.2) crystallizes in the triclinic space group $P\bar{1}$, $Z=1$, with the cell dimensions $a=8.196(7)$, $b=9.094(4)$, $c=9.352(3)$ Å, $\alpha=84.51(3)$, $\beta=74.83(6)$, $\gamma=63.57(5)°$ and $V=602$ Å^3, $D_{calc}=1.73$ Mg m^{-3}; the final agreement values were $R=0.0335$ and $R_w=0.0427$ for 3947 independent significant reflections. $[Cu(C_4N_4S_2O_3H_5)_2(C_3N_2H_{10})_2]$ (**II**) (MW = 654.3) crystallizes in the monoclinic space group $P2_1/n$, $Z=2$, with the cell dimensions $a=9.336(3)$, $b=10.232(1)$, $c=14.138(3)$ Å, $\beta=103.80(2)$ and $V=1312$ Å^3, $D_{calc}=1.66$ Mg m^{-3}; the final agreement values were $R=0.0327$ and $R_w=0.0405$ for 1932 independent significant reflections. The structures were solved by using the copper coordinates (at the inversion center) for repeated Fourier calculations (AUTOFOUR, SHELXS-86). Ligand field and EPR spectra for both complexes are in agreement with the tetragonal Cu(II)N_4O_2 (**I**) and Cu(II)N_4N_2' (**II**) chromophores, respectively.

Introduction

The ligand acetazolamide (hereafter abbreviated as H_2acm, previously abbreviated as Acm) [1] (Fig. 1) is a diuretic sulfonamide widely studied because it is a strong inhibitor of the Zn(II) metalloenzyme carbonic anhydrase. The mechanism of the inhibition involves the binding of the active site metal ion by the sulfonamide. An X-ray crystal structure of the acetazolamide binding the enzyme has been determined. At 3.0 Å

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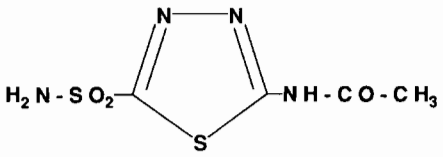

Fig. 1. Acetazolamide (H_2acm).

resolution, the electronic density map clearly revealed the position of the two S atoms of the inhibitor molecule but only a few further details of enzyme–inhibitor interactions were visible [2a, b]. Furthermore, ^{15}N NMR experiments of complexed carbonic anhydrase have shown that sulfonamides bind via a deprotonated N atom to the Zn(II) [2c]; however, there is no experimental evidence whether the sulfonamide group binds monodentate (through the N atom only) or bidentate (through the N and one O atom) [2d]. Besides, some of the direct evidences of metal–nitrogen binding in aromatic sulfonamide complexes of carbonic anhydrases, have only been carried out with sulfonamides whose structure differs considerably from that of the acetazolamide [2e, f]. Due to the difficulty in getting proper direct data of how acetazolamide coordinates the M(II) in the enzyme, studies on divalent metal complexes of H_2acm have been carried out [1] (although keeping always in mind that driving forces for the coordination features of the metals when the ligands are in solution are presumably rather different from those in the enzyme environment).

On the other hand, our interest in the coordination behavior of this ligand arises from the different chelating possibilities that it offers. In this sense, the crystal and molecular structure of two previously described complexes of acetazolamide, $[Ni(Hacm)_2(NH_3)_4]$ and $[Cu(acm)(NH_3)_2(OH_2)]_2\cdot(H_2O)_2$ [1a, b], showed that there is a remarkable influence of the linked metal ion on the way of deprotonation of the ligand and, concomitantly, on its way of coordination. In $[Ni(Hacm)_2(NH_3)_4]$, the ligand is deprotonated at the acetamido group, the donor atom being the N(2) nitrogen atom of the thiadiazole ring. In $[Cu(acm)(NH_3)_2(OH_2)]_2\cdot(H_2O)_2$, the acetazolamide is deprotonated both at the sulfonamido and at the acetamido groups; interaction with the copper(II) takes place through N(1) and N(2) of the thiadiazole ring and through N(4) of the sulfonamido group. IR spectra of two other acetazolamide complexes, $\{[M(Hacm')_2(NH_3)_2]$, M = Zn(II), Co(II)$\}$ [1c], suggested that deprotonation and coordination only through the sulfonamido group is also possible, although no direct crystallographic data of this behavior is available so far.

In all cases tested, addition of a base (such as ammonia) was necessary to isolate the complexes of acetazolamide. Now, we have undertaken a study of the coordination behavior of this ligand in the presence of chelating non-aromatic amines such as 1,2-ethanediamine (en) and 1,3-propanediamine (tn) in order to investigate also the influence of the base in the interaction of the acetazolamide with the copper(II) and the importance of the network of H bonds in the geometry and properties of the complexes formed. In this paper, the crystal and molecular structures of an acetazolamide–Cu(II)–en and an acetazolamide–Cu(II)–tn complex are presented and the spectroscopic properties are discussed. In the first compound, acetazolamide coordinates in a completely unprecedented way.

Experimental

Syntheses

Acetazolamide was supplied as powder material by Cyanamid Laboratories and by Lancaster Synthesis, Ltd. All reagents used were of analytical grade.

$[Cu(Hacm)_2(en)_2]$ (I) and $[Cu(Hacm)_2(en)_2]$ (III)

Solid H_2acm (2.5 mmol) was dissolved in a hot ethanolic solution of $Cu(NO_3)_2$ (0.5 mmol in 50 cm^3) (molar ratio H_2acm:Cu(II) = 5:1) with heating and stirring. Then, 5 mmol of 1,2-ethanediamine was added dropwise with stirring. After a few minutes, a violet microcrystalline product (**III**) precipitated. This solid was separated by filtration and the resulting blue–violet solution was allowed to stand at room temperature. After several hours (4–24 h) purple single crystals (**I**) grew which were collected on filter paper. (In a few cases, violet crystals corresponding to **III** were observed, but with time they change to purple, probably because the purple compound is the most stable species). (Approx. yield for **I**: 60%; for **III**: 30%). *Anal.* Calc. for $C_{12}CuH_{26}N_{12}O_6S_4$ (MW = 626.2): C, 23.0; H, 4.2; N, 26.8; S, 20.5; Cu, 10.2. Found for **I**: C, 23.2; H, 4.3; N, 27.2; S, 20.0; Cu, 9.5. Found for **III**: C, 23.3; H, 4.2; N, 26.7; S, 20.5; Cu, 10.3%. Compound **III** has not been investigated in detail because it transforms rather fast within a few days, both in contact with the mother liquor and as a dry solid, into compound I.

$[Cu(Hacm)_2(tn)_2]$ (II)

The compound was prepared analogously to I with slight differences: solid H_2acm (2.5 mmol) was dissolved in a hot ethanolic solution of $CuBr_2$ (0.5 mmol in 50 cm^3) (molar ratio H_2acm:Cu(II) = 5:1) with heating and stirring. Then, 3 mmol of 1,3-propanediamine was added dropwise with stirring. The resulting bright blue solution was allowed to stand at 4°. After 3–4 days, bright dark blue single crystals grew which were collected on filter paper (approx. yield 90%). *Anal.* Calc. for

$C_{13}CuH_{28}N_{12}O_6S_4$ (MW = 654.3): C, 25.7; H, 4.6; N, 25.7; S, 19.6; Cu, 9.7. Found: C, 25.4; H, 4.6; N, 25.7; S, 19.9; Cu, 10.0%.

Elemental analyses were performed by the Microanalytical Laboratory, University College, Dublin, Ireland.

Physical measurements

IR spectra were obtained with a Perkin-Elmer model 580B IR spectrophotometer in the region 4000–180 cm^{-1} as KBr pellets. Ligand field spectra were registered in the region 28 000–4000 cm^{-1} on a Perkin-Elmer 330 UV–Vis spectrophotometer, by the use of the diffuse-reflectance technique with MgO as a reference. EPR spectra on powdered samples were recorded at X-band frequencies on a Jeol JES-RE2X ESR spectrometer.

Crystallographic data collection and refinement of the structure

Information concerning conditions for crystallographic data collection and structure refinement is summarized in Table 1 for both compounds. Prismatic-shaped crystals, purple (compound **I**) and bright dark blue (compound **II**), were selected and sealed in a glass capillary. The density was determined by flotation in a mixture of n-hexane and 1,2-dibromoethane. The X-ray data were collected with a CAD-4 automatic four-circle Enraf Nonius diffractometer by using graphite-monochromated Mo Kα radiation. Cell dimensions were obtained by least-squares fit from the setting angles of 24 well-centered reflections with $10 \leqslant \theta \leqslant 12°$. A total of 7863 (**I**)/4163 (**II**) reflections were measured ($2 \leqslant \theta \leqslant 40°$, $-14 \leqslant h \leqslant 14$, $-16 \leqslant k \leqslant 16$, $0 \leqslant l \leqslant 16$) (**I**)/($2 \leqslant \theta \leqslant 30°$, $-13 \leqslant h \leqslant 13$, $0 \leqslant k \leqslant 14$, $0 \leqslant l \leqslant 19$) (**II**) of which 7452 (**I**)/4017 (**II**) were independent and 3947 (**I**)/1932 (**II**) considered significant ($I > 2\sigma(I)$). Only significant reflections were used in the refinement. Lorentz and polarization corrections were applied; absorption correction was not applied. Atomic scattering factors and corrections for anomalous dispersion for the Cu atom were taken from ref. 3.

For **I**, the space group $P\bar{1}$ was assumed throughout the structure analysis and was confirmed by the successful refinement of the structure. All calculations were carried out on the Leiden University computer (IBM-3083) using a set of computer programs locally written or modified by E. W. Rutten-Keulemans and R. A. G. de Graaff. The structure was solved by automatic Fourier techniques with the program AUTOFOUR [4], that, starting from the copper coordinates (at the inversion center), located seven non-H atoms. Successive cycles of least-squares refinement and Fourier syntheses gave the positions of the remaining non-H atoms. After several iterations of refinement a difference Fourier map yielded the positions of all the hydrogen atoms. (The two sulfonamido H atoms were clearly located). Hydrogen atoms were refined with an overall isotropic temperature factor. All non-H atoms were given individual anisotropic thermal parameters in the refinement. The final values of the discrepancy indices are given in Table 1.

Coordination to the copper via the sulfonamido O atom is quite surprising; an attempt was made to refine the structure with the sulfonamido N and O atoms interchanged. Evaluation of the resulting R factors and thermal parameters clearly indicates the structure proposed to be the correct one. In the final difference map corresponding to the definitive structure, the largest positive peak is at 3.07 Å from the Cu and at 1.47 Å from the S; the peak is not statistically significant as the height of 0.36 e $Å^{-3}$ compares to a noise level of 0.13 e $Å^{-3}$. The configuration proposed is also supported by the S(2)–O(2), S(2)–O(3) and S(2)–N(4) distances (Table 4) (*vide infra*).

Analysis of systematic absences revealed that **II** crystallizes in the monoclinic system, space group $P2_1/n$. The crystal structure was solved with the SHELXS-86 package [5] extending the model based on the copper positions to the complete structure. The refinement was carried out with SHELX-76 [6]. Non-H atoms were refined with anisotropic thermal parameters. All the H were clearly visible in the difference map, except for the hydrogens of the methyl group, which were included in the model at calculated positions with thermal factors about 30% greater than that of the corresponding C atom. The final difference map showed no residual density other than a peak of 0.35 e $Å^{-3}$ located near the C(4) atom. The refinement converged to the R values indicated in Table 1.

Illustrations were prepared with the aid of a modified version of the computer program ORTEP [7]. Geometrical calculations were performed with the local program GEOMSTDV (Rutten-Keulemans, 1990).

Results and discussion

Description of the structures

Figures 2 and 3 show an ORTEP drawing of the complexes with the atomic numbering and the thermal ellipsoids. Final atomic coordinates are listed in Tables 2 and 3. Geometric data, including relevant bond distances (Å) and angles (°) in the coordination sphere and in the organic ligands, are presented in Table 4. Inter and intramolecular hydrogen bonds with symmetry codes are given in Tables 5 and 6. Figures 4 and 5 contain ORTEP drawings showing the hydrogen-bond interactions.

Coordination polyhedron

The structures consist of discrete $[Cu(Hacm\text{-}O)_2(en)_2]$ (**I**)/$[Cu(Hacm\text{-}N)_2(tn)_2]$ (**II**) units linked together by

TABLE 1. Physical properties and main data relating to measurement and refinement of the structures of $[Cu(Hacm)_2(en)_2]$ (**I**) and $[Cu(Hacm)_2(tn)_2]$ (**II**)

Physical and crystallographic properties		
Formula	$C_{12}CuH_{26}N_{12}O_6S_4$ (**I**)	$C_{14}CuH_{30}N_{12}O_6S_4$ (**II**)
Molecular weight	626.2	654.3
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$
Z	1	2
a (Å)	8.196(7)	9.336(3)
b (Å)	9.094(4)	10.232(1)
c (Å)	9.352(3)	14.138(3)
α (°)	84.52(3)	90.00
β (°)	74.83(6)	103.80(2)
γ (°)	63.57(5)	90.00
V (Å^3)	602	1312
D_{exp}, D_{calc} (Mg m^{-3})	1.78, 1.78	1.65, 1.66
μ (cm^{-1})	13.03	11.35
$F(000)$	323.73	679.46
Crystal size (mm)	0.55×0.20×0.16	0.50×0.13×0.13
Data pertinent to measurement		
Temperature (K)	293	293
Radiation	λ(Mo Kα)=0.71073 Å	λ(Mo Kα)=0.71073 Å
Scan type	ω–2θ	ω–2θ
θ range (°)	2–40	2–30
Standard reflections		
Intensity (every 90 min)		
Orientation (every 200)	(−3, −4, 1), (0, 4, −1), (2, −1, 4)	(3, −3, 2), (3, 0, 5), (−1, 4, 5)
Decay of scattered powder (%)	6.39	4.48
No. measured	7863	4163
R_{int}	0.040	0.047
Transmission factor range	84.5–108.8	93.8–105.6
Data treatment and refinement		
No. reflections used ($I>2\sigma(I)$) (NO)	3947	1932
No. variables (NV)	212	218
Agreement factors[a]		
R	0.0335	0.0327
R_w	0.0427	0.0405
s	1.1607	1.1365
$\Delta\rho_{max}$ (e Å^{-3})	0.36	0.35

[a]Weighting scheme: $w=1/\sigma^2(F)$.

van der Waals contacts and hydrogen bonds. In both cases, Cu(II) ions, lying on symmetry centers, present an elongated tegragonally distorted octahedral environment. In the basal plane, the four N atoms of the two en (**I**)/tn (**II**) molecules form a slightly distorted square planar arrangement around copper, Cu–N distances being 2.000(1) (from N(5)) and 2.009(1) (from N(6)) Å (**I**)/2.044(3) (from N(5)) and 2.048(3) (from N(6)) Å (**II**). The axial positions are occupied by two sulfonamido O atoms (O(3), O(3)') (**I**)/two ring N atoms (N(2), N(2)'; the N ring atom closest to the acetamido moiety) (**II**) from different *trans* ligand molecules at semicoordinating distances of 2.652(1) (**I**)/2.457(2) (**II**) Å, thus leading to a coordination '4+2' for copper, although the axial ligand binding is much weaker for compound **I**. In both compounds, the acetazolamide is deprotonated at N(3).

The structure of **II** closely resembles the structure of the $[Ni(Hacm)_2(NH_3)_4]$ complex, previously reported [1b], but in the tn compound the axial distortion on the apical positions of the octahedron is much more pronounced, as could be expected for a Cu(II) complex. In **I**, surprisingly, in spite of having four potentially N chelating atoms, and in spite of being deprotonated at the acetamido group, the ligand acetazolamide coordinates the metal ion via one of the O atoms of the sulfonamido group. This behavior contrasts with that observed in **II** and in all acetazolamide complexes studied up to now (see 'Introduction'). So, whereas in the $[Ni(Hacm)_2(NH_3)_4]$ compound the nickel(II) ion forms NiN_6 chromophores with a quite regular (slightly elongated) octahedral geometry, in the present structure copper(II) prefers to bind weaker coordinating atoms (O atoms) in the apical positions to form a severely tetragonally distorted octahedron with four strong equa-

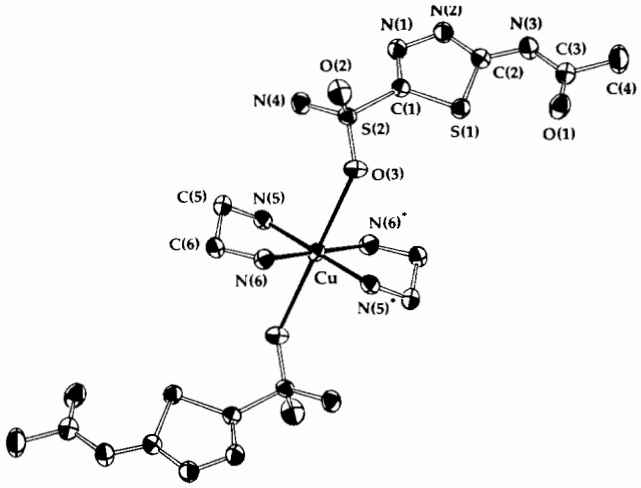

Fig. 2. An ORTEP representation of I showing the atom labelling scheme and the 90% probability ellipsoids. Hydrogen atoms have been omitted for clarity.

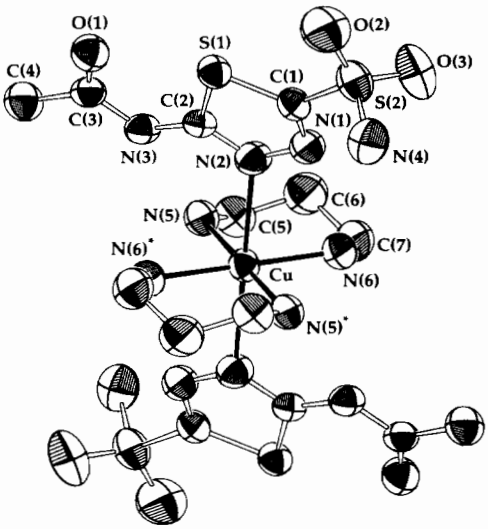

Fig. 3. An ORTEP representation of II showing the atom labelling scheme and the 90% probability ellipsoids. Hydrogen atoms have been omitted for clarity.

torial Cu–N bonds and two long axial Cu–O bonds, approaching a square coplanar geometry. Therefore, in the synthesis conditions mentioned, the acetazolamide seems to be an unusually weak ambidentate anionic ligand. The reason for this unusual behavior must be connected with the hydrogen bonding in the lattice and the copper(II) Jahn–Teller effect. The structure II would represent an intermediate situation between I and the Ni(II) compound. The long Cu–N bond, however, is unusual for the deprotonated Hacm ligand.

Two comments should be made in relation to the Cu–O coordination in the apical positions. As was explained in 'Experimental', the crystal structure determination showed quite clearly that O(3) (and not N(4)) is the atom coordinated to the Cu(II). Current

TABLE 2. Fractional atomic coordinates and isotropic thermal parameters for the non-hydrogen atoms of $[Cu(Hacm)_2(en)_2]$ (I), with e.s.d.s in parentheses

Atom	*x/a*	*y/b*	*z/c*	B_{iso}
Cu	0	0	0	1618(7)
S(2)	345(0)	191(0)	−166(0)	1677(13)
O(2)	4001(2)	2853(2)	−915(2)	273(5)
N(4)	1786(2)	3141(2)	−2361(2)	222(5)
O(3)	2913(2)	711(1)	−840(1)	256(4)
S(1)	718(0)	−109(0)	−289(0)	1915(13)
C(1)	5394(2)	794(2)	−3126(2)	177(4)
N(1)	5595(2)	1393(2)	−4437(2)	238(5)
N(2)	7235(2)	359(2)	−5398(2)	244(5)
C(2)	8235(2)	−987(2)	−4769(2)	178(4)
N(3)	9858(2)	−2155(2)	−5573(2)	218(4)
C(3)	10905(2)	−3443(2)	−4869(2)	216(5)
O(1)	10505(2)	−3656(1)	−3505(1)	263(4)
C(4)	12686(4)	−4674(3)	−5847(3)	352(7)
N(5)	−1679(2)	1755(2)	−1127(2)	188(4)
N(6)	−1367(2)	1629(2)	1693(2)	202(4)
C(5)	−2484(2)	3330(2)	−306(2)	229(5)
C(6)	−3024(2)	3001(2)	1316(2)	226(5)

TABLE 3. Fractional atomic coordinates and isotropic thermal parameters for the non-hydrogen atoms of $[Cu(Hacm)_2(tn)_2]$ (II), with e.s.d.s in parentheses

Atom	*x/a*	*y/b*	*z/c*	B_{iso}[a]
Cu	0	0	0	2826(14)
S(2)	21439(11)	−53575(10)	−5649(7)	409(2)
O(2)	3224(3)	−5826(2)	−1035(3)	635(10)*
N(4)	575(4)	−5748(4)	−1224(3)	486(11)
O(3)	2138(3)	−5748(3)	404(2)	612(9)
S(1)	35047(11)	−28243(10)	−11068(7)	308(2)
C(1)	2333(3)	−3644(3)	−534(2)	308(8)
N(1)	1576(3)	−2931(3)	−86(2)	347(7)
N(2)	1864(3)	−1627(3)	−160(2)	357(7)
C(2)	2851(3)	−1393(3)	−672(2)	279(7)
N(3)	3243(2)	−160(2)	−819(2)	309(7)
C(3)	4218(3)	19(3)	−1371(2)	314(7)
O(1)	4796(2)	−890(2)	−1744(1)	396(6)
C(4)	4585(4)	1410(4)	−1543(3)	432(10)
N(5)	1613(3)	1259(3)	689(2)	342(8)
N(6)	−127(4)	−858(3)	1287(2)	362(9)
C(5)	1750(5)	1660(4)	1704(3)	439(10)
C(6)	1777(5)	517(5)	2366(4)	543(13)
C(7)	343(4)	−197(5)	2239(3)	482(12)

[a]The atom marked * shows high thermal anisotropy.

research on the coordination behavior of an H_2acm-like ligand, the methazolamide (4-Methyl-Δ^2-1,3,4-thiadiazoline-2-sulfonamide) (Hmacm), carried out by Borrás and co-workers [8], has resulted in the synthesis of the compound $[Ni(macm)_2(NH_3)_4]$, with stoichiometry identical to that displayed by the acetazolamide compound, but with the Ni(II) coordinated to the sulfonamido N atom.

TABLE 4. Bond distances and angles for $[Cu(Hacm)_2(en)_2]$ (**I**) and $[Cu(Hacm)_2(tn)_2]$ (**II**), with e.s.d.s in parentheses

Distances (Å)	I	II	Angles (°)	I	II
Cu–O(3)	2.652(1)		N(5)–Cu–O(3)	97.41(5)	
Cu–N(2)		2.457(2)	N(6)–Cu–O(3)	97.45(5)	
Cu–N(5)	2.009(1)	2.044(3)	N(5)–Cu–N(2)		90.8(1)
Cu–N(6)	2.001(3)	2.048(3)	N(6)–Cu–N(2)		90.0(1)
C(1)–S(1)	1.727(2)	1.726(3)	N(5)–Cu–N(6)	84.77(6)	87.8(1)
C(2)–S(1)	1.759(2)	1.753(3)	C(2)–S(1)–C(1)	86.01(7)	85.9(1)
O(2)–S(2)	1.432(1)	1.417(3)	O(3)–S(2)–O(2)	118.71(9)	121.4(2)
O(3)–S(2)	1.434(1)	1.427(3)	N(4)–S(2)–O(2)	108.19(8)	107.5(2)
N(4)–S(2)	1.587(1)	1.588(4)	N(4)–S(2)–O(3)	108.63(8)	106.2(2)
C(1)–S(2)	1.768(2)	1.762(3)	C(1)–S(2)–O(2)	107.36(8)	105.7(1)
C(3)–O(1)	1.250(2)	1.254(4)	C(1)–S(2)–O(3)	105.51(7)	106.2(2)
N(2)–N(1)	1.379(2)	1.371(4)	C(1)–S(2)–N(4)	107.99(8)	109.7(2)
C(1)–N(1)	1.294(2)	1.283(4)	C(1)–N(1)–N(2)	111.7(1)	113.1(2)
C(2)–N(2)	1.318(2)	1.323(4)	N(1)–N(2)–Cu		119.8(2)
C(3)–N(3)	1.340(2)	1.346(4)	C(2)–N(2)–Cu		122.0(2)
C(2)–N(3)	1.354(2)	1.343(4)	C(2)–N(2)–N(1)	113.2(1)	113.1(2)
C(4)–C(3)	1.505(2)	1.497(5)	C(2)–N(3)–C(3)	118.6(1)	117.7(2)
N(5)–C(5)	1.477(2)	1.469(5)	S(2)–C(1)–S(1)	122.82(9)	122.9(2)
C(6)–C(5)	1.505(3)	1.494(6)	N(1)–C(1)–S(1)	116.0(1)	116.2(2)
C(7)–C(6)		1.498(6)	N(1)–C(1)–S(2)	121.1(1)	120.9(2)
N(6)–C(6)	1.477(2)		N(3)–C(3)–O(1)	124.9(2)	124.2(3)
N(6)–C(7)		1.476(5)	C(4)–C(3)–O(1)	120.1(2)	119.9(3)
			C(4)–C(3)–N(3)	115.0(2)	115.9(3)
			N(2)–C(2)–S(1)	113.0(1)	112.8(2)
			N(3)–C(2)–S(1)	126.3(1)	126.9(2)
			N(3)–C(2)–N(2)	120.6(1)	120.3(3)
			N(5)–C(5)–C(6)	107.5(1)	112.2(4)
			N(6)–C(6)–C(5)	107.8(1)	
			C(5)–C(6)–C(7)		115.2(4)
			N(6)–C(7)–C(6)		113.3(3)

TABLE 5. Probable hydrogen bonds for $[Cu(Hacm)_2(en)_2]$ (**I**)

A–H...B[a]	H...B (Å)	A...B (Å)	A–H...B (°)
N(4)–H(N42)...O(1)^{i}	1.99(2)	2.829(2)	153(2)
N(4)–H(N41)...N(3)^{ii}	2.31(2)	3.020(2)	169(2)
N(5)–H(N51)...O(2)^{iii}	2.59(2)	3.178(2)	139(2)
N(5)–H(N52)...N(3)^{ii}	2.32(2)	3.121(2)	171(2)
N(6)–H(N61)...N(2)^{iv}	2.20(6)	3.000(2)	165(2)
N(6)–H(N62)...O(1)^{v}	2.27(2)	3.026(2)	141(2)

[a]The second atom (B) is related to the atom listed in Table 2 by the following symmetry operations: (i) $-1+x$, $1+y$, z; (ii) $1-x$, $-y$, $-1-z$; (iii)$1+x$, y, z; (iv) $-1+x$, y, $1+z$; (v) $1-x$, $-y$, $-z$.

TABLE 6. Probable hydrogen bonds for $[Cu(Hacm)_2(tn)_2]$ (**II**)

A–H...B[a]	H...B (Å)	A...B (Å)	A–H...B (°)
N(4)–H(N41)...O(1)^{i}	1.93(4)	2.814(4)	169(4)
N(5)–H(N51)...O(3)^{ii}	2.47(3)	3.143(4)	140(3)
N(6)–H(N62)...N(3)^{iii}	2.40(4)	3.012(4)	134(3)

[a]The second atom (B) is related to the atom listed in Table 3 by the following symmetry operations: (i) $0.5-x$, $-0.5+y$, $-0.5-z$; (ii) x, $1+y$, z; (iii) $-x$, $-y$, $-z$.

As for the equatorial arrangement, in both structures the crystallographic symmetry, with the copper in the inversion center, causes the five involved atoms to lie in the same plane, although the square planar geometry around the metal center exhibits a small rhombic distortion (see Table 4). The observed Cu–N distances (short), as well as the bond length and bond angle distortions (small), are similar to those obtained for other complexes which involve this kind of chelate ligands [9–11]. In **I**, the en molecules adopt the *gauche* configuration, usual for chelating en, with a dihedral N(5),C(5),C(6)–C(5),C(6),N(6) angle of 52.3(2) Å, one C atom being 0.416(3) Å below the Cu,N(5),N(6) plane, and the other C 0.275(3) Å above it. In **II**, the tn molecules are twisted in the chair conformation with the following deviations from the in-plane CuN_4 chromophore: C(5), −0.568(6) Å; C(7); −0.489(7) Å; and C(6), −0.028(8) Å.

The out-of-plane coordination displays an important distortion, especially in **I**. In this complex, the long Cu–O apical distance (with a tetragonality of 0.74, value

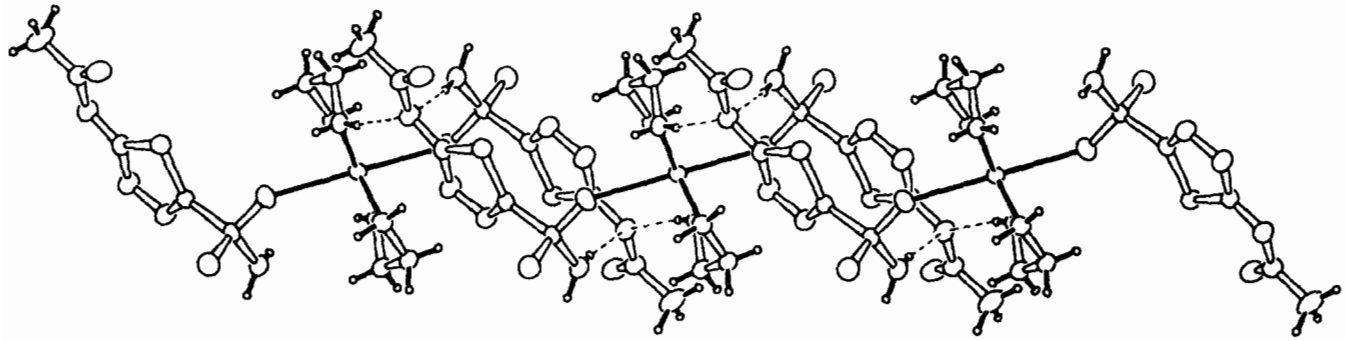

Fig. 4. An ORTEP drawing of three formula units of **I** showing important hydrogen bonds (dashed lines). Hydrogen atoms have been given an arbitrary isotropic factor for illustrative purposes. Only asymmetric units related with the reference at (x, y, z) by the symmetry operations ($-x$, $-y$, $-z$) and ($1-x$, $-y$, $-1-z$) have been represented.

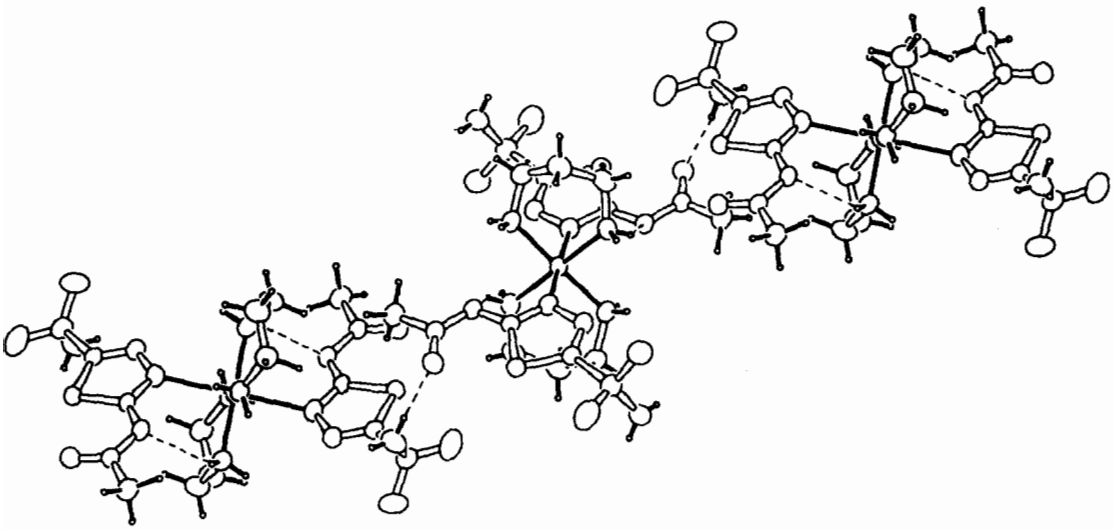

Fig. 5. An ORTEP drawing of three formula units of **II** showing important hydrogen bonds (dashed lines). Hydrogen atoms have been given an arbitrary isotropic factor for illustrative purposes. Only asymmetric units related with the reference at (x, y, z) by the symmetry operations ($-x$, $-y$, $-z$) and ($0.5-x$, $-0.5+y$, $-0.5-z$) have been represented.

estimated from Hathaway's definition [10]*) is of the same order of magnitude as the corresponding values reported for comparable systems such as the octahedral $[Cu(en)_2(OH_2)Cl]Cl$ and $[Cu(imidazole)_4(OH_2)_2]F_2$ complexes [10]. In addition, the four O(3)–Cu–N angles, falling within the range of an octahedral environment, are also clearly different.

Ligand conformation

A comparison of the ligand bond distances in **I** and **II** with those of the parent H_2acm [12] and those of the ligand in the previously reported acetazolamide complexes [1] confirms that in both cases deprotonation takes place on the acetamido moiety. This fact was already suggested by the analysis of the IR spectra (*vide infra*). Furthermore, the study of the ligand conformation shows that, in **I**, the mentioned interaction via the O of the sulfonamido group has little effect on the geometry of this part of the ligand, in accordance with the semicoordination found.

So, when the sulfonamido bond lengths are considered, no significant changes with respect to the parent H_2acm are observed, neither for **II**, nor for **I**. In **I** even both S–O distances are almost the same. With regard to the acetamido group distances, it may be appreciated that, as was observed in previous structures, there is a reduction of the C(3)–O(1) bond order and, at the same time, a shortening of the C(3)–N(3) and N(3)–C(2) bond distances, all indicating the N(3) deprotonation

*For equivalent ligands, the term tetragonality has been introduced as T=(mean in-plane distance R_s)/(mean out-of-plane distance R_l). The tetragonality of complexes involving non-equivalent ligands may be estimated if the values R_s and R_l are corrected to a standard Cu–L distance, such as that for nitrogen, using the respective values of Pauling covalent radii and the expression $R_l(\text{corrected}) = R_l(\text{observed} \times R_s^N/R_s^X$.

and the concomitant delocalization of the negative charge. The possibility of formation of the tautomeric N(3)=C(3)–O(1)H form instead of the N–H deprotonation was taken into account. The distances C(3)–O(1), however, although shortened, still fall within the range of the double C–O bonds [13]. The angles C(3)–N(3)–C(4), smaller than in the corresponding free ligand, are consistent with the loss of the proton, but do not give any new definitive information.

As far as the thiadiazole bond lengths are concerned, in both compounds the changes are equivalent and comparable to those observed in all the Hacm/acm complexes [1]. Notice that in **I**, the ring N(2) atom is not interacting with the copper; no matter whether the thiadiazole N atoms act as donors or not, the ring distances suffer the same changes, probably because these changes are due mainly to the deprotonation in the acetamido group and the subsequent delocalization of the negative charge through the ring bonds.

H-bond system and crystal packing

The H-bond system and concomitantly the packing pattern of both structures are very different, as could be expected from the different way of coordination displayed by the Hacm in each case. In both cases the hydrogen bond networks are very important in stabilizing the solids.

The coordination polyhedron of **II** is equivalent to that of the previously reported $[Ni(Hacm)_2(NH_3)_4]$ complex, as mentioned, but differs in the longer apical position, which is related to the different orientation of the nearly planar Hacm molecules with respect to the CuN_4 equatorial plane. In the Ni(II) complex, the Hacm plane is almost perpendicular to the Ni,N(5),N(6) plane, apparently to minimize the steric hindrance between the acetamido moiety and the ammonia molecules. In the present case, the Hacm plane is bent in such a way that there is an approach between N(3) (the deprotonated acetazolamide atom) and one of the tn N atoms to stabilize the structure by means of an 'intramolecular' H bridge. No apparent bulk effect is produced between the acetamido group and the tn molecules as reflected by the similarity of the angles Cu–N(2)–C(2) = 122.0(2)° and Cu–N(2)–N(1) = 119.8(2)°. Finally, in the crystal each asymmetric unit interacts basically only with two other asymmetric units through H bonds comparable to those observed in the Ni(II) structure.

Although in **II** Hacm does not interact with the metal through the group with the negative charge, the thiadiazole donor atom participates in the increase in the electronic density, because there is a delocalization of the negative charge, as explained before [1]. In compound **I**, however, the coordination is reached through an atom completely isolated from the deprotonated group (Mathew and Palenik [12], when reporting the crystal structure of the ligand, already pointed out that sulfonamido and the tdz ring are not connected in the same way as the thiadiazole ring and the acetamido group). This unusual behavior strongly suggests that the structure must be stabilized by a network of strong H bonds. Indeed, Table 5 shows that although no strong H bond is formed by N(3), five H bonds involving the three atoms with apparently higher electronic density (N(3), O(1) and N(2)) are observed, thus stabilizing the structure and leading to a packing pattern far different from **II**. As a result, in **I**, two ligand molecules related by the specified symmetry operation indicated in Fig. 4 are stacked in such a way that N(3) forms two intermolecular H bonds: one with the en N(6)′ atom and the other with the N(4)′ atom of the second ligand, whose N(3)′ atom, in turn, is connected to the en N(6) and the N(4) atoms of the former asymmetric unit. In **II**, N(3) is involved in only one H bond, 'intramolecular', with one tn N atom (that is why the almost planar Hacm ligands are approaching the equatorial plane). Intermolecular H bonds established by other donor atoms than N(3) link the ligand with other molecules placed at the positions of the specified symmetry operations (Fig. 5).

Spectroscopic properties

IR spectra

The most significant bands for **I** are: 3305, 3285(d); 2990, 2975(d); 1620(m); 1550(s); 1330(s); 1160(s); 740(m); for **II**: 3315(b); 2950(b); 1580(sh); 1540(s,b); 1355(s); 1170(s); (d = doublet; m = medium; s = strong; b = broad; sh = shoulder). In previous papers [1], a correlation between the different coordination modes of the acetazolamide and the IR of the corresponding compounds was established from the available crystallographic data. For compound **I**, the new coordinating mode of the ligand is also reflected in a different IR pattern. Two groups of bands are considered the most significant: (A) ν(C=O) and (B) $\nu(SO_2)_{sym,\ asym}$.

(A) In the complexes reported up to now in which the acetamido group of acetazolamide is deprotonated, the ν(C=O) absorption almost disappears yielding a very weak peak around 1600 cm^{-1}, or a shoulder overlapped to the intense broad 1550 cm^{-1} band. In **I**, the carbonyl vibration is also shifted to lower wavenumbers, but displays a clear medium intensity band. This change, probably related with the fact that the coordination is not produced via the ring N atom connected with the acetamido group, had already been observed in another acetazolamide compound [1d], but single crystals of it could not be obtained. The IR spectrum of **II** displays only a shoulder (*vide supra*) in agreement with the method of coordination found. It

has to be pointed out that in this IR region en and tn also exhibit an important band ($\delta(NH_2)$); the lower wavenumber expected for the chelating amines (1595 and 1565 cm^{-1}, respectively) [14] has led us to the former assignment (the amine band would be included in the broad band at 1550 cm^{-1}).

(B) In the reported compounds, when deprotonation is produced through the sulfonamido group, with respect to the parent H_2acm spectrum the SO_2 sym. and asym. stretching bands are shifted to lower wavenumbers; when this group does not interact, the bands remain unchanged or move slightly to higher wavenumbers. In **I**, an intermediate behavior is observed: the asym. vibration is slightly shifted to higher wavenumbers and the sym. one to lower, which is logical considering the small changes in the group (no deprotonation, weak interaction with the copper). The spectrum of **II** is comparable to that of $[Ni(Hacm)_2(NH_3)_4]$, as expected.

In the region 2900–3400 cm^{-1}, the bands above listed correspond to the NH_2 and CH_2 stretching vibrations of the diamine molecules. In **I**, the band at 740 cm^{-1}, not observed in the IR of the parent H_2acm, could be tentatively assigned to the $(NH_2)_{rock}$ vibration of the en molecules [14]. The IR spectrum of **III** only exhibits slight differences with respect to that of **I**, the most important concerning the H-bond region (2900–3200 cm^{-1}) and the M–N region (200–500 cm^{-1}).

Ligand field spectra

The reflectance spectrum of **I** (purple compound) exhibits a maximum at 19.8×10^3 cm^{-1}; that of **II** (bright dark blue compound) shows a maximum at 16.6×10^3 cm^{-1} and a shoulder at 11.3×10^3 cm^{-1}. These ligand field spectra agree with distorted octahedral (4+2) (almost square coplanar for **I**) coordinating geometries around Cu(II) in both complexes, the differences between the respective λ_{max} (and concomitantly between the respective color) being also in accordance with the very long axial distance for **I** and the shorter distance for **II** (Table 4) [15, 16].

The violet compound (**III**) isolated during the synthesis of **I**, with the same formula as **I**, shows a red shift in the ligand field spectrum ($\lambda_{max}=18.1\times10^3$ cm^{-1}) when compared to **I**. This shift could be ascribed to a different geometry in the violet compound, as a result of either different hydrogen-bonding and crystal-packing forces and/or a coordination via the N instead of the O sulfonamido atoms. Analog effects have also been observed in several alkylethylenediamine–copper(II) salts upon changing the temperature (thermochromism) [17]. Lever and co-workers have provided convincing support for a model of tetragonal distortion in these complexes, in which the in-plane bond strength increases as the axial ligation decreases, as the mechanism of thermochromism. In the present case, the transition is produced at room temperature, but a larger stability of the violet compound has been appreciated at low temperature (4 °C).

EPR

EPR spectra have been recorded on microcrystalline samples at room and liquid N_2 temperatures. Compound **I** exhibits an isotropic spectrum with a g value of 2.05. The EPR spectrum of **II** displays a not resolved asymmetric and broad $g_{\parallel}$ region, $g_{\perp}$ being 2.07. The origin of this behaviour must be the existence of an exchange or interaction between Cu(II) centers in the crystal lattice [16].

Conclusions

The previous discussions have led to the following conclusions: (i) although the acetazolamide has to be deprotonated to allow the isolation of the complexes, the deprotonated group does not have to be involved in the direct binding of the metal ion; (ii) when the deprotonated group is not directly bonded to the metal, there is a network of H bonds (involving specially N(3)) stabilizing the 'excess' of negative charge; in the case of **I**, with the mentioned unexpected coordination via O(3), a 'pairing' of Hacm ions is observed; (iii) the Jahn–Teller effect of copper(II) together with the mentioned packing pattern should account for the unexpected O semicoordination in the apical positions observed in **I**, and for the stronger apical distortion displayed by **II** when compared with the equivalent Ni(II) structure; (iv) the *O*-sulfonamido coordination of Hacm has little effect on the geometry and IR spectra of the sulfonamido part when compared with H_2acm; deprotonation in the acetamido moiety and hydrogen bridging in compound **I** are of greater importance; this fact is in accordance with the semicoordination found; (v) thus, as a global conclusion, in the present synthesis conditions, the ambidentate acetazolamide can be considered an unusually weak anionic coordinating ligand. These results further emphasize that the acetazolamide has a rich and diverse coordination chemistry, which could be of relevance to a proper understanding of the mechanism of inhibition of the carbonic anhydrase metalloenzyme.

Supplementary material

Tables of anisotropic thermal parameters for **I** and **II**; positional parameters of hydrogen atoms for **I** and **II**; structure factors of **I** (15 pages) and **II** (7 pages); and equations of least-squares planes for **I** and **II** are available form the authors on request.

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