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Copper complexes modelling the interaction between benzolamide and Cu-substituted carbonic anhydrase. Crystal structure of $Cu(bz)(NH_3)_4$ complex

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Abstract

New copper benzolamide (H_2bz, 5-phenylsulfonamide-1,3,4-thiadiazole-2-sulfonamide) complexes with ammonia, diethylentriamine (dien) and dipropylentriamine (dipn) have been prepared. The complex $[Cu(bz)(NH_3)_4]$ crystallises in the monoclinic space group $P2_1/n$ with $a=7.621(3)$, $b=19.91(5)$, $c=11.291(3)$ Å, $\beta=93.17(4)°$ and $Z=4$. The Cu(II) is five-coordinated with an almost regular square pyramidal geometry. The dideprotonated sulfonamide behaves as monodentate ligand interacting with the metal ion through the N atom of the unsubstituted sulfonamide group. In the EPR spectrum, exchange coupling between Cu(II) polyhedra of different orientations in the unit cell is observed. The dien and dipn ligands provide a model of the histidine environment of the metal ion in carbonic anhydrase (CA). From the spectroscopic properties, the ternary triamine complexes can be considered as analogous of the adducts formed by Cu-CA and the inhibitor benzolamide.

Keywords: Copper complexes; Benzolamide complexes; Ternary complexes; Crystal structures

1. Introduction

Catalytic mechanisms of zinc-containing carbonic anhydrases (CA) have consistently been interesting bioinorganic subjects [1,2]. Most of the strong inhibitors of CA are anions (e.g., SCN^-, CN^-, I^-), the inhibition of which is understandable in light of the known enzyme–substrate complex formed between CA and anionic HCO_3^-. On the other hand, neutral sulfonamides (e.g., acetazolamide, methazolamide, *p*-toluenesulfonamide, 4-nitro-benzenesulfonamide) are even stronger inhibitors of CA. From spectroscopic studies and X-ray analysis it is accepted that sulfonamides bind to Zn(II) as unidentate anions in a hydrophobic pocket of the CA active centre [3–6].

Our studies on the interaction of neutral sulfonamides with the metals ions (Zn(II), Co(II), Ni(II) and Cu(II)) have shown that these inhibitors, except for methazolamide [7,8], can bind in several ways [9–11] and not only as monodentate anions through the sulfonamido N atom. We have proved that the binding of the sulfonamide depends on the deprotonation (i.e. mono- or dideprotonated sulfonamide) and on the metal ion. Owing to this variety of coordination behaviour and as a part of our research we have initiated an investigation of the binding of acetazolamide (H_2acm) to model complexes with ligands that can be considered as mimics of CA enzyme [12]. Now, for these studies, we have chosen a new sulfonamide, the benzolamide (Fig. 1) that, as the acetazolamide, presents two dissociable protons hence different coordination possibilities can be expected. Moreover, benzolamide is a stronger CA inhibitor than H_2acm [13].

In this paper we describe the interaction of benzolamide with the copper(II) ion on the basis of the crystal structure of the $[Cu(bz)(NH_3)_4]$ complex. We also report the synthesis and characterisation of Cu(II)–benzolamide complexes with the tridentate nitrogen ligands, diethylenetri-

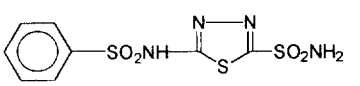

Fig. 1. Benzolamide (H_2bz).

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amine and dipropylenetriamine that can model the environment of the enzyme metal ion.

2. Experimental

2.1. Materials and methods

Analytical data (C, H, N) were obtained in a Carlo Erba Instrument model MOG 1106 of the Inorganic Department of the University of Salamanca, Spain. IR spectra were recorded on a Perkin-Elmer 843 instrument. Samples were prepared using the KBr technique. Electronic spectra were registered on a Shidmazu UV 2101PC spectrophotometer. EPR spectra were carried out at room temperature with a Brucker ER 200 D spectrometer. Magnetic susceptibility measurements at room temperature were taken with a fully-automated AZTEC DSM8 pendulum-type susceptometer. Mercury tetrakis(thyocianato)cobaltate(II) was used as a susceptibility standard. Corrections for the diamagnetism were estimated from Pascal constants.

Reagents were of the highest grade commercially available and were used without further purification. Benzolamide (H_2bz) was a gift from Professor T.H. Maren (University of Florida, Gainesville).

2.2. Synthesis of the complexes

2.2.1. $Cu(bz)(NH_3)_4$

12 ml of concentrated ammonia (30%) were added dropwise with continuous stirring to 25 ml of an ethanolic solution containing 0.25 mmol of $Cu(ClO_4)_2 \cdot 6H_2O$ and 0.5 mmol of benzolamide. Then, the resulting blue solution was heated at 60°C for 15 min and left to stand at 4°C. After 1 day, prismatic blue crystals suitable for X-ray measurements were obtained. The crystals were filtered, washed with cooled ethanol and dried under vacuum.

2.2.2. $Cu(bz)(dien)(H_2O)$ and $Cu(bz)(dipn)(H_2O)$

0.5 mmol of triamine [diethylenetriamine (dien) or bis(3-aminopropyl)amine (dipn)] were added to an ethanolic solution of $CuCl_2 \cdot 2H_2O$ (0.5 mmol in 20 ml) with continuous stirring. The solution turned dark blue, and 0.5 mmol of benzolamide were then added. The resulting solution was stirred for several minutes, and a violet precipitate was obtained which was isolated by filtration, washed with ethanol and dried under vacuum.

Anal. Found: C, 28.73; N, 20.26; H, 4.00. Calc. for $C_{12}N_7S_3O_5H_{21}Cu$: C, 28.65; N, 19.50; H, 4.18%.

Anal. Found: C, 32.37; N, 18.84; H, 4.40. Calc. for $C_{14}N_7S_3O_5H_{25}Cu$: C, 31.66; N, 18.47; H, 4.71%.

2.3. Crystal data

$C_8H_{18}CuN_8O_4S_3$, $M_r = 450.01$, monoclinic, space group $P2_1/n$, $a = 7.621(3)$, $b = 19.91(5)$, $c = 11.291(3)$ Å, $\beta = 93.17(4)°$, $V = 1711(4)$ Å^3, $Z = 4$, $D_x = 1.75$ g cm^{-3}, Mo Kα radiation (graphite crystal monochromator, $\lambda = 0.71073$ Å), $\mu = 16.61$ cm^{-1}, $F(000) = 924$, $T = 200(2)$ K [14]. Final conventional $R = 0.035$ and $wR2 = 0.056$ for 1047 'observed' reflections and 242 variables.

2.4. X-ray experimental

A blue crystal with dimensions of $0.26 \times 0.13 \times 0.13$ mm was used. Mo Kα radiation was used with a graphite crystal monochromator on an Enraf-Nonius CAD-4 single-crystal diffractometer ($\lambda = 0.71073$ Å). The unit cell dimensions were determined from the angular settings of 25 reflections with θ between 13 and 20°. The space group was determined to be $P2_1/n$ from the systematic absences. The intensity data of 3504 reflections, in hkl range (0, −23, 0) to (9, 23, 13) and θ limits ($0 < \theta < 25°$) were measured using the ω–2θ scan technique and a variable scan rate with a maximum scan time of 60 s per reflection. The final drift correction factors were between 0.99 and 1.05. On all reflections profile analysis was performed [15,16]. Some doubly measured reflections were averaged, $R_{int} = \Sigma(I - \langle I \rangle)/\Sigma I = 0.116$, resulting in 1649 'unique' reflections, of which only 1047 were 'observed' with $I > 2\sigma(I)$. Lorentz and polarisation corrections were applied and the data were reduced to $|F_o|$ values. The heavy atom and most non-hydrogen atoms were found using the program DIRDIF [17]. The remainder of the non-H atoms were located from the Fourier synthesis. Isotropic least-squares refinement on F^2, using SHELXL93 [18], converged to $R = 0.102$. At this stage an empirical absorption correction was applied using XABS2 [19]. The minimum and maximum transmission factors were 0.61 and 1.00, respectively. During the final stages of the refinement, the positional parameters and the anisotropic thermal parameters of the non-H atoms were refined. Some hydrogen atoms were geometrically placed and some were found in the Fourier synthesis. The final conventional agreement factors were $R = 0.035$ and $wR2 = 0.056$ for the 1047 'observed' reflections and 242 variables. The function minimised was $(\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2)^{1/2}$, $w = 1/[\sigma^2(F_o^2) + (0.0000P)^2]$ with $\sigma(F_o)$ from counting statistics and $P = (\max.(F_o^2, 0) + 2F_c^2)/3$. The maximum shift in the e.s.d. ratio in the last full-matrix least-squares cycle was 0.007. The final difference Fourier map showed no peaks higher than 0.30 e Å^{-3} or deeper than −0.27 e Å^{-3}. Atomic scattering factors were taken from the International Tables for X-ray Crystallography [20]. Geometrical calculations were made with PARST [21]. The figure showing the coordination and the atomic numbering scheme was drawn by EUCLID package [22]. All calculations were made at the University of Oviedo on the Scientific Computer Centre and X-ray Group VAX/AXP computers.

3. Results and discussion

3.1. Crystal structure of the $Cu(bz)(NH_3)_4$ complex

An ORTEP drawing of the $Cu(bz)(NH_3)_4$ complex with the atomic numbering scheme is shown in Fig. 2. Atomic coordinates are collected in Table 1. Table 2 lists selected bond distances and angles.

The structure consists of discrete units which interact through a network of weak hydrogen bonds. The Cu(II) is coordinated by five nitrogen atoms in an almost regular square pyramidal geometry. The τ value of 0.016 ($\tau=(\beta-\alpha)/60$ where β=N(1)–Cu–N(5), 168.6° and α=N(7)–Cu–N(8), 167.6°) is very close to zero, characteristic of a perfect square-basal pyramidal arrangement [23]. The metal ion is 0.21 Å above the basal plane formed by three ammonia N atoms, N(5), N(7) and N(8) and the N sulfonamido, N(1), from the benzolamidate ligand. The axial position is occupied by a fourth ammonia molecule at a longer distance (2.292(5) Å) than the equatorial ones (Cu–N ammonia; 2.041(4), 2.037(7) and 2.042(5) Å and Cu–N sulfonamido, 2.019(8) Å). Metal–ligand bond distances are considered as normal and are similar to those found in other copper–sulfonamide–ammonia complexes [11,23]. Angles in the basal plane are close to 90°, ranging from 86.1(2) to 98.9(3)°.

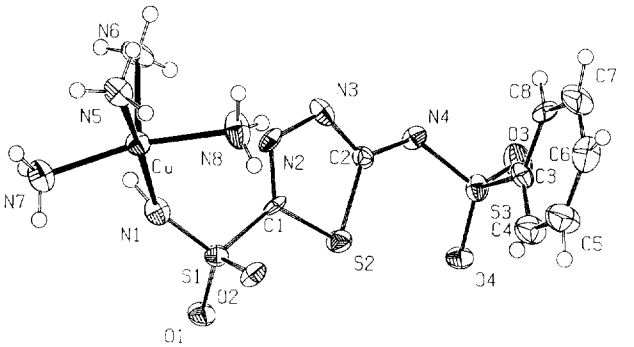

Fig. 2. ORTEP drawing of the $Cu(bz)(NH_3)_4$ complex with the atomic numbering scheme.

Table 1
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for $Cu(bz)(NH_3)_4$

	x	y	z	U_{eq} [a]
Cu	871(1)	8135(1)	561(1)	23(1)
S(1)	4044(3)	8507(1)	−1149(2)	20(1)
S(2)	5001(3)	9838(1)	−2319(2)	26(1)
S(3)	4761(3)	11331(1)	−3466(2)	25(1)
O(1)	5915(7)	8370(2)	−1244(4)	28(2)
O(2)	2929(7)	8261(2)	−2138(3)	26(2)
O(3)	5214(8)	12031(2)	−3544(4)	39(2)
O(4)	6017(7)	10859(2)	−3852(4)	29(2)
N(1)	3315(10)	8308(3)	26(5)	27(3)
N(2)	2911(9)	9752(3)	−610(4)	23(2)
N(3)	2957(9)	10433(2)	−909(5)	27(2)
N(4)	4173(9)	11208(2)	−2142(4)	21(2)
N(5)	−1575(8)	7795(3)	892(5)	31(2)
N(6)	942(8)	9068(2)	1750(5)	32(2)
N(7)	2013(9)	7431(2)	1669(4)	35(2)
N(8)	−232(10)	8681(4)	−819(7)	39(3)
C(1)	3912(11)	9406(3)	−1279(6)	20(3)
C(2)	3955(11)	10565(3)	−1784(6)	20(3)
C(3)	2786(9)	11206(3)	−4364(6)	24(3)
C(4)	2753(14)	10694(4)	−5199(10)	38(4)
C(5)	1173(15)	10584(4)	−5853(8)	47(4)
C(6)	−306(12)	10979(4)	−5676(7)	40(3)
C(7)	−213(13)	11496(4)	−4829(9)	45(3)
C(8)	1369(11)	11605(4)	−4185(6)	28(3)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 2
Selected bond lengths (Å) and angles (°) for $Cu(bz)(NH_3)_4$

Cu–N(1)	2.019(8)	Cu–N(5)	2.037(7)
Cu–N(7)	2.041(4)	Cu–N(8)	2.042(5)
Cu–N(6)	2.292(5)	S(1)–O(2)	1.450(4)
S(1)–O(1)	1.461(7)	S(1)–N(1)	1.519(8)
S(1)–C(1)	1.800(8)	S(2)–C(1)	1.707(8)
S(2)–C(2)	1.776(8)	S(3)–O(4)	1.426(6)
S(3)–O(3)	1.441(6)	S(3)–N(4)	1.603(6)
S(3)–C(3)	1.785(5)	N(2)–C(1)	1.300(9)
N(2)–N(3)	1.398(8)	N(4)–C(2)	1.355(8)
N(3)–C(2)	1.307(9)	C(4)–C(5)	1.40(1)
C(3)–C(8)	1.37(1)	C(3)–C(4)	1.39(1)
C(5)–C(6)	1.40(2)	C(6)–C(7)	1.40(1)
C(7)–C(8)	1.39(1)		
N(1)–Cu–N(5)	168.6(2)	N(1)–Cu–N(7)	86.1(2)
N(5)–Cu–N(7)	91.3(3)	N(1)–Cu–N(8)	91.6(3)
N(5)–Cu–N(8)	88.5(3)	N(7)–Cu–N(8)	167.6(3)
N(1)–Cu–N(6)	92.6(3)	N(5)–Cu–N(6)	98.9(3)
N(7)–Cu–N(6)	101.7(2)	N(8)–Cu–N(6)	90.6(3)
O(2)–S(1)–O(1)	114.4(4)	O(2)–S(1)–N(1)	110.9(3)
O(1)–S(1)–N(1)	114.9(3)	O(2)–S(1)–C(1)	104.2(2)
O(1)–S(1)–C(1)	103.3(4)	N(1)–S(1)–C(1)	108.0(4)
C(1)–S(2)–C(2)	86.1(4)	O(4)–S(3)–O(3)	116.9(4)
O(4)–S(3)–N(4)	114.3(3)	O(3)–S(3)–N(4)	106.6(3)
O(4)–S(3)–C(3)	107.1(3)	O(3)–S(3)–C(3)	107.3(3)
N(4)–S(3)–C(3)	103.7(4)	S(1)–N(1)–Cu	134.0(3)
C(1)–N(2)–N(3)	110.6(7)	C(2)–N(3)–N(2)	113.6(7)
C(2)–N(4)–S(3)	117.9(5)	N(2)–C(1)–S(2)	117.1(5)
N(2)–C(1)–S(1)	120.8(6)	S(2)–C(1)–S(1)	122.0(5)
N(3)–C(2)–N(4)	120.1(7)	N(3)–C(2)–S(2)	112.6(5)
N(4)–C(2)–S(2)	127.2(7)	C(8)–C(3)–C(4)	122.9(6)
C(8)–C(3)–S(3)	118.9(5)	C(4)–C(3)–S(3)	118.1(6)
C(3)–C(4)–C(5)	117.3(8)	C(5)–C(6)–C(7)	120.0(7)
C(4)–C(5)–C(6)	121.0(7)	C(8)–C(7)–C(6)	118.7(9)
C(3)–C(8)–C(7)	120.1(7)		

Equivalent position: $-x+1/2, +y-1/2, -z-1/2$. Selected non-bonding distances: Cu–O(3)* 3.239(6).

The coordination behaviour of benzolamide is the most relevant feature of the sulfonamide in the complex. It must be noted that, although it is dideprotonated, it acts as a monodentate ligand via the nitrogen atom from the unsubstituted sulfonamido group. This fact contrasts with the ligand behaviour of the related sulfonamide acetazolamide (H_2acm) in the complex $[Cu(acm)(NH_3)_2(H_2O)]_2 \cdot 2H_2O$ [11], where the doubly ionised acetazolamide, by loss of the acetamido and sulfonamido protons, coordinates the Cu(II) through the N sulfonamido and N thiadiazole atoms. Here, the interaction

with the N thiadiazole adjacent to the acetamido group is markedly stronger than that of the other thiadiazole nitrogen. Considering the dideprotonated nature of benzolamide it could be expected that the interaction to the metal ion takes place, at least, through two donor atoms. The reason why the behaviour of the two sulfonamides is so different can be inferred from the stronger interaction between the thiadiazole ring and the acetamido group rather than between the interaction of the thiadiazole ring and the sulfonamido group. In acetazolamide, the acetamido group and the ring are conjugated. Thus, the negative charge is able to move towards the N thiadiazole favouring its coordination.

The bond distances of the sulfonamidate ligand are similar to those found in previously reported complexes of thiadiazole sulfonamide derivatives (i.e. acetazolamide, methazolamide) [7–11]. Interestingly, the two S–N bond lengths are quite different (S(1)–N(1), 1.519(8) Å and S(3)–N(4), 1.603(6) Å), suggesting a different charge delocalisation through these bonds and adjacent groups upon deprotonation. In fact, the negative charge on N(3) in the thiadiazole ring can move towards the heterocyclic while the delocalisation of the negative charge on N(1) is hindered by the tetrahedral geometry of the sulfonamido moiety and hence is more localised on the S(1)–N(1) bond.

3.2. IR spectra

The most significant IR bands of the free ligand and the complex are collected in Table 3. As we have pointed out previously for other sulfonamide complexes the IR spectral data can give some information about the coordination site of the sulfonamide ligand [11,12,24,25].

In general, the bands corresponding to the ν(C=N) vibrations of the thiadiazole ring, which in the free ligand appear as a doublet at 1580–1570 cm^{-1} and a peak at 1500 cm^{-1}, are shifted to 1430 cm^{-1} in the complexes. By analogy with the IR spectra of the $[Cu(bz)(NH_3)_4]$ complex whose crystal structure is known, the lack of this band could be due to the modifications that take place on the π-thiadiazole system upon deprotonation of the substituted sulfonamido group.

The $\nu(SO_2)_{asym}$ and $\nu(SO_2)_{sym}$ stretching frequencies undergo marked modifications on complex formation. In general, of the two bands assigned to each vibration mode, only one is observed and it is shifted to lower frequencies. This spectral feature is associated with the binding of the sulfonamides through the deprotonated sulfonamido group [12]. As expected from the shortening of the S–N bond length, its characteristic ν(S–N) vibration is shifted to higher frequencies.

Table 3
Selected IR bands (cm^{-1})

Compound	$\nu(C{=}N)_{ring}$	$\nu(SO_2)_{asym}$	$\nu(SO_2)_{sym}$	ν(S–N)
Benzolamide(H_2bz)	1580–1570d 1500	1360, 1320	1180, 1140	940, 910
$Cu(bz)(NH_3)_4$	1430	1270	1140	990, 940
Cu(bz)(deta)(H_2O)	1430	1275	1140	970, 950
Cu(bz)(dipn)(H_2O)	1430	1300–1280d	1140–1130d	950–940d

d = doublet.

Because the IR spectra of all compounds show the same pattern it can be deduced that the benzolamide behaves as ligand as in the $[Cu(bz)(NH_3)_4]$ complex.

3.3. RD spectra, magnetic data and EPR spectra

The solid state spectrum of the ammonia compound exhibits a broad band at ~ 15 625 cm^{-1}, which can be assigned to the $^2B_1 \rightarrow {}^2B_2$ and $^2B_1 \rightarrow {}^2E_2$ transitions in a square pyramidal geometry [26]. The reflectance diffuse spectrum of the dien and dipn compounds show absorption maxima centred at 16 000 and 15 380 cm^{-1}, respectively. The asymmetric band of the dipn compound seems to suggest a more distorted geometry.

The $Cu(bz)(NH_3)_4$ compound exhibits a normal value of the magnetic moment for an orbitally non-degenerate ground state, 1.84 BM. The effective magnetic moment values of the Cu(bz)(dien)(H_2O) and Cu(bz)(dipn)(H_2O) complexes, 1.60 and 1.38 BM, respectively, suggest an antiferromagnetic coupling.

The $Cu(bz)(NH_3)_4$ compound presents an anisotropic polycrystalline EPR spectrum which is reversed in form. This reversed type of EPR spectrum with $g_\perp > g_\parallel$ can be understood in terms of CuN_5 chromophores misaligned by about 90° [27]. From the four CuN_5 square pyramids in the unit cell, those around Cu(1) and Cu(2) as well as Cu(3) and Cu(4) are connected by an inversion centre with an antiparallel orientation of the Cu–N(6) axes. The angle between the planes N(31)–N(51)–N(71)–N(81)[Cu(1)] and N(33)–N(53)–N(73)–N(83)[Cu(3)] (Cu···Cu distance 7.62 Å) is $2\varepsilon' = 95.66°$. It seems reasonable to assume that the two sublattices with a distance below 8 Å are exchange coupled. A direct Cu···Cu exchange is rather improbable. The exchange presumably occurs via an overlap between the spacious ligand rings of different $Cu(bz)(NH_3)_4$ polyhedra. The experimental g values are $g_\parallel = 2.07$ and $g_\perp = 2.17$. They obviously do not reflect the square pyramidal geometry of the CuN_5 entity. Exchange interactions between differently oriented polyhedra with the canting angle 2ε will induce a coupled g tensor:

$$g_1^{ex} = \cos^2\varepsilon g_\parallel + \sin^2\varepsilon g_\perp \quad g_2^{ex} = \sin^2\varepsilon g_\parallel + \cos^2\varepsilon g_\perp$$
$$g_3^{ex} = g_\perp \qquad (1)$$

For $2\varepsilon = 90°$ (antiferrodistortive order of SPs) [27] the above equation simplifies to:

$$g_\parallel^{ex} = g_\perp \text{ and } g_\perp^{ex} = 1/2(g_\parallel + g_\perp) \qquad (2)$$

The resulting molecular g tensor is $g_\parallel = 2.27$ and $g_\perp = 2.07$. This sequence, $g_\parallel > g_\perp$ is indicative of a $d_{x^2-y^2}$ ground state for a square pyramid. The calculated g parameters are in good agreement with those found in the square pyramidal

$[Cu(NH_3)_5][PF_6]_2$ complex studied by Tomlinson and Hathaway [26].

The EPR spectrum of Cu(bz)(dipn)(H_2O) is axial with EPR parameters $g_{\parallel} = 2.20$ and $g_{\perp} = 2.07$. The solid-state EPR spectrum of the Cu(bz)(dien)(H_2O) is also axial with the poorly resolved parallel component. The calculated EPR parameters are $g_{\parallel} \approx 2.20$ and $g_{\perp} = 2.05$. The Cu(bz)-(dien)(H_2O) complex doped in the analogous zinc derivative [1] shows clearly the hyperfine coupling, $A_{\parallel} = 154 \times 10^{-4}\ cm^{-1}$ which is consistent with a square pyramidal stereochemistry [28]. This axial spectrum ($g_{\parallel} > g_{\perp}$), with reduced $A_{\parallel}$ value, is similar to those of the adducts of copper carbonic anhydrase with sulfonamide inhibitors described by Bertini et al. [29]. By combining the ^1H NMR data and the low $A_{\parallel}$ values observed in the case of the copper substituted bovine CA–sulfonamide adducts, Bertini et al. conclude that two kinds of sulfonamide derivatives are obtained with the two isozymes (copper-substituted bovine and human CAs) involving two different copper chromophores: one, pseudotetrahedral with the water substituted by the sulfonamide and the other, five-coordinated with the water molecule still present in the copper coordination sphere and the sulfonamide added in a fifth coordination position. In the case of acetazolamide both human and bovine enzymes give rise to five-coordinated adducts. Since benzolamide in the Cu(bz)(dien)(H_2O) and Cu(bz)(dipn)(H_2O) complexes is expected to bind through the N sulfonamide atom as in the Cu(bz)$(NH_3)_4$ compound and a five coordination with an N_4O donor set is consistent with both the optical and EPR data, these copper complexes can be considered good models of the Cu-CA–sulfonamide adducts.

4. Supplementary material

Atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic thermal parameters, torsion angles, angles between square planes and lines, hydrogen bonds and observed and calculated structure factors are available from the authors on request.

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