Coordination behaviour of methazolamide [*N*(-4-methyl-2-sulfamoyl-Δ^2-1,3,4-thiadiazolin-5-ylidene)] acetamide, an inhibitor of carbonic anhydrase enzyme. Synthesis, crystal structure and properties of bis(methazolamidate)tetrammine nickel(II)

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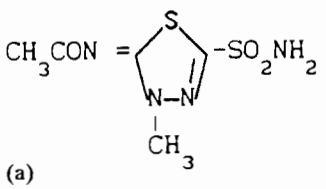
Abstract

The interaction of methazolamide (Hmacm) with Ni(II) ion and ammonia molecules gives rise to the complex of formula $[Ni(macm)_2(NH_3)_4]$. The complex crystallizes in the monoclinic $P2_1/n$ space group with $a = 14.255(4)$, $b = 7.126(2)$, $c = 12.444(3)$ Å, $\beta = 113.12(3)°$ and $Z = 2$. The structure was refined to $R = 0.065$ ($R_w = 0.065$). The complex consists of monomeric units which interact through hydrogen bonds and van der Waals contacts. The Ni(II) ion is coordinated with the deprotonated sulfonamido nitrogen of the $macm^-$ ligand in axial sites and the ammonia molecules in equatorial positions. IR, electronic spectra and ^1H NMR results are also reported.

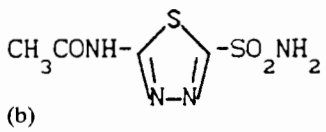
Introduction

Methazolamide (hereafter Hmacm), (Fig. 1(a)), derivative of acetazolamide (H_2acm) (Fig. 1(b)), is, like the latter, an inhibitor of the Zn metalloenzyme carbonic anhydrase [1].

Vedani and Dunitz [2] have used the lone-pair directionality of hydrogen bonding to study the interaction between carbonic anhydrase (CA) and the sulfonamides. Their refinements have indicated that the monodeprotonated sulfonamide N atom occupies the fourth coordination site of the Zn(II), replacing the zinc-bound water molecule in the native enzyme. One oxygen atom of the sulfonamide group binds weakly to the metal to give a distorted (4+1) 'tetrahedron'. Therefore they have concluded that acetazolamide and methazolamide bind the active site in a rather similar way. Recently, Liljas and co-workers [3] have determined the crystal structure of the acetazolamide–HCA complex at 1.9 Å of resolution. The structure shows that the interaction of the sulfonamide takes place through the N atom of the deprotonated sulfonamido group.



(a)



(b)

Fig. 1. (a) Methazolamide; (b) acetazolamide.

These drugs are used clinically as diuretics, anticonvulsants etc. due to their inhibitory capacity. Young *et al.* [4] have indicated that *in vitro* methazolamide is 1.5 times more active than acetazolamide. Maren [5] has reported a comparison between these two drugs which shows that methazolamide is superior to acetazolamide in virtually every pharmacological parameter including the important ones of diffusion into tissue, lower plasma binding and longer activity. Likewise, he has indicated that methazolamide is now the sulfonamide drug of choice in the treatment of glaucoma.

Although acetazolamide binds the Zn in CA through the sulfonamido moiety, we have shown, in previous papers [6–11], that this drug can also act as a ligand through the N thiadiazole atom closest to the deprotonated acetamido group. We have chosen methazolamide as a continuation of our study in order to compare

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its coordination behaviour with that of H_2acm, considering that the former exhibits a substituent on the N thiadiazole atom, likely the best donor atom in the acetazolamide.

In the present paper, we describe the crystal structure of the $Ni(macm)_2(NH_3)_4$ complex, the first reported metal complex of Hmacm.

Experimental

Synthesis

Blue prismatic crystals were prepared by dissolving 10^{-4} mol of solid methazolamide in a hot solution of 5×10^{-4} mol of $NiCl_2\cdot6H_2O$ in ethanol (100 ml). Afterwards, 10 ml of concentrated ammonia were added dropwise with stirring. The resulting blue solution was allowed to stand at room temperature. Within one day crystals were formed. *Anal.* Calc. for $C_{10}H_{26}N_{12}O_6S_4Ni$: C, 20.1; H, 4.3; N, 28.1; Ni, 9.8. Found: C, 20.1; H, 4.1; N, 27.9; Ni, 9.6%.

Crystallographic data collection and refinement of the structure

Information concerning conditions for crystallographic data collection and structure refinements is summarized in Table 1. A prismatic crystal ($0.1\times0.1\times0.15$ mm) was selected and mounted on a Philips PW-1100 diffractometer. Unit cell parameters were determined from automatic centring of 25 reflections ($8\leqslant\theta\leqslant12°$) and refined by the least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using ω scan technique. A total of 2235 reflections was measured in the range $2\leqslant\theta\leqslant25.5°$, of which 1159 reflections were assumed as observed by applying the condition $I\geqslant2.5\ \sigma(I)$. R_{int} on F was 0.041. Three reflections were measured every 2 h as orientation and intensity control, significant intensity decay was not observed. Lorentz–polarization but no absorption corrections were made. The structure was solved by direct methods, using MULTAN84 [12] and refined by the full-matrix least-squares method, with the SHELX76 [13] computer program. The function minimized was $\Sigma\|F_o|-|F_c\|^2$, where $w=(\alpha^{-2}(F_o)+0.0090|F_o|^2)^{-1}$; f', f'' were taken from the International Tables of X-ray Crystallography [14]. The position of 13 H atoms was computed and refined with an overall isotropic temperature factor, using a riding model, while the remaining atoms were refined anisotropically. The final R factor was 0.065 (R_w 0.065) for all observed reflections. No. of refined parameters was 152. Max. shift/e.s.d. = 0.01 in U_{11} of N(1) atom. Max. and min. peaks in final difference synthesis were 0.4 and -0.4 e Å^{-3}, respectively.

TABLE 1. Physical properties and main data relating to measurement and refinement of structure

Physical and crystallographic properties	
Formula	$C_{10}H_{26}N_{12}O_6S_4Ni$
Molecular weight	597.36
Crystal system	monoclinic
Space group	$P2_1/n$
Z	2
Cell constants	
a (Å)	14.255(4)
b (Å)	7.126(2)
c (Å)	12.444(3)
β (°)	113.12(3)
Volume (Å^3)	1162.5(9)
ρ_{calc} (g cm^{-3})	1.706
μ(Mo Kα) (cm^{-1})	12.35
Crystal shape	prismatic
Crystal size (mm)	$0.1\times0.1\times0.15$
Data pertinent to measurement	
Temperature (K)	298
Radiation, λ(Mo Kα) (Å)	0.71969
Monochromator	graphite
Scan type	ω
θ Range (°)	2–25.5
No. reflections measured	2235
Data treatment and refinement	
No. reflections used with $I\geqslant2.5\sigma(I)$	1159
No. variables	152
Weighting scheme, ω	$(\alpha^{-2}(F_o)+0.0090\|F_o\|^2)^{-1}$
Agreement factors	
final R factor	0.065
R_w	0.065

Results and discussion

The molecular structure of $[Ni(macm)_2(NH_3)_4]$ with the atomic numbering scheme is shown in Fig. 2. Final atomic coordinates are given in Table 2. Table 3 lists the bond distances and angles of this complex.

Description of the structure; coordination polyhedron

The structure consists of discrete units of $[Ni(macm)_2(NH_3)_4]$ that interact only through van der Waals contacts and hydrogen bonds. The geometry around the Ni(II) ion, situated on a crystallographic inversion center, can be described as a slightly elongated rhombic octahedron. The equatorial plane is formed by four ammonia nitrogen atoms N(1), N(2), N(1*), N(2*), which are coordinated to the Ni(II) with distances Ni–N(1) 2.092(6) Å and Ni–N(2) 2.118(6) Å. The slightly smaller Ni–N(1) bond when compared to Ni–N(2) one must be related to the different hydrogen bonding involving the ammonia molecules and the sulfonamido moiety (Table 4). The axial positions are occupied by the deprotonated sulfonamido nitrogen atom, N(3), of two $macm^-$ ligands, with Ni–N(3) distances of 2.216(6) Å.

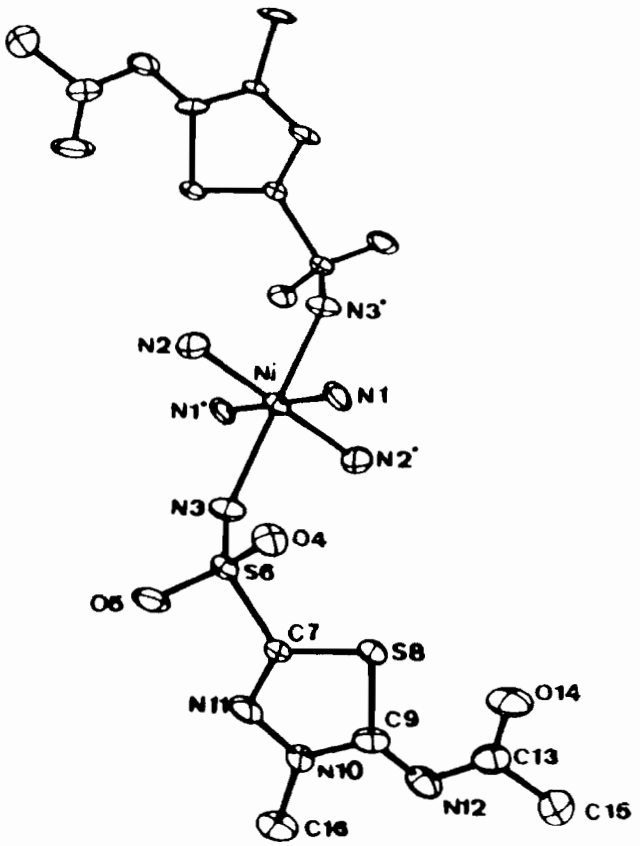

Fig. 2. ORTEP drawing of $[Ni(macm)_2(HN_3)_4]$.

TABLE 2. Final atomic coordinates (×10000)

	x/a	*y/b*	*z/c*	B_{eq}[a]
Ni	10000	0	0	1.96(5)
N(1)	8851(5)	2036(9)	−511(5)	2.43(25)
N(2)	10651(5)	1312(9)	−1073(5)	2.92(28)
N(3)	10990(5)	1641(8)	1541(5)	2.57(26)
O(4)	10068(4)	4599(7)	1357(4)	2.51(23)
O(5)	11910(4)	4574(8)	2462(4)	2.97(23)
S(6)	10973(1)	3557(2)	2069(1)	1.92(7)
C(7)	10749(6)	3227(10)	3392(5)	2.04(29)
S(8)	955(1)	2889(3)	3338(1)	2.47(8)
C(9)	10088(7)	2537(11)	4863(6)	2.55(33)
N(10)	11098(5)	2773(10)	5230(5)	2.47(27)
N(11)	11505(5)	3132(10)	4413(5)	2.76(28)
N(12)	9664(5)	2173(9)	5570(5)	2.86(29)
C(13)	8663(7)	2064(12)	5084(6)	3.07(37)
O(14)	8100(6)	2360(12)	4036(5)	5.09(35)
C(15)	8114(8)	1598(14)	5889(8)	3.88(43)
C(16)	11811(7)	2583(13)	6459(6)	3.74(41)

[a] $B_{eq} = \frac{8}{3} U_{ij} a^*_i a^*_j \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

Both Ni(II)–N(ammonia) bond distances are similar to those of the previously reported $[Ni(Hacm)_2(NH_3)_4]$ complex [8]. The axial Ni–N(sulfonamido) bond length (2.216(6) Å) is longer than the Ni–N(thiadiazole) distance (2.150(5) Å) in the $[Ni(Hacm)_2(NH_3)_4]$ compound.

TABLE 3. Bond distances (Å) and angles (°)

N(1)–Ni	2.092(6)
N(2)–Ni	2.118(6)
N(3)–Ni	2.216(6)
S(6)–N(3)	1.520(6)
S(6)–O(4)	1.450(5)
S(6)–O(5)	1.427(5)
C(7)–S(6)	1.811(7)
S(8)–C(7)	1.694(8)
N(11)–C(7)	1.306(9)
C(9)–S(8)	1.763(7)
N(10)–C(9)	1.339(11)
N(12)–C(9)	1.274(10)
N(11)–N(10)	1.379(9)
C(16)–N(10)	1.473(8)
C(13)–N(12)	1.316(11)
O(14)–C(13)	1.251(10)
C(15)–C(13)	1.531(12)
N(2)–Ni–N(1)	89.3(3)
N(3)–Ni–N(1)	93.1(2)
N(3)–Ni–N(2)	91.4(2)
S(6)–N(3)–Ni	137.3(4)
O(4)–S(6)–N(3)	111.0(3)
O(5)–S(6)–N(3)	115.6(4)
O(5)–S(6)–O(4)	115.9(3)
C(7)–S(6)–N(3)	108.4(3)
C(7)–S(6)–O(4)	101.0(3)
C(7)–S(6)–O(5)	103.3(3)
S(8)–C(7)–S(6)	121.0(4)
N(11)–C(7)–S(6)	121.2(6)
N(11)–C(7)–S(8)	117.6(5)
C(9)–S(8)–C(7)	88.6(4)
N(10)–C(9)–S(8)	107.5(5)
N(12)–C(9)–S(8)	130.7(6)
N(12)–C(9)–N(10)	121.8(6)
N(11)–N(10)–C(9)	118.6(5)
C(16)–N(10)–C(9)	123.7(7)
C(16)–N(10)–N(11)	117.6(6)
N(10)–N(11)–C(7)	107.5(7)
C(13)–N(12)–C(9)	114.6(7)
O(14)–C(13)–N(12)	127.2(9)
C(15)–C(13)–N(12)	116.9(7)
C(15)–C(13)–O(14)	115.8(9)

As the coordination polyhedron in both complexes is similar, these different axial distances could be connected with the different ligand fields created by the donor N atoms. The higher bond strength of the N(thiadiazole) atom seems to be the result of the strong π delocalization in the thiadiazole ring of the $Hacm^-$ anion.

Ligand conformation and crystal packing

A comparison of the structure of Hmacm [15] with that of $macm^{-1}$ in the complex shows several interesting aspects. One relevant feature is the stronger double bond character of the S(6)–N(3) distance (1.520(6) Å) when compared with undeprotonated sulfonamide derivatives whose corresponding S–N bond distances were found to be in the 1.57–1.65 Å range. An opposite

TABLE 4. Hydrogen bonds

A–H	B	DAB (Å)	DCB (Å)	Symmetry code
N(1)–H(1′)	O(4)i	3.243	2.19	i = (2−x, 1−y, −z)
N(1)–H(1)	O(5)ii	3.136	2.09	ii = (x−½, ½−y, z−½)
N(2)–H(2′)	O(4)i	3.062	2.26	i
N(3)–H(3)	O(5)iii	3.120	2.14	iii = (5/2 −x, y−½, ½−z)
N(1)–H(1″)	N(11)ii	3.305	2.79	ii

strong lengthening of the contiguous S(6)–C(7) bond distance (1.811(7) Å) is observed [16]. The S(6)–O(4) bond length shows an increase (from 1.423(2) to 1.450(5) Å) while the S(6)–O(5) distance remains unchanged. The O(4)–S(6)–N(3) and O(4)–S(6)–O(5) bond angles have also changed. Similar modifications in the sulfonamido group have been observed in the sodium sulfacetamide with respect to sulfacetamide [17] so that they must be related mainly with the deprotonation.

The acetamido group also presents unexpected modifications. The C(9)–N(12) and N(12)–C(13) distances show an important decrease in the complex (1.321(3) and 1.378(3) Å in the ligand to 1.274(10) and 1.316(11) Å) and the C(13)–O(14) distance increases (from 1.232(3) to 1.25(10) Å). Likewise, the O(14)–C(13)–N(12) and C(15)–C(13)–O(14) angles have changed (127.2(9) and 115.8(9)° in the complex and 123.5(2) and 122.0(2)° in the free ligand). These modifications may be justified by the planarity of the thiadiazole ring in the complex which leads to a different delocalization of the π electrons in the acetamido–thiadiazole conjugate system with respect to the parent ligand in which the S atom is deviated from the plane formed by C(9), N(10), N(11) and C(7) atoms, achieving an envelope configuration [15]. This effect seems to be in agreement with the slight decrease of the cyclic C(9)–S(8) bond length (from 1.777(2) to 1.763(7) Å).

All the ligand atoms, except for the N and O atoms of the sulfonamido group, lie approximately in the plane defined by C(7), S(8), C(9), N(10), N(11) (equation of the plane $-0.0890\ x_0 + 0.9798\ y_0 + 0.1792\ z_0 = 0.6804$; root mean square deviation 0.0099 Å).

Interaction between the $[Ni(macm)_2(NH_3)_4]$ units is made through an extensive network of weak hydrogen bonds involving the ammonia molecules, the monodeprotonated sulfonamido N and O atoms and the N atom of the thiadiazole ring (Table 4).

Spectroscopic properties and magnetic data

IR spectra of the title compound and the ligand were recorded in the range 4000–200 cm^{-1}. Table 5 shows the most significant IR bands. The strong band at 1600 cm^{-1} in the spectrum of the free ligand due to the ν(C=O) vibration remains unaltered in the complex, despite the changes observed in the crystal structure. The asymmetric and symmetric vibrations of the SO_2 group are split and shifted to lower frequencies in agreement with the modifications of this group on complex formation. The ν(S–N) vibration appears at higher frequencies, indicating a strong double bond character as could be expected from the shortening of the S(6)–N(3) bond length. The ligand exhibits the ν(C–S) vibration at 637–609 cm^{-1} whereas the title complex shows a broad band at 630–590 cm^{-1} in agreement with the increase of the S(6)–C(7) bond distance. The new bands at 460 and 335 cm^{-1} have been tentatively assigned to ν(Ni–N(ammonia)) and ν(Ni–N(sulfonamido)) vibrations, respectively. The analysis of this spectrum is according to the postulated diagnostic tool suggested for H_2acm complexes reported in previous works [8–10].

The reflectance spectrum of the complex, typical of d^8 configurations in a near octahedral ligand field, exhibits the three allowed transitions [$^3A_{2g} \rightarrow {}^3T_{2g}(\nu_1)$; $^3A_{1g} \rightarrow {}^3T_{1g}(F)(\nu_2)$ and $^3A_{1g} \rightarrow {}^3T_{1g}(P)(\nu_3)$] with maxima at the frequencies 10 300, 16 720 and 26 960 cm^{-1}, respectively. The first band yields an octahedral splitting parameter of 10 300 cm^{-1}. For the octahedral case, by calculation in the strong field coupling scheme with a d^8 configuration, the Racah parameter B is found to be 800 cm^{-1} which leads to a nephelauxetic ratio of 0.75. A comparison of the $10Dq$ value in the present compound with that of $[Ni(Hacm)_2(NH_3)_4]$ (10 800 cm^{-1}) shows that the N(thiadiazole) atom produces a higher ligand field strength than the N(sulfonamido) atom, as has been indicated by the axial Ni–N distances in the crystal structures.

The magnetic behaviour of the complex ($\mu = 3.1$ BM) is rather simple and could be directly explained on the basis of octahedral coordination. Low temperature magnetic susceptibility measurements in the range 10–270 K were determined. The magnetic moment shows a temperature independent paramagnetism; a $1/\chi_M^{corr}$ versus T plot gives a straight line with a value of θ as 0 K.

The title compound is soluble in DMSO. The conductivity measurements indicate that in this solvent the complex behaves as a 1:1 electrolyte. The electronic spectrum of the solution shows bands at 15 260 ($\epsilon = 6.7$) and 24 700 cm^{-1}, suggesting that the DMSO molecules

TABLE 5. Selected IR frequencies (cm^{-1}) for methazolamide and methazolamide–Ni(II) complex

Compound	ν(C=O)	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$	ν(S–N)
Hmacm	1600s	1310s	1174s	930s
$Ni(macm)_2(NH_3)_4$	1600s	1300–1285s,d	1140–1150s,d	965s

s = strong; d = doublet.

interact directly with the Ni(II) ion. According to this, we can propose the following equation for the equilibrium

$$[Ni(macm)_2(NH_3)_4] \overset{DMSO}{\longleftrightarrow} [Ni(macm)(NH_3)_x(DMSO)_y]^+ + macm^- + (4-x)NH_3$$

$x+y=5$

The ligand field parameter, $10Dq$, obtained from the ν_2 and ν_3 transitions, 9460 cm^{-1}, is in agreement with the presence of O atoms in the new complex chromophore.

^1H NMR spectra of the ligand and of the title compound in DMSO-d_6 solution (the concentration of the ligand was the same in both samples) show the proton signals of the methyl(acetamido) group at 2.21 and 2.14 ppm, respectively. The singlet at 3.90 ppm, assigned to CH_3(thiadiazole), is shifted upfield by 0.17 ppm on complex formation. The ligand signal at 8.34 ppm, due to the protons of the sulfonamido moiety, does not appear in the complex. The interchange of the $macm^-$ between complexed and uncomplexed sites is rapid resulting in a time-averaged spectrum [18]. Furthermore, the lack of proton resonance of the sulfonamido moiety is in agreement with the deprotonation and coordination through this group [19, 20].

Supplementary material

Equations of least-squares planes and atomic deviations there from, fractional coordinates of hydrogen atoms, and anisotropic thermal parameters (3 pages); and a table of observed and calculated structure factors (5 pages) are available from the authors on request.

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