Structure of Methazolamide: an Inhibitor of Carbonic Anhydrase

By G. Alzuet, S. Ferrer and J. Borrás

Departamento de Química Inorgánica, Universidad de Valencia, Blasco Ibáñez 13, 46010 Valencia, Spain

and X. Solans

Departamento de Cristalografía, Mineralogía y Depósitos Minerales, Universidad de Barcelona, Martí y Franqués s/n, 08028 Barcelona, Spain

Abstract. N-(3-Methyl-5-sulfamoyl-1,3,4-thiadiazol-2(3H)-ylidene)acetamide (methazolamide), C_5H_8-$N_4O_3S_2$, $M_r = 236\cdot27$, monoclinic, $P2_1/n$, $a = 8\cdot586 (2)$, $b = 10\cdot508 (2)$, $c = 10\cdot676 (2)$ Å, $\beta = 95\cdot64 (2)°$, $V = 958\cdot5 (6)$ Å^3, $Z = 4$, $D_x = 1\cdot637$ g cm^{-3}, λ(Mo $K\alpha$) $= 0\cdot71069$ Å, $\mu = 5\cdot31$ cm^{-1}, $F(000) = 488\cdot0$, $T = 298$ K, $R = 0\cdot045$ for 1744 observed reflections. As has been observed in most sulfonamides the arrangement around the S atom is distorted from ideal tetrahedral geometry. Bond lengths of methazolamide can be explained from three proposed resonance forms which result from the electronic delocalization between the thiadiazole ring and the acetamido group. Structural features in the compound are compared with those of N-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide (acetazolamide). The sulfonamide N atom forms intermolecular hydrogen bonds with the acetamido N atom.

Introduction. The crystal and molecular structure of methazolamide (MAcm) has been solved as a part of our general program of synthesis and characterization of metal complexes of sulfonamides (Alzuet, Ferrer & Borrás, 1991). The title ligand is a derivative of the well-known inhibitor of carbonic anhydrase acetazolamide (Acm). The MAcm was synthesized by Young, Wood, Eichler, Vaughan & Anderson (1956) but its crystal structure has not been reported. Prior to a study of its complexing ability, we have determined its structure.

Experimental. Colourless crystals were obtained from a saturated ethanol solution of MAcm. A prismatic crystal $(0\cdot1 \times 0\cdot1 \times 0\cdot2$ mm$)$ was selected and mounted on an Enraf–Nonius CAD-4 diffractometer. Unit-cell parameters were determined from automatic centring of the setting angles of 25 reflections $(12 \le \theta \le 16°)$ and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo $K\alpha$ radiation using the ω–2θ

scan technique. 1895 reflections were measured in the range $2 \le \theta \le 25°$, $(\sin\theta)/\lambda_{max} = 0\cdot5947$ Å^{-1}, $h -10 \rightarrow 10$, $k\ 0 \rightarrow 12$, $l\ 0 \rightarrow 12$. 1744 reflections with $I \ge 2\cdot5\sigma(I)$ were considered observed, $R_{int}(F) = 0\cdot024$ (1744 unique reflections). Three reflections were measured every 2 h as orientation and intensity control, no significant intensity decay was observed. Lorentz–polarization but no absorption corrections were made. The structure was solved by direct methods, using *SHELXS*86 (Sheldrick, 1990) and refined by the full-matrix least-squares method, with *SHELX*76 (Sheldrick, 1976). The function minimized was $\sum w\||F_o| - |F_c|\|^2$, where $w = [\sigma^2(F_o) + 0\cdot0045F_o^2]^{-1}$. Atomic scattering factors and anomalous-dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Positions of three hydrogen atoms were obtained from a $\Delta\rho$ map and the remaining positions were calculated. They were refined with an overall isotropic temperature factor using a riding model. The final discrepancy indices were $R = 0\cdot045$, $wR = 0\cdot065$ for all observed reflections. The number of refined parameters was 137. Max. shift/e.s.d. $= 0\cdot1$, max. and min. heights in final $\Delta\rho$ map were $0\cdot4$ and $-0\cdot4$ e Å^{-3}, respectively.

Discussion. Atomic coordinates are listed in Table 1, bond lengths and bond angles are given in Table 2.* An *ORTEP* (Johnson, 1965) drawing of the molecule showing the thermal ellipsoids and the atomic numbering is given in Fig. 1.

The C—S bond lengths in the thiadiazole ring $[C(5)$—$S(1)$ $1\cdot741 (2)$, $C(2)$—$S(1)$ $1\cdot726 (3)$ Å$]$ are similar to the C—S bond distance in the thiophene ring (Allen, Kennard, Watson, Brammer, Orpen &

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54228 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Taylor, 1987) indicating a substantial π-bond character. The partial double-bond character results from the delocalization of the negative density charge through the thiadiazole ring. The C—N bond lengths of the ring [C(2)—N(3) 1·283 (3), C(5)—N(4) 1·347 (3) Å] appear to be significantly different as a consequence of the higher double-bond character in the former. The shortening of the C(5)—N(4) bond distance with respect to a single-bond length (C_{sp^2}—N_{sp^3} = 1·416 Å) confirms the delocalized nature of the thiadiazole ring. Likewise the N(3)—N(4) distance [1·374 (3) Å] is shorter than the normal single-bond length (1·420 Å) (Allen et al., 1987).

In the acetamido group the C(12)—C(14) distance [1·494 (3) Å] is typical of a single C_{sp^2}—C_{sp^3} bond. In the same way, the C(12)—O(13) distance [1·232 (3) Å] is equal to that found in amides. It is noteworthy that the distance C(12)—N(11) = 1·378 (3) Å is rather short and C(5)—N(11) = 1·321 (3) Å is rather long. These bond lengths together with those of the thiadiazole ring mentioned previously can be explained by strong interactions between the acetamido group and the ring, which can be represented as follows:
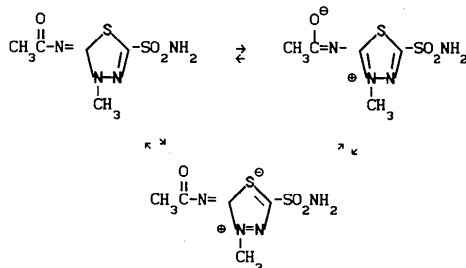
There is a distorted tetrahedral arrangement around the S(6) atom. The largest deviation is in the angle O(7)—S(6)—O(8) (120·8°) while the other angles are in the range 103·9–109·5°. This distorted arrangement has been observed in most of the sulfonamides (Chatterjee, Dattagupta & Saha, 1981). The bond lengths S(6)—O(7) = 1·421 (2) and S(6)—O(9) = 1·423 (2) Å are both intermediate between a single and a double bond, the double-bond character being more pronounced. S(6)—N(8) [1·575 (2) Å] is one of the shortest S—N distances found in sulfonamides (Allen et al., 1987). The S(6)—C(2) distance of 1·777 (3) Å seems to be the largest in the present molecule and it appears to have less π character in terms of π-bonding molecular orbitals formed by C with the 3d orbitals of the S atom (Cruickshank, 1961). This indicates the weak interaction between the sulfonamido moiety and the thiadiazole ring.

The thiadiazole ring is almost planar with a slight envelope configuration. The S(1) atom is displaced by 0·054 Å from the C(2)N(3)N(4)C(5) plane.

Table 1. Atomic coordinates ($\times 10^4$) of methazolamide

$$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq} (Å²)
S(1)	9885 (1)	−598 (1)	2336 (1)	2·36 (4)
C(2)	7878 (3)	−434 (2)	2086 (2)	2·37 (10)
N(3)	7205 (2)	−838 (2)	1035 (2)	2·59 (9)
N(4)	8319 (2)	−1347 (2)	342 (2)	2·24 (8)
C(5)	9806 (3)	−1350 (2)	878 (2)	2·07 (9)
S(6)	6745 (1)	278 (1)	3204 (1)	2·78 (4)
O(7)	7839 (2)	482 (2)	4272 (2)	3·98 (10)
N(8)	5494 (3)	−734 (2)	3530 (2)	2·95 (9)
O(9)	5925 (2)	1317 (2)	2590 (2)	4·33 (10)
C(10)	7777 (3)	−1928 (3)	−868 (2)	2·68 (10)
N(11)	10937 (2)	−1890 (2)	311 (2)	2·36 (8)
C(12)	12404 (3)	−1764 (2)	949 (2)	2·46 (9)
O(13)	12670 (2)	−1138 (2)	1922 (2)	3·20 (8)
C(14)	13669 (3)	−2464 (3)	371 (3)	4·15 (13)

Table 2. Bond lengths (Å) and bond angles (°) with e.s.d.'s in parentheses

C(2)—S(1)	1·726 (3)	N(11)—C(5)	1·321 (3)
C(5)—S(1)	1·741 (2)	O(7)—S(6)	1·421 (2)
N(3)—C(2)	1·283 (3)	N(8)—S(6)	1·575 (2)
S(6)—C(2)	1·777 (2)	O(9)—S(6)	1·423 (2)
N(4)—N(3)	1·374 (3)	C(12)—N(11)	1·378 (3)
C(5)—N(4)	1·347 (3)	O(13)—C(12)	1·232 (3)
C(10)—N(4)	1·463 (3)	C(14)—C(12)	1·494 (3)

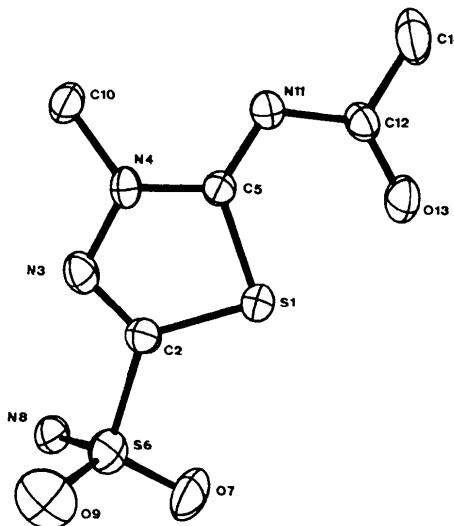| C(5)—S(1)—C(2)	87·5 (1)	O(7)—S(6)—C(2)	103·9 (1)
N(3)—C(2)—S(1)	117·3 (2)	N(8)—S(6)—C(2)	107·1 (1)
S(6)—C(2)—S(1)	122·8 (1)	N(8)—S(6)—O(7)	109·6 (1)
S(6)—C(2)—N(3)	119·8 (2)	O(9)—S(6)—C(2)	107·0 (1)
N(4)—N(3)—C(2)	108·8 (2)	O(9)—S(6)—O(7)	120·8 (1)
C(5)—N(4)—N(3)	117·0 (2)	O(9)—S(6)—N(8)	107·6 (1)
C(10)—N(4)—N(3)	117·4 (2)	C(12)—N(11)—C(5)	114·2 (2)
C(10)—N(4)—C(5)	125·5 (2)	O(13)—C(12)—N(11)	123·5 (2)
N(4)—C(5)—S(1)	109·3 (2)	C(14)—C(12)—N(11)	114·5 (2)
N(11)—C(5)—S(1)	129·7 (2)	C(14)—C(12)—O(13)	122·0 (2)
N(11)—C(5)—N(4)	121·0 (2)		

Fig. 1. ORTEP (Johnson, 1965) drawing of methazolamide.

An intermolecular hydrogen bond is formed between the sulfonamido N(8) atom and the acetamido N(11) atom. The result is an infinite chain of hydrogen-bonded MAcm.

A comparison of the crystal structure of Acm reported by Mathew & Palenik (1974) with that of MAcm, shows the following remarkable facts:

(1) The N(3)—N(4) distance [1·374 (3) Å in MAcm, 1·372 (3) Å in Acm] does not change despite the presence of a methyl group bonded to N(4) in MAcm.

(2) The S(6)—N(8) bond length is significantly shorter in MAcm [1·575 (2) Å] than in Acm [1·594 (3) Å].

(3) The C(2)—N(3)—N(4), N(3)—N(4)—C(5) and C(5)—N(11)—C(12) angles are modified in MAcm compared to Acm probably due to differences in the C(5)—N(4) and C(5)—N(11) bonds.

(4) The hydrogen-bond system is clearly different in both structures, as could be expected since, on the one hand, there is one less H atom available and on the other, the methyl substituent on N(4) prevents the formation of hydrogen bonds by the N(3) and N(4) ring atoms. Thus, only one significant hydrogen bond is observed from MAcm in contrast to the

three (involving the N-thiadiazole atoms as well) exhibited by Acm.

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Hydrogen-Bonding Interactions in Thiosemicarbazones of Carboxylic Acids: Structure of 2-Ketobutyric Acid Thiosemicarbazone Hemihydrate

BY PRAMILA SONAWANE, RAJEEV CHIKATE, AVINASH KUMBHAR AND SUBHASH PADHYE

Department of Chemistry, University of Poona, Pune 411 007, India

AND ROBERT J. DOEDENS

Department of Chemistry, University of California, Irvine, California 92717, USA

Abstract. 2-Thiosemicarbazonobutanoic acid hemihydrate, $C_5H_9N_3O_2S.0.5H_2O$, $M_r = 184.22$, triclinic, $P\bar{1}$, $a = 8.163$ (2), $b = 8.868$ (2), $c = 12.438$ (2) Å, $\alpha = 72.99$ (2), $\beta = 79.47$ (2), $\gamma = 84.06$ (2)°, $V = 845.3$ (3) Å^3, $Z = 4$, $D_x = 1.447$ Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, $\mu = 0.332$ mm^{-1}, $F(000) = 392$, $T = 296$ K, $R = 0.038$ for 3830 independent reflections with $I > 3\sigma(I)$. Three hydrogen bonds link the two crystallographically independent molecules in a pairwise fashion. The two molecules both have E configurations about each C—N and N—N bond, but differ by nearly 180° in the orientation of the —COOH group.

Introduction. The structure of the title compound was determined in order to provide a point of comparison with a series of complexes of trivalent transi-

tion metal ions in which it is present as a ligand in its singly and doubly deprotonated forms. One such metal complex of a closely related ligand has already been reported (Timken, Wilson & Hendrickson, 1985).

Experimental. The compound was prepared as described by Sah & Daniels (1950). Large rhombic-shaped plates were grown by slow evaporation of a saturated solution in boiling water. Data were collected on a Nicolet/Siemens $R3m/V$ diffractometer from a fragment of dimensions 0·60 × 0·50 × 0·33 mm that had been cut from a larger crystal. Unit-cell parameters were obtained from the setting angles of 32 reflections with $30 \leq 2\theta \leq 40°$. $\theta/2\theta$ scans. Data collected for $4 \leq 2\theta \leq 60°$ with $0 \leq h \leq 11$, $-12 \leq k \leq 12$, $-16 \leq l \leq 17$. No absorption