Crystal and Molecular Structure of Acetazolamide (5-Acetamido-1,3,4-thiadiazole-2-sulphonamide), a Potent Inhibitor of Carbonic Anhydrase

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Crystals of the title compound, a potent inhibitor of carbonic anhydrase, are colourless, triclinic, with unit-cell dimensions, $a = 5{\cdot}318(4)$, $b = 9{\cdot}065(4)$, $c = 9{\cdot}430(7)$ Å, $\alpha = 105{\cdot}44(2)$, $\beta = 98{\cdot}59(2)$, $\gamma = 100{\cdot}42(2)°$, $Z = 2$. The structure was solved by the heavy-atom method and refined by least-squares techniques to a final R of 0·028 for 1054 observed reflections. The distances and angles are compared with those in other sulphonamides of varying biological activity. The mechanism of inhibition of carbonic anhydrase is discussed.

SULPHONAMIDES are well-known inhibitors of carbonic anhydrase with acetazolamide (5-acetamido-1,3,4-thiadiazole-2-sulphonamide) being one of the most potent.[1] It is used clinically for treating glaucoma since administration of the drug decreases intraocular pressure.[2] However, the mechanism whereby sulphonamides inhibit the action of carbonic anhydrase is not well understood. *X*-Ray studies of the enzyme carbonic anhydrase with the inhibitor 3-acetoxymercurio-4-aminobenzenesulphon-

[1] W. H. Miller, A. M. Dessert, and R. O. Roblin, jun., *J. Amer. Chem. Soc.*, 1950, **72**, 4893.

[2] T. H. Maren, *Physiolog. Rev.*, 1967, **47** 595; H. Davson 'The Physiology of the Eye,' 2nd edn. Little Brown, Bostong, 1963, p. 39.

amide have suggested an interaction between the inhibitor and the zinc atom;[3] however, no complexes of sulphonamides with metal ions have been reported.[4] As part of a broad study of models for carbonic anhydrase activity and sulphonamide inhibition of the enzyme, we have determined the crystal structure of the potent inhibitor acetazolamide.

EXPERIMENTAL

Plate-like crystals were obtained by slow evaporation of an aqueous solution. Preliminary precession photographs indicated that the crystals were triclinic, with the probable space groups $P1$ or $P\bar{1}$. Analysis of the intensity distribution suggested the former, and this was confirmed by the subsequent analysis.

A crystal ground to a sphere *ca.* 0·4 mm diameter was used for intensity measurements. Unit cell dimensions were determined by a least-squares fit of 2θ, ω, ϕ, and x values for 15 reflections measured on the diffractometer by use of graphite-monochromatized Mo-K_α radiation.

Crystal Data.—$C_4H_6N_4O_3S_2$, $M = 222{\cdot}245$. Triclinic, $a = 5{\cdot}318(4)$, $b = 9{\cdot}065(4)$, $c = 9{\cdot}430(7)$ Å, $\alpha = 105{\cdot}44(2)$, $\beta = 98{\cdot}59(2)$, $\gamma = 100{\cdot}42(2)°$, $U = 421{\cdot}5(1)$ Å^3, $D_c = 1{\cdot}749$, $Z = 2$, $D_m = 1{\cdot}75$. Space group $P\bar{1}$. Mo-K_α radiation = $\lambda\alpha_1$ 0·70926, $\lambda\alpha_2$ 0·71354 Å. μ(Mo-K_α) = 6·0 cm^{-1}.

The intensity data were measured on a Syntex $P\bar{1}$ diffractometer using graphite-monochromatized Mo-K_α radiation. A θ—2θ scan at a variable rate (2° min^{-1} for intensities <150 counts s^{-1} and 24° min^{-1} for intensities >1500 counts s^{-1} with a linear interpolation for intermediate values) was used to measure all the independent reflections to 2θ 45°. The scan range was from 1° below the α_1-peak to 1° above the α_2-peak. Background was measured at each end of the scan range for a time equal to one-half the scan time. The four standard reflections which were measured after every 96 reflections showed only a small variation with time. Of 1111 independent reflections measured, 1054, having $I \geqslant 1{\cdot}3\sigma(I)$ were considered observed and were used in the analysis. The remaining 57 reflections were given a minus sign, assigned a value of $0{\cdot}65\sigma(I)$, and were not used in the analysis. These data were reduced to a set of structure amplitudes on an arbitrary scale by the application of Lorentz-polarization factors, assuming that the monochromator was a 50% mosaic and 50% perfect crystal.

Solution and Refinement of the Structure.—The positions of the two sulphur atoms were determined from a sharpened three-dimensional Patterson function. A Fourier synthesis was calculated using the phases determined by the two sulphur atoms and all the remaining non-hydrogen atoms were easily located. R was 0·19 when all the atoms were included in a structure-factor calculation. After three full-matrix least-squares cycles with individual isotropic thermal parameters, R was 0·086. The thermal parameters were converted into their anisotropic equivalent and three additional least-squares cycles reduced R to 0·043. Hydrogen atoms were located in a difference Fourier synthesis, and their contributions were included and refined in three additional least-squares cycles which reduced R to 0·028. The shifts of the non-hydrogen parameters were $<0{\cdot}1\sigma$, and the refinement was terminated. Final atomic parameters are given in Tables 1 and 2.

TABLE 1

Final positional and thermal parameters * (×10^4) of the non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S(1)	876(1)	3076(1)	4960(1)	225(3)	60(1)	81(1)	−1(2)	67(2)	14(1)
S(2)	2691(1)	1908(1)	1992(1)	236(3)	84(1)	81(1)	23(3)	92(3)	35(2)
O(1)	−438(4)	4430(2)	7641(2)	335(8)	85(3)	129(3)	−30(8)	122(8)	−19(4)
O(2)	3084(4)	400(2)	1260(2)	360(8)	120(3)	120(3)	165(8)	157(8)	46(5)
O(3)	4841(4)	3186(2)	2818(2)	303(8)	143(3)	129(3)	−56(8)	68(8)	53(5)
N(1)	−1057(4)	351(2)	3003(2)	286(9)	82(3)	85(3)	27(9)	108(8)	22(5)
N(2)	−2494(4)	423(2)	4103(2)	275(9)	76(3)	84(3)	−4(8)	100(8)	9(5)
N(3)	−2982(4)	2047(2)	6350(2)	247(9)	71(3)	89(3)	9(9)	99(8)	22(5)
N(4)	994(5)	2451(3)	769(3)	449(12)	83(4)	93(3)	56(11)	59(10)	36(6)
C(1)	726(5)	1632(3)	3306(3)	238(10)	77(4)	76(3)	39(10)	53(9)	29(5)
C(2)	−1718(4)	1767(3)	5178(3)	199(9)	65(4)	84(3)	36(9)	42(9)	43(6)
C(3)	−2329(5)	3382(3)	7529(3)	264(11)	75(4)	89(4)	80(11)	50(10)	23(6)
C(4)	−4107(6)	3450(4)	8615(3)	365(13)	126(5)	93(4)	85(14)	133(12)	4(8)

* In the form exp $[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$.

TABLE 2

Final parameters for the hydrogen atoms, with estimated standard deviations in parentheses

Atom	Bonded to	$x \times 10^3$	$y \times 10^3$	$z \times 10^3$	B/Å^2
H(1)	N(3)	−407(8)	147(5)	629(4)	1·8(1·0)
H(2)	N(4)	76(8)	330(5)	122(5)	1·9(1·0)
H(3)	N(4)	−2(8)	169(5)	25(5)	1·8(1·0)
H(4)	C(4)	−318(8)	399(5)	953(5)	3·1(1·0)
H(5)	C(4)	−553(8)	395(5)	830(4)	4·7(1·0)
H(6)	C(4)	−490(8)	238(5)	865(5)	3·2(1·0)

The quantity minimized in the least-squares calculations was $\Sigma w(|F_o| - |F_c|)^2$. The weighting scheme used was $\sqrt{w} = |F_o|/F(\text{low})$ if $|F_o| < F(\text{low})$, $\sqrt{w} = 1$ if $F(\text{low}) \leqslant |F_o| \leqslant F(\text{high})$, and $\sqrt{w} = F(\text{high})/|F_o|$ if $F_o > F(\text{high})$, where F(low) was 2·0 and F(high) was 10·0. Scattering factors were from ref. 5, and all calculations were carried out on an IBM 360/65 with programs written or modified by G. J. P.*

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

An ORTEP drawing of the molecule showing the thermal ellipsoids and the atomic numbering is given in

* Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20905 (3 pp., 1 microfiche). For details see Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

[3] A. Liljas, K. K. Kannan, P. C. Bergsten, I. Waara, K. Fridborg, B. Strandberg, U. Carlbom, L. Jarup, S. Lovgren, and M. Petel, *Nature New Biol.*, 1972, **235**, 131.

[4] S. Linkskog, *Structure and Bonding*, 1970, **8**, 153.

[5] H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

Figure 1. Individual bond distances and angles, together with their estimated standard deviations, are listed in Table 3. The molecules are held together in the

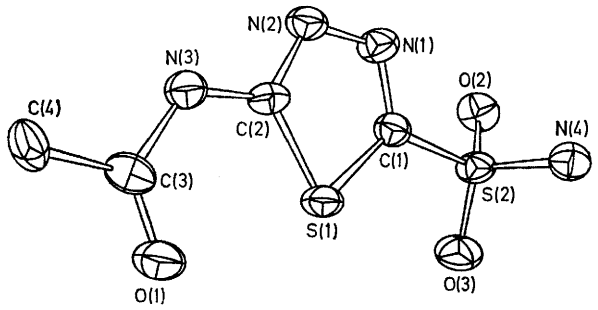

FIGURE 1 An ORTEP drawing of the molecule showing the atomic numbering and thermal ellipsoids (50% probability)

TABLE 3

Bond distances (Å) and bond angles (deg.), with estimated standard deviations in parentheses

(*a*) Bond distances

C(1)–S(1)	1·730(3)	C(1)–S(2)	1·774(3)
C(2)–S(1)	1·724(2)	S(2)–O(2)	1·426(2)
C(1)–N(1)	1·294(3)	S(2)–O(3)	1·425(2)
N(1)–N(2)	1·372(3)	S(2)–N(4)	1·594(3)
N(2)–C(2)	1·311(3)	N(3)–H(1)	0·69(5)
C(2)–N(3)	1·369(3)	N(4)–H(2)	0·82(5)
N(3)–C(3)	1·355(3)	N(4)–H(3)	0·78(5)
C(3)–O(1)	1·222(2)	C(4)–H(4)	0·89(4)
C(3)–C(4)	1·492(4)	C(4)–H(5)	1·00(4)
		C(4)–H(6)	1·00(5)

(*b*) Bond angles

C(1)–S(1)–C(2)	85·0(1)	C(2)–N(3)–C(3)	124·7(2)
S(1)–C(1)–N(1)	116·4(2)	N(3)–C(3)–O(1)	120·9(2)
C(1)–N(1)–N(2)	111·3(2)	N(3)–C(3)–C(4)	114·6(2)
N(1)–N(2)–C(2)	112·1(2)	O(1)–C(3)–C(4)	124·5(3)
N(2)–C(2)–S(1)	115·3(2)	C(2)–N(3)–H(1)	115(4)
S(1)–C(1)–S(2)	123·1(1)	C(3)–N(3)–H(1)	120(4)
N(1)–C(1)–S(2)	120·4(2)	S(2)–N(4)–H(2)	106(3)
C(1)–S(2)–O(2)	106·6(1)	S(2)–N(4)–H(3)	106(3)
C(1)–S(2)–O(3)	105·4(1)	H(2)–N(4)–H(3)	130(5)
C(1)–S(2)–N(4)	106·6(1)	C(3)–C(4)–H(4)	109(3)
O(2)–S(2)–O(3)	121·2(1)	C(3)–C(4)–H(5)	109(3)
O(2)–S(2)–N(4)	107·8(1)	C(3)–C(4)–H(6)	112(3)
O(3)–S(2)–N(4)	108·4(1)	H(4)–C(4)–H(5)	112(4)
S(1)–C(2)–N(3)	125·1(2)	H(4)–C(4)–H(6)	107(4)
N(2)–C(2)–N(3)	119·6(2)	H(5)–C(4)–H(6)	109(4)

crystal by strong N–H · · · O and N–H · · · N hydrogen bonds (Figure 2). The 1,3,4-thiadiazole ring is planar within the limits of the present analysis, but both side-chains are bent out of the plane of the ring (see Table 4). However, the dihedral angle between the ring and the planar acetylamino-group is only 4·9° so that the group is approximately coplanar with the ring.

The C–S bond lengths in the thiadiazole ring [C(1)–S(1) 1·730(2), C(2)–S(1) 1·724(2) Å] are significantly shorter than the commonly accepted values of 1·80 (ref. 6) or 1·81 Å (ref. 7) for a C–S single bond. An example of a C(sp^3)–S single bond is found in 1,3,5-trithian [1·814(9) Å].[8] Since the C–S distances in the thiadiazole ring involve sp^2-hybridized carbon atoms, a C(sp^2)–S single-bond would be *ca.* 0·04 Å shorter or *ca.* 1·77 Å. In fact, the present C(1)–S(2) distance is a good example of such a bond. However, the C–S bonds in the ring

TABLE 4

Equations of least-squares planes in the form $10^4AX + 10^4BY + 10^4CZ + 10^4D = 0$ where X, Y, and Z are orthogonal co-ordinates in Å. Deviations (Å × 10^3) of relevant atoms from the planes are listed in square brackets

Plane (I):

S(1), N(1), N(2), C(1), C(2) $\quad 6631X - 5631Y + 4932Z + 0{\cdot}9247 = 0$

[S(1) 3, N(1) 0, N(2) 3, C(1) −2, C(2) 4, S(2) −138, N(3) −30, C(3) −22, O(1) 62, C(4) −143]

Plane (II):

N(3), C(3), O(1), C(4) $\quad -5969X + 6066Y - 5252Z - 1{\cdot}2622 = 0$

[S(1) 204, N(1) 160, N(2) 53, C(1) 245, C(2) 71, S(2) 524, N(3) 2, C(3) −5, O(1) 2, C(4) 1, H(1) 8]

have some double-bond character resulting from delocalization in the thiadiazole ring. The C–S distances are similar to those found in other cases where delocalization occurs: 1·746(7) and 1·738(5) in 5-amino-2-mercapto-1,3,4-thiadiazole,[9] 1·714(2) in thiophen,[10] and 1·722(3) Å in thiophen thiosemicarbazole.[11]

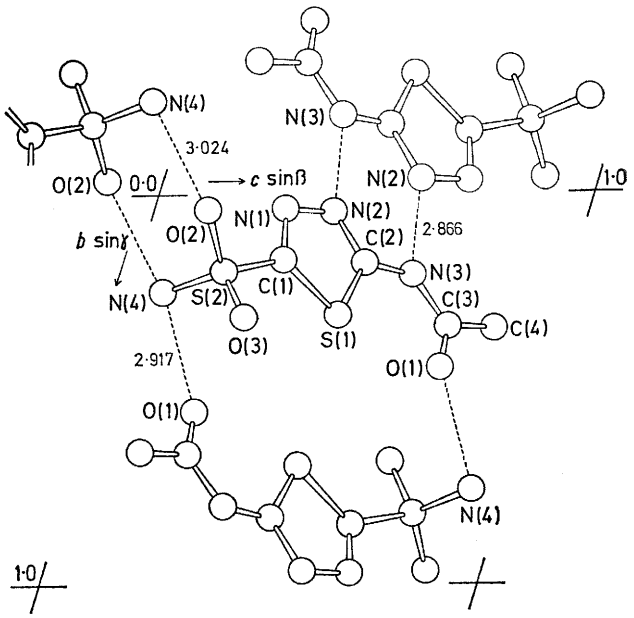

FIGURE 2 A packing diagram; hydrogen bonds are indicated by broken lines

The C–N bond lengths [C(1)–N(1) 1·294(3), C(2)–N(2) 1·311(3) Å] appear to be significantly different, although both are close to the value for C:N (1·28 Å) found for some alkylsemicarbazones and (alkyl)thiosemicarbazones.[12] The shorter value for C(1)–N(1) appears to be

[6] L. E. Sutton, *Chem. Soc. Special Publ.*, No. 18, 1965.
[7] A. I. Kitaigorodsky, 'Organic Chemical Crystallography,' Consultants Bureau, New York, 1961.
[8] G. Valle, V. Busetti, M. Mammi, and G. Carazzolo, *Acta Cryst.*, 1969, **25B**, 1432.
[9] T. C. Downe, W. Harrison, E. S. Raper, and M. A. Hepworth, *Acta Cryst.*, 1972, **28B**, 1584.
[10] B. Bak, D. Christensen, L. Hanson-Nygaard, and J. Rastrup-Anderson, *J. Mol. Spectroscopy*, 1961, **7**, 58.
[11] M. Mathew and G. J. Palenik, *Acta Cryst.*, 1971, **27B**, 596.
[12] D. Naik and G. J. Palenik, unpublished results; G. J. Palenik, D. F. Rendle, and W. S. Carter, to be published.

related to the single-bonded sulphonamide group on C(1). These observations are in agreement with the pattern of distances found in 5-amino-2-mercapto-1,3,4-thiadiazole.[9] Furthermore, the N(1)–N(2) distance [1·372(3) Å] is shorter than the normal single-bond distance (1·40 Å),[6] in keeping with the delocalized nature of the thiadiazole ring.

The acetylamino-group is planar (Table 4) and twisted slightly (4·9°) from the plane of the thiadiazole ring. The C(3)–C(4) distance [1·492(4) Å] is typical of a single-bonded C(sp^2)–C(sp^3). Similarly, the C(3)–O(1) distance [1·222(2) Å] is approximately equal to that found in ketones or aldehydes [1·215(5) Å] or amides [1·235(5) Å]. The most interesting feature of the acetamido-group is the amino-nitrogen N(3) which has rather short C–N bonds [C(2)–N(3) 1·369(3), C(3)–N(3) 1·355(3) Å]. In addition, the planarity of the atoms bonded to N(3) is indicated by the sum of the angles about it, as well as the fact that H(1) is coplanar to the acetamido-grouping. These results indicate an sp^2 hybridization around N(3) and the possibility of a strong interaction between N(3) and the thiadiazole ring. The longer C(2)–N(2) distance in the ring is consistent with a higher interaction between the ring and the acetamido compared to the sulphonamide group interaction. Planar sp^2-nitrogen atom groupings have been found in other molecules of biological interest, the antihistamine 2-[(2-dimethylaminoethyl)-2-thenylamino]pyridine hydrochloride [13] and an inactive cephalosporin.[14] In the latter case, the absence of biological activity was related to the interaction between the trigonal nitrogen atom and the β-lactam ring. In the case of acetazolamide, the activity of the drug may be dependent on the pK which results in part from the interaction between the ring and the acetamido-group.

The various angles in the sulphonamide group [105·4(1)—121·2(1)°] indicate the distorted tetrahedral geometry around the sulphur atom. Bond distances and pK values for various sulphonamides are summarized in Table 5. Unfortunately, there is no apparent correlation between these: for example, acetazolamide has one of the shortest S–N and the longest S–C bond lengths but an intermediate pK value. The S–O bonds distances in acetazolamide are identical with those in sulphaisoxazole, but the pK values differ by 2·5 units. One conclusion could be that the structure in the crystalline state is not readily correlated with the properties in solution. However, a comparison of the structures of the compounds in Table 5 indicates that substitution on the nitrogen of a sulphonamide RSO_2NH_2 greatly affects the pK value. Furthermore, there are two ionizable hydrogens in acetazolamide, but there is no reported evidence to demonstrate which proton is more acidic. Therefore, one might expect to find little or no correlation between the S–O bond lengths and the pK values.

TABLE 5

Summary of pertinent distances (Å) and pK values in a variety of sulphonamides

Compound	S–O(1)	S–O(2)	S–N	S–C	pK
Acetazolamide [a]	1·426(2)	1·425(2)	1·594(3)	1·774(3)	7·4, 9·1
α-Sulphanilamide [b]	1·41(1)	1·47(1)	1·61(1)	1·74(1)	10·4
β-Sulphanilamide [c]	1·448(2)	1·454(2)	1·620(2)	1·750(2)	10·4
γ-Sulphanilamide [d]	1·453(14)	1·438(19)	1·666(15)	1·739(14)	10·4
Methanesulphonamide	1·443(2)	1·425(2)	1·633(2)	1·764(2)	
Sulphathiazole I [f]	1·432(6)	1·437(6)	1·615(8)	1·749(9)	7·1
	1·436(7)	1·415(7)	1·612(7)	1·748(9)	7·1
Sulphathiazole III [f]	1·450(4)	1·446(4)	1·610(5)	1·745(5)	7·1
	1·440(4)	1·435(4)	1·602(5)	1·769(6)	7·1
Sulphathiazole II [g]	1·444(2)	1·435(2)	1·589(3)	1·759(3)	7·1
Sulphadimethoxine [h]	1·428(4)	1·440(4)	1·637(4)	1·747(4)	5·9
Sulphadoxine [h]	1·434(4)	1·436(4)	1·644(4)	1·747(4)	6·1
Sulphaisoxazole [h]	1·422(4)	1·426(4)	1·658(4)	1·725(4)	4·9
Sulphaguanidine [i]	1·461	1·456	1·586	1·752	

[a] This work. [b] B. H. O'Connor and E. N. Maslen, *Acta Cryst.*, 1965, **18**, 363. [c] A. M. O'Connel and E. N. Maslen, *Acta Cryst.*, 1967, **22**, 134. [d] M. Alleaume and J. Decap, *Acta Cryst.*, 1965, **19**, 934. [e] H. P. Klug, *Acta Cryst.*, 1968, **24B**, 792. [f] G. J. Kruger and G. Gafner, *Acta Cryst.*, 1972, **28B**, 272. [g] G. J. Kruger and G. Gafner, *Acta Cryst.*, 1971, **27B**, 326. [h] E. Shefter, Z. F. Chmielewicz, J. F. Blount, T. F. Brennan, B. F. Sackman, and P. Sackman, *J. Pharm. Sci.*, 1972, **61**, 872. [i] F. H. Herbstein A. Gulko, M. Kapon, M. Alleaume, and R. E. Marsh, Amer. Cryst. Meeting, June, 1972, Storrs, Connecticut, Paper M1.

One of the difficulties in extrapolating between the solid-state and the solution properties lies in the difference in the hydrogen-bonding patterns in the two states. The solute–solvent interactions which are of prime importance in an aqueous solution do not exist in the crystal. In crystalline acetazolamide there are three intermolecular hydrogen bonds formed involving the three N–H protons capable of hydrogen bonding (Table 6 and Figure 2). We see that the NH_2 group hydrogen-bonds to an oxygen of the sulphonamide across a centre of symmetry to form dimer-like units similar to those in crystalline carboxylic acids. These

TABLE 6

Probable hydrogen bonds, distances (Å), angle (°)

D–H · · · A *	D–H	H · · · A	D · · · A	D–H · · · A
N(3)–H(1) · · · N(2^{I})	0·69(5)	2·18(5)	2·866(3)	175(4)
N(4)–H(2) · · · O(1^{II})	0·82(5)	2·10(5)	2·917(3)	176(4)
N(4)–H(3) · · · O(2^{III})	0·78(5)	2·25(5)	3·024(3)	177(5)

* Roman numeral superscripts refer to the following equivalent positions relative to the reference molecule at x, y, z:

I $-x-1, -y, 1-z$ III $-x, -y, -z$
II $-x, 1-y, 1-z$

[13] G. R. Clark and G. J. Palenik, *J. Amer. Chem. Soc.*, 1972, **94**, 4005.

[14] R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.

units are then hydrogen-bonded to each other across another centre of symmetry by an interaction of the amide hydrogen atom with the ring nitrogen N(2). The result is an infinite chain of hydrogen-bonded acetazolamide molecules. The chains are held together by a hydrogen-bond involving the other hydrogen of the sulphonamide group and O(1) of the acetyl group. The final result is an extensive network of hydrogen bonds in the crystal which may account, in part, for its low solubility in water.

TABLE 7

Non-bonded intermolecular contacts (Å)

N(1) · · · O(2^{IV})	3·312(3)	N(2) · · · N(2^{VI})	3·252(3)
N(1) · · · N(2^{V})	3·386(3)	N(2) · · · C(2^{VI})	3·360(3)
N(1) · · · C(2^{V})	3·291(3)	N(2) · · · N(2^{I})	3·443(3)
N(1) · · · N(3^{V})	3·423(3)	O(3) · · · C(2^{VII})	3·334(3)
N(2) · · · O(2^{IV})	3·284(3)	O(2) · · · O(2^{VIII})	3·375(3)
N(2) · · · O(3^{IV})	3·484(3)		

* Roman numeral superscripts denote the following equivalent positions:

IV $x-1, y, z$	VII $1+x, y, z$
V $-x, -y, 1-z$	VIII $1-x, -y, -z$
VI $-x, -y, -z-1$	

Mechanism of Inhibition of Carbonic Anhydrase by Acetazolamide.—Unfortunately, the mechanism of hydration of CO_2 by carbonic anhydrase is not well understood, much less the action of inhibitors. However, a comparison of CO_2 with CO_3^{2-} reveals that their O · · · O separation is 2·32 and 2·27 Å. Therefore, a CO_2 molecule could be held by hydrogen bonds in a position which favoured attack on the positive carbon atom by a negative hydroxide ion. Orbital steering arguments[15] can be used to explain enhancement of the hydration rate under these conditions. The carbon atom would shift towards the hydroxide ion, giving the bent arrangement found in the CO_3^{2-} ion. An important feature of sulphonamides is the O · · · O separation of 2·48 Å which is only slightly longer than that found in CO_2. The sulphonamide could therefore occupy approximately the same site as a CO_2 molecule without the possibility of a hydroxide transfer. In addition, the NH_2 group may interact directly with the metal ion or with a water molecule co-ordinated to the zinc ion, further stabilizing the inhibitor in the enzyme. The fact that metal complexes of sulphonamides are not known suggests that the interaction of the NH_2 group may involve a co-ordinated water molecule or a hydroxide ion. The *X*-ray results on the enzyme carbonic anhydrase suggest that the inhibitor is co-ordinated to the metal;[3] however, these results reflect that input model and can easily be in error by a few Å.

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[15] T. C. Bruice, 'Symposia on Quantitative Biology,' vol. 36, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1972, p. 21.