Acta Cryst. (1974). B30, 557

Structural Studies of Analgesics and Their Interactions. II.* The Crystal Structure of a 1:1 Complex Between Antipyrine and Salicylic Acid (Salipyrine)

BY T. P. SINGH AND M. VIJAYAN

Department of Physics, Indian Institute of Science, Bangalore-560012, India

(*Received* 3 *October* 1973; *accepted* 15 *October* 1973)

The complex crystallizes in the space group $P2_1/c$ with four formula units in a unit cell of dimensions $a=12{\cdot}747$, $b=7{\cdot}416$, $c=17{\cdot}894$ Å and $\beta=90{\cdot}2°$. The structure has been solved by the symbolic addition procedure using three-dimensional photographic data and refined to an R value of 0·079 for 2019 observed reflexions. The pyramidal nature of the two hetero nitrogen atoms in the antipyrine molecule is intermediate between that observed in free antipyrine and in some of its metal complexes. The molecule is more polar than that in crystals of free antipyrine but less so compared with that in metal complexes. In the salicylic acid molecule, the hydroxyl group forms an internal hydrogen bond with one of the oxygen atoms in the carboxyl group. The association between the salicylic acid and the antipyrine molecules is achieved through an intermolecular hydrogen bond with the other carboxyl oxygen atom in the salicylic acid molecule as the proton donor and the carboxyl oxygen atom of the antipyrine molecule as the acceptor.

Introduction

Antipyrine is the first pyrazole derivative to be introduced as an analgesic and antipyretic drug. Though rarely used alone nowadays on account of its toxicity, antipyrine forms part of some combination products used as pain-relieving medicines. Also, many of its derivatives like amidopyrine and metamizol are well known and widely used analgesics. Therefore a detailed knowledge of the structure and the possible modes of interaction of antipyrine is important in elucidating the molecular mechanism of the action of pain-relieving medicines. The crystal and molecular structure of antipyrine was reported in part I of the series (Singh & Vijayan, 1973). It was then observed that the molecular geometry and the electronic structure of antipyrine in the free state were significantly different from those found in some of its metallic complexes, the structures of which were determined earlier (Vijayan & Viswamitra, 1968). We here report the structure of the compound salipyrine, in which antipyrine is expected to have a different mode of association. Salipyrine is the trivial name for the 1:1 molecular complex between antipyrine and salicylic acid. As is well known, salicylic acid is also a widely used analgesic.

Experimental

Transparent platy crystals of the 1:1 molecular complex of antipyrine and salicylic acid were obtained by slowly evaporating a solution in alcohol of the components in molar ratio. The composition of the crystals was confirmed by an examination of the ultraviolet absorption spectra of the two components and the complex in 50% alcohol. The density of the sample was measured at room temperature by flotation in a mixture of carbon tetrachloride and benzene. The space group and unit-cell dimensions were determined from oscillation and Weissenberg photographs. The cell parameters were subsequently refined by the least-squares method using 16 high-angle reflexions.

Crystal data

Salipyrine, $C_{11}H_{12}N_2O.C_7H_6O_3$.
Space group $P2_1/c$;
$a=12{\cdot}747\pm0{\cdot}006$, $b=7{\cdot}416\pm0{\cdot}006$,
$c=17{\cdot}894\pm0{\cdot}010$ Å, $\beta=90{\cdot}2\pm0{\cdot}2°$, $M=326{\cdot}35$,
$U=1691{\cdot}556$ Å^3, $D_m=1{\cdot}300\pm0{\cdot}020$ g cm^{-3},
$Z=4$, $D_x=1{\cdot}281$ g cm^{-3}, $\lambda=1{\cdot}5418$ Å, $\mu=7{\cdot}77$ cm^{-1}.

The intensity data were recorded on multiple-film equi-inclination Weissenberg photographs corresponding to reciprocal levels hkl, $k=0$ to 6, using Cu $K\alpha$ radiation from a nearly cylindrical specimen of mean radius 0·03 cm cut and ground along the b axis. The $hk0$ zonal data were also collected to facilitate inter-level scaling. The intensities were visually estimated by comparison with calibrated strips. Out of a total of 3990 independent reflexions in the copper sphere 3377 were recorded, of which 2019 were in the measurable range. The data were corrected for Lorentz and polarization effects and spot shape but not for absorption ($\mu r=0{\cdot}23$). The initial scale and temperature factors were determined from Wilson's statistics.

Structure analysis

The structure was determined by the symbolic addition procedure (Karle & Karle, 1966). The E map com-

* Part I: *Acta Cryst.* (1973). B29, 714–720.

puted using 286 reflexions with $|E| \geq 1{\cdot}60$ revealed the positions of 23 out of 24 non-hydrogen atoms in the structure. The position of the remaining non-hydrogen atom was determined from a subsequent difference Fourier map. The positional parameters and individual isotropic temperature factors were then refined to an R value of 0·164 on the IBM 360/44 computer at this Institute using a block-diagonal *SFLS* program originally written for the IBM 1130 computer by Dr R. Shiono and modified by Mr B. Swaminatha Reddy for the IBM 360/44 system. Further refinement of the structure with individual anisotropic temperature factors of the form

$$\exp\left[-(b_{11}h^2+b_{22}k^2+b_{33}l^2+2b_{12}hk+2b_{13}hl+2b_{23}kl)\right]$$

reduced R to 0·113. A three-dimensional difference Fourier synthesis computed at this stage revealed the positions of all the hydrogen atoms except those belonging to the two methyl groups. The positional and isotropic thermal parameters of these hydrogen atoms were also refined in subsequent *SFLS* cycles. A second difference Fourier map computed when the R value was 0·098 gave the positions of the methyl hydrogen atoms which were also included in further least-squares calculations. The refinement was terminated when all the shifts became much smaller than the corresponding estimated standard deviations. The final R value was 0·079 for 2019 observed reflexions. The weighting function used in the final cycle had the form

$$\frac{1}{a+b(kF_o)}$$

where $a=0{\cdot}76$ and $b=0{\cdot}12$ for $k=\frac{1}{2}$. In these calculations the form factors of the non-hydrogen atoms were taken from Cromer & Waber (1965) and those of the hydrogen atoms from Stewart, Davidson & Simpson (1965). The final positional and thermal parameters of the non-hydrogen and hydrogen atoms are listed in Tables 1 and 2.*

Table 2. *Final positional coordinates* ($\times 10^3$) *and isotropic temperature factors for hydrogen atoms*

The estimated standard deviations are given in parentheses.

	x	y	z	B
H(4)	506 (7)	261 (12)	384 (5)	5 (2)
H(10)	147 (8)	564 (15)	390 (6)	7 (3)
H(11)	11 (9)	762 (17)	334 (7)	8 (3)
H(12)	12 (9)	808 (16)	206 (6)	8 (3)
H(13)	131 (9)	649 (16)	114 (7)	8 (3)
H(14)	268 (10)	442 (18)	170 (7)	9 (4)
H(17)	964 (9)	717 (16)	534 (6)	8 (3)
H(18)	930 (10)	1036 (18)	557 (7)	9 (4)
H(19)	755 (11)	1179 (19)	543 (8)	10 (4)
H(20)	632 (9)	980 (15)	499 (6)	7 (3)
H(22)	475 (10)	649 (18)	433 (7)	9 (4)
H(24)	764 (9)	466 (17)	441 (7)	8 (3)
H(61)	253 (12)	1 (21)	224 (9)	12 (5)
H(62)	172 (10)	88 (18)	291 (7)	9 (3)
H(63)	182 (11)	192 (19)	215 (8)	10 (4)
H(71)	510 (10)	− 73 (18)	315 (7)	9 (4)
H(72)	424 (11)	− 94 (19)	234 (8)	10 (4)
H(73)	372 (12)	−138 (21)	324 (8)	15 (5)

The crystal structure viewed along the b axis is shown in Fig. 1. The basic repeating unit in the structure consists of an antipyrine molecule and a salicylic acid molecule which are held together by an intermolecular

* The list of observed and calculated structure factors can be obtained from the authors, and has also been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30252 (10 pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Final positional coordinates* ($\times 10^4$) *and thermal parameters* ($\times 10^4$) *of the non-hydrogen atoms*

The standard deviations are given in parentheses.

	x	y	z	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
N(1)	2871 (5)	3760 (9)	3122 (4)	57 (4)	169 (16)	34 (2)	1 (7)	−8 (3)	−14 (5)
N(2)	3108 (5)	2124 (9)	2768 (4)	57 (4)	168 (16)	37 (3)	3 (7)	−3 (3)	−11 (5)
C(3)	3980 (7)	1479 (12)	3113 (5)	62 (6)	177 (20)	34 (3)	7 (8)	6 (3)	4 (6)
C(4)	4361 (7)	2698 (13)	3606 (5)	58 (5)	206 (21)	30 (3)	−4 (8)	−5 (3)	13 (6)
C(5)	3677 (6)	4184 (12)	3607 (5)	56 (5)	195 (20)	29 (3)	−13 (8)	−4 (3)	−3 (6)
C(6)	2212 (8)	1005 (15)	2537 (6)	78 (7)	238 (25)	53 (4)	−33 (11)	1 (4)	38 (8)
C(7)	4373 (9)	383 (16)	2939 (7)	104 (9)	254 (27)	55 (5)	55 (13)	−4 (5)	−11 (9)
O(8)	3700 (5)	5702 (9)	3938 (4)	74 (5)	250 (16)	44 (3)	0 (7)	−16 (3)	−22 (5)
C(9)	2120 (6)	4967 (12)	2804 (5)	51 (5)	191 (19)	30 (3)	−7 (8)	−7 (3)	−10 (6)
C(10)	1422 (7)	5860 (13)	3276 (6)	57 (6)	202 (22)	45 (4)	−3 (9)	−7 (4)	−16 (7)
C(11)	675 (8)	7020 (15)	2966 (7)	65 (7)	233 (26)	69 (5)	7 (10)	−17 (5)	−37 (10)
C(12)	646 (9)	7271 (15)	2197 (8)	89 (8)	199 (24)	76 (6)	5 (11)	−38 (6)	2 (10)
C(13)	1354 (9)	6403 (16)	1737 (6)	112 (10)	265 (29)	50 (4)	−14 (13)	−32 (6)	24 (9)
C(14)	2102 (8)	5243 (16)	2030 (5)	76 (7)	313 (28)	34 (3)	−3 (11)	−11 (4)	−6 (8)
C(15)	7112 (7)	7564 (14)	4739 (5)	75 (6)	261 (23)	26 (3)	−52 (10)	−0 (3)	3 (7)
C(16)	8115 (8)	6825 (16)	4810 (5)	79 (7)	294 (27)	33 (3)	−31 (11)	−3 (4)	7 (7)
C(17)	8935 (9)	7784 (18)	5144 (6)	81 (8)	397 (35)	43 (4)	−61 (14)	−4 (5)	−2 (10)
C(18)	8731 (9)	9489 (19)	5390 (6)	101 (9)	404 (36)	41 (4)	−106 (15)	6 (5)	−12 (10)
C(19)	7738 (10)	10315 (18)	5317 (7)	118 (10)	323 (32)	47 (4)	−80 (15)	13 (5)	−13 (10)
C(20)	6943 (9)	9318 (16)	4982 (6)	88 (8)	287 (28)	40 (4)	−55 (12)	2 (4)	−7 (8)
C(21)	6245 (7)	6524 (14)	4418 (5)	76 (7)	256 (25)	29 (3)	−20 (10)	−5 (4)	−5 (7)
O(22)	5322 (6)	7231 (10)	4461 (4)	88 (5)	284 (18)	48 (3)	−17 (8)	−22 (3)	−13 (6)
O(23)	6405 (6)	4999 (11)	4137 (4)	88 (5)	328 (21)	54 (3)	−20 (9)	−11 (3)	−36 (7)
O(24)	8332 (6)	5105 (12)	4584 (5)	90 (6)	345 (22)	58 (4)	−15 (9)	−10 (4)	−18 (7)

hydrogen bond. Neither of the molecules is involved in any other intermolecular hydrogen bond. The arrangement of the basic units in the crystal is thus stabilized by van der Waals interactions. A perspective view of the complex as seen along a direction perpendicular to the five-membered pyrazolone ring of the antipyrine molecule is shown in Fig. 2. The bond lengths and valency angles in the structure are given in Fig. 3. The equations of the mean planes calculated by the method suggested by Blow (1960), of different planar groups in the complex along with the displacements of the relevant atoms from the planes are given in Table 3.

Antipyrine molecule

In the antipyrine molecule, the five-membered pyrazolone ring is nearly planar and is inclined with respect to the planar phenyl ring at an angle of 52·1°. The molecular geometry of antipyrine in the structure differs significantly from that observed in free antipyrine (Singh & Vijayan, 1973) as well as in some of its metallic complexes (Vijayan & Viswamitra, 1968) mainly as a result of the differences of the hybridization state of the hetero nitrogen atoms in the pyrazolone ring. It may be recalled that the nitrogen atoms were more pyramidal in free antipyrine than in the metallic complexes. As can be seen from Table 4, the pyramidal nature of these atoms in salipyrine is intermediate between that observed in free antipyrine and in the metallic complexes. In order to assess the differences in the geometry of the molecule as a consequence of these changes in the hybridization state, the positional parameters of the molecule in the three cases were referred to a common molecular coordinate system with the x axis along the normal to the pyrazolone ring, the y axis along the line joining C(5) and N(2) and the z axis perpendicular to both x and y axes. The common origin was fixed at the mid-point of the N(1)–N(2) bond. Subsequent examination showed that the conformational differences are indeed considerable, especially for the groups of atoms attached to N(1) and N(2). For example phenyl carbon C(12) in salipyrine is displaced by 0·77 ± 0·02 Å from its position in the free molecule. The corresponding displacement of the same atom in the metallic complexes is 1·01 ± 0·02 Å.

The bond lengths and valency angles in the molecule are broadly similar to those observed in free antipyrine and in its metallic complexes, though there are interesting differences in detail which are best explained by reference to the canonical forms used earlier to explain the molecular dimensions of antipyrine (I, II and

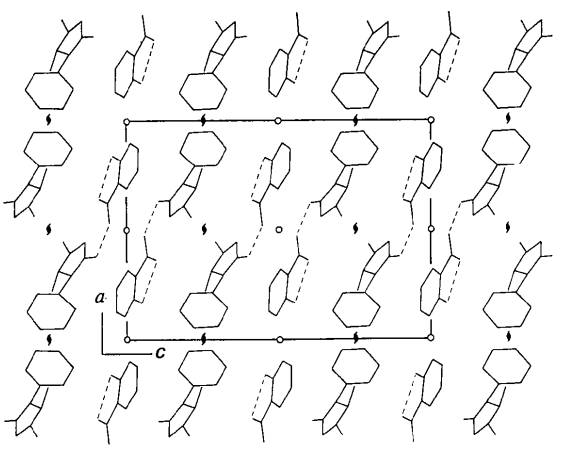


Fig. 1. The crystal structure viewed along the *b* axis.

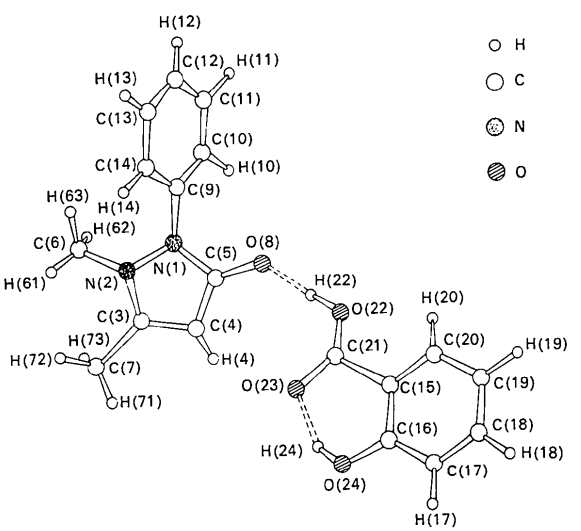


Fig. 2. A perspective view of the complex, seen along a direction perpendicular to the five-membered pyrazolone ring of the antipyrine molecule.

Table 3. *Equations of the mean planes, displacements* (Å) *of atoms from the planes and their standard deviations* (Å)

1. Phenyl ring (antipyrine moiety)

$$-0{\cdot}6393X' - 0{\cdot}7632Y' - 0{\cdot}0944Z' + 5{\cdot}0106 = 0$$

	Δ	σ
C(9)	0·009	0·009
C(10)	−0·006	0·009
C(11)	−0·002	0·011
C(12)	0·006	0·011
C(13)	−0·003	0·012
C(14)	−0·005	0·012

2. Pyrazolone ring (antipyrine moiety)

$$0{\cdot}5335X' + 0{\cdot}4448Y' - 0{\cdot}7198Z' + 0{\cdot}7986 = 0$$

N(1)	−0·039	0·008
N(2)	0·039	0·008
C(3)	−0·025	0·010
C(4)	0·000	0·010
C(5)	0·024	0·008

3. Benzene ring (salicylic acid moiety)

$$0{\cdot}2598X' + 0{\cdot}3603Y' - 0{\cdot}8960Z' + 3{\cdot}2171 = 0$$

C(15)	−0·012	0·010
C(16)	0·008	0·012
C(17)	0·001	0·012
C(18)	−0·006	0·011
C(19)	0·002	0·012
C(20)	0·007	0·012

III in Fig. 4 of Singh & Vijayan, 1973). Form I does not involve charge separation and hence is neutral, whereas in the other two forms there is a formal negative charge on the carbonyl oxygen O(8). Charge compensation is achieved in these two forms by placing a positive charge on N(2) in form II and a positive charge on N(1) in form III. It has been shown that the bond lengths in free antipyrine are best explained when the contributions of forms I, II and III are 66%, 22% and 12% respectively. On the same basis, the contributions of the three forms were calculated to be 41%, 37% and 22% in some metal antipyrine complexes (Vijayan & Viswamitra, 1968). The molecule is thus considerably more planar when it is bonded to metal ions than in the free state. In salipyrine, however, the best fit between observed and calculated bond lengths is obtained when the contributions of I, II and III are assumed to be 45%, 34% and 21% respectively. Hence, it is clearly seen that the antipyrine moiety in salipyrine is more polar than in free antipyrine but less so compared to the antipyrine moiety in the metal complexes.

Thus a close examination of the structural features of antipyrine in the free state, in its metal complexes and in salipyrine, reveals systematic changes in the molecular geometry and the electronic structure of the molecule as a function of its state of association. In the metal complexes as well as in salipyrine the association is achieved by an interaction at the carbonyl group. In the metal complexes the metal ion is coordinated to the carbonyl oxygen, whereas in the present case the carbonyl oxygen functions as a proton acceptor in a hydrogen bond with salicylic acid. As shown in the preceding paragraphs the effect of association in both cases is (1) to make hetero nitrogen atoms more planar and (2) to increase the polar nature of the molecule. The metal–oxygen interaction is expected to be stronger than that arising from a hydrogen bond and hence, as is to be expected, the planarity of the nitrogen atoms and the polar nature of the molecule are more pronounced in the metal complexes than in salipyrine.

Salicylic acid molecule

The molecular dimensions of salicylic acid in the structure are similar to those observed in free salicylic acid (Cochran, 1953; Sundaralingam & Jensen, 1964), many of its derivatives (Bertinotti, Giacomello & Liquori, 1954; Sasada, Takano & Kakudo, 1964; Wheatley, 1964; Mootz & Fayos, 1970) and its hydrogen-bonded complexes with caffeine (Shefter, 1968) and with theophylline (Shefter, 1969). The benzene ring in the molecule is planar and the plane of the carboxyl group is inclined at 8·1° to the benzene plane. This angle is somewhat larger than that observed in free salicylic acid and its derivatives. In the latter, this angle varies from 1 to 3·1°. As in the related compounds the hydroxyl group in the molecule is internally hydrogen-bonded to one of the carboxyl oxygens, the former being the proton donor and the latter the acceptor, with comparable values for the hydrogen-bond parameters.

The six-membered ring, though fully conjugated, formally deviates substantially from hexagonal symmetry with some C–C bond lengths varying significantly from those observed in benzene. Also, though bonds C(16)–O(24) and C(21)–O(22) are formally single, their lengths are much shorter than those of pure single C–O bonds. On the other hand, the C(21)–O(23) bond, which is formally double, is longer than a normal C–O double bond. These features can be qualitatively accounted for if the contributions from the canonical structures I, II and III indicated by Cochran (1953, Fig. 5) are 50%, 35% and 15% respectively. This shows that even though form I, in which the six-membered ring is fully conjugated, bonds C(16)–O(24) and C(21)–O(22) are single and the C(21)–O(23) bond is double, is the major contributor to the resonance state of the molecule, other (polar) forms also contribute substantially. Similar calculations show that the contribution of form I to the resonance state of the molecule varies from 50 to 65% in salicylic acid (Sundaralingam & Jensen, 1964) and its hydrogen-bonded complexes with caffeine (Shefter, 1968) and theophylline (Shefter, 1969).

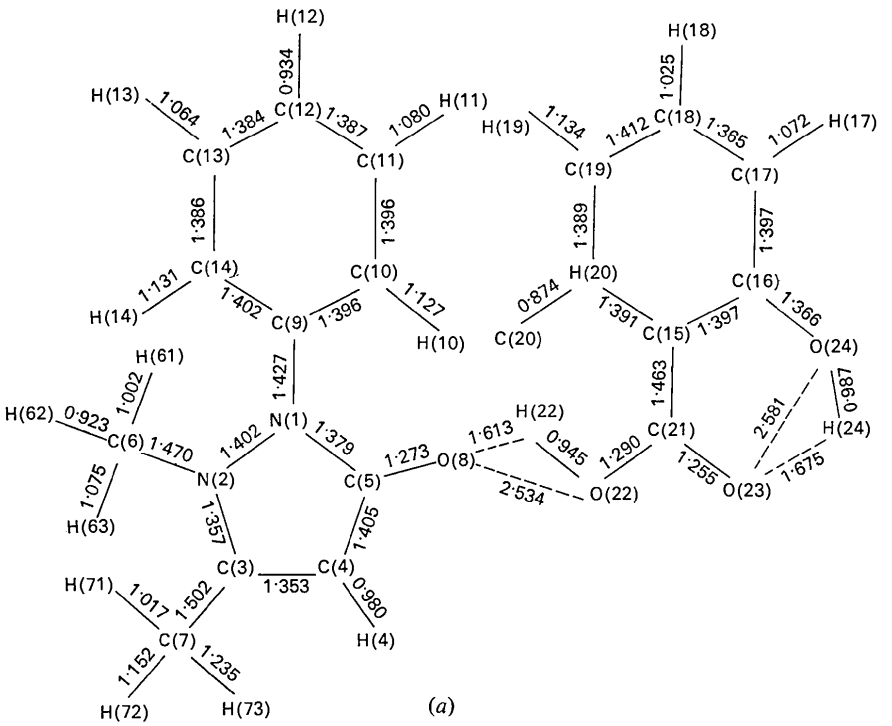
Molecular association between antipyrine and salicylic acid

As mentioned above, the association between the salicylic acid and the antipyrine molecules is achieved through an intermolecular hydrogen bond with one of the carboxyl oxygen atoms in the salicylic acid molecule as the proton donor and the carbonyl oxygen in the antipyrine molecule as the acceptor. Thus the compound is not antipyrine salicylate, but a hydrogen-bonded complex between antipyrine and salicylic acid. The parameters of the hydrogen bond are shown in

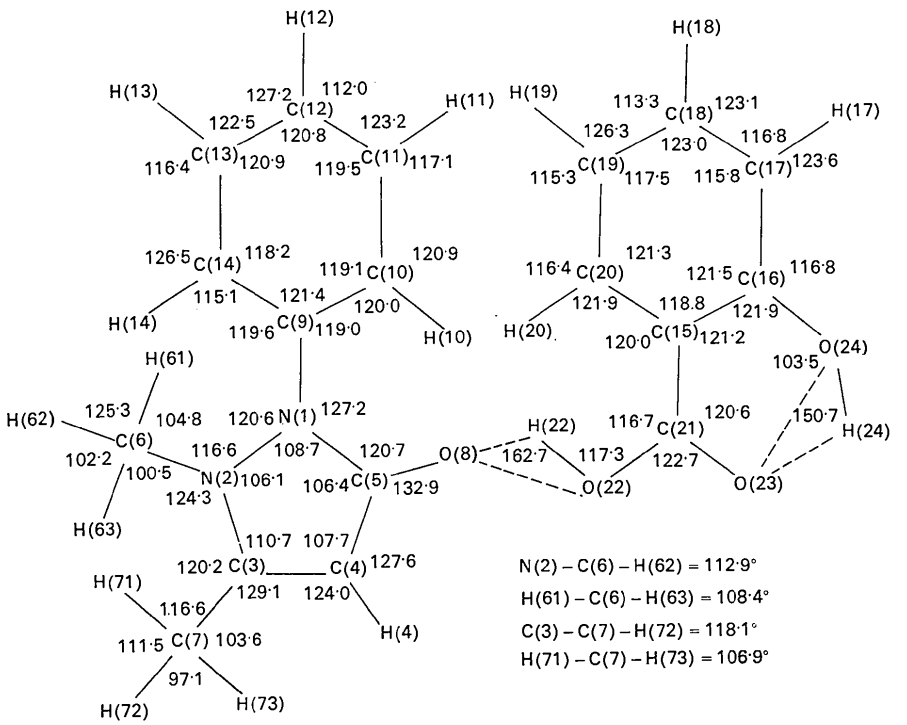
Table 4. *Comparison of the displacements* (Å) *of some atoms in the pyrazolone ring from their nearest neighbours in free antipyrine, salipyrine and calcium hexa-antipyrine perchlorate*

Estimated standard deviations (Å) are given in the parentheses.

	Nearest neighbours	Antipyrine	Salipyrine	The calcium compound
N(1)	C(9) N(2) C(5)	−0·247 (5)	−0·154 (8)	−0·098 (11)
N(2)	N(1) C(3) C(6)	0·347 (5)	0·295 (8)	0·188 (12)
C(3)	N(2) C(4) C(7)	−0·011 (5)	0·013 (9)	0·008 (13)
C(5)	N(1) C(4) O(8)	−0·028 (6)	−0·010 (7)	−0·043 (13)



(a)



(b)

Fig. 3. (*a*) Bond lengths (Å), (*b*) valency angles (°) in the complex. Mean standard deviations for the bond lengths are: σ(C–C) = 0·012, σ(N–N) = 0·010, σ(C–O) = 0·010, σ(C–N) = 0·010, σ(C–H) = 0·14, σ(O–H) = 0·13 Å. The e.s.d.'s of bond angles involving non-hydrogen atoms vary between 0·4 and 0·8°, whereas the mean e.s.d.'s of C–C–H (or N–C–H or C–O–H) and H–C–H angles are 5° and 10° respectively.

Fig. 3. The O···O hydrogen-bonded distance is rather short (2·534 ± 0·009 Å). This indicates that the bond is strong. So far, crystallographic studies of three other salicylic acid complexes, caffeine–5-chlorosalicylic acid (Shefter, 1968), theophylline–3,5-chlorosalicylic acid (Shefter, 1969) and nicotine–salicylic acid (Kim & Jeffrey, 1971), have been reported. In the last-mentioned, the salicylic acid exists in the ionized form as a salicylate anion. In the other two, complex formation is achieved through a hydrogen bond, one of the carboxyl oxygen atoms in the salicylic acid molecule being the proton donor as in the present structure. The acceptors in these two complexes are nitrogen atoms, and hence their hydrogen-bond parameters are not directly comparable with those in salipyrine where the acceptor is an oxygen.

References

BERTINOTTI, F., GIACOMELLO, G. & LIQUORI, A. M. (1954). *Acta Cryst.* **7**, 808–812.

BLOW, D. M. (1960). *Acta Cryst.* **13**, 168.

COCHRAN, W. (1953). *Acta Cryst.* **6**, 260–268.

CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* **18**, 104–109.

KARLE, J. & KARLE, I. L. (1966). *Acta Cryst.* **21**, 849–859.

KIM, H. S. & JEFFREY, G. A. (1971). *Acta Cryst.* B**27**, 1123–1131.

MOOTZ, D. & FAYOS, J. (1970). *Acta Cryst.* B**26**, 2046–2054.

SASADA, Y., TAKANO, T. & KAKUDO, M. (1964). *Bull. Chem. Soc. Japan*, **37**, 940–946.

SHEFTER, E. (1968). *J. Pharm. Sci.* **57**, 1163–1168.

SHEFTER, E. (1969). *J. Pharm. Sci.* **58**, 710–714.

SINGH, T. P. & VIJAYAN, M. (1973). *Acta Cryst.* B**29**, 714–720.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

SUNDARALINGAM, M. & JENSEN, L. H. (1965). *Acta Cryst.* **18**, 1053–1058.

VIJAYAN, M. & VISMAWITRA, M. A. (1968). *Acta Cryst.* B**24**, 1067–1076.

WHEATLEY, P. J. (1964). *J. Chem. Soc.* pp. 6036–6048.

Acta Cryst. (1974). B**30**, 562

A Neutron Diffraction Study of the Structure of L-Cystine.2HCl

BY SATISH C. GUPTA, A. SEQUEIRA AND R. CHIDAMBARAM

Nuclear Physics Division, Bhabha Atomic Research Centre, Trombay, Bombay 400 085, *India*

(*Received* 14 *September* 1973; *accepted* 16 *October* 1973)

A neutron diffraction study of L-cystine.2HCl, $[SCH_2CH(NH_3^+)COOH.Cl^-]_2$, has been carried out. The structure is monoclinic, space group $C2$, with two molecules per unit cell. The cell parameters are $a=18{\cdot}582$ (7), $b=5{\cdot}242$ (2), $c=7{\cdot}228$ (3) and $\beta=103{\cdot}74$ (1)°. Intensities of 749 independent reflexions have been measured at a wavelength of 1·178 Å, with the diffractometer in the symmetrical setting. The positions of the seven hydrogen atoms in the symmetric unit have been determined from a Fourier map of the nuclear scattering density computed with the phases from the X-ray heavy-atom positions. The structure has been refined by the method of least squares and the final value of the R index (on F^2) is 0·055. The structure is extensively hydrogen bonded. Details of hydrogen bonding and molecular conformation are discussed.

Introduction

The neutron diffraction study of the structure of L-cystine dihydrochloride, $[SCH_2CH(NH_3^+)COOH.Cl^-]_2$, was undertaken as a part of the programme of studies currently in progress in our laboratory on the structure and hydrogen bonding in crystalline amino acids. A detailed knowledge of the hydrogen-atom positions and the side-group conformations in amino acids is of considerable interest in the calculation of the configuration of the side groups associated with polypeptide chains. Studies of cystine structures assume added importance since they lead to information about the conformation around the disulphide bond which is one of the important factors stabilizing the conformation of polypeptides.

Preliminary studies of the space group and cell constants of L-cystine.2HCl were carried out by Steinrauf & Jensen (1956) and Srinivasan (1956). The X-ray study was carried out by Steinrauf, Peterson & Jensen (1958), in which approximate positions of the hydrogen atoms were determined.

Experimental

Large, clear and well formed single crystals of L-cystine dihydrochloride were easily obtained by slow evaporation from a saturated aqueous solution with about 20% excess hydrochloric acid. The crystals were generally needle shaped and elongated along the b axis with $\{\bar{2}01\}$, $\{001\}$ and $\{100\}$ as the principal faces. The density of the crystals measured by flotation in a mix-