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## The Crystal Structure of Lidocaine Hydrochloride Monohydrate\*

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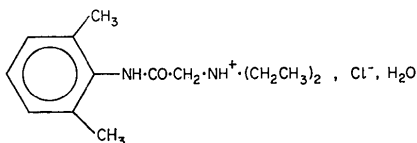
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Crystals of the title compound,  $C_{14}H_{22}N_2O \cdot HCl \cdot H_2O$ , are monoclinic,  $P2_1/c$ , with  $a = 8.490$  (5),  $b = 7.110$  (5),  $c = 27.58$  (2) Å,  $\beta = 106.87$  (5)°,  $Z = 4$ . 2385 of a possible 2694 independent reflexions in the range  $\sin \theta / \lambda \leq 0.59$  were observed and measured diffractometrically. The crystal structure was determined by symbolic addition procedures and refined by block-diagonal least-squares calculations to a final  $R$  index of 0.11. There appears to be some disorder, with an alternative structure present at about 5% occupancy. Only the predominant structure has been characterized. This structure is fully hydrogen bonded, with adjacent lidocaine cations linked by water molecules into endless chains parallel to  $b$ . Adjacent chains related by the screw axes are joined in pairs by chloride ions, which bind  $N^+H$  and  $H_2O$  groups in different chains.

### Introduction

The hydrogen-bonding properties of lidocaine in the hydrohexafluoroarsenate salt (I) have been studied by means of a determination of the crystal structure (Hanson, 1972). It also seemed of interest to study these properties in the hydrochloride monohydrate (II), as the environment of the lidocaine cation could be expected to approximate more closely the physiological environment in which it functions as a local anaesthetic. The hydrogen-bonding arrangement, and the conformation of the lidocaine cation, are found to be quite different in the two salts.



(II)

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### Experimental

Crystal data: F.W. 288.8,  $V = 1593$  Å<sup>3</sup>,  $D_m = 1.21$ ,  $D_x = 1.20$  g.cm<sup>-3</sup>,  $\mu = 21.3$  cm<sup>-1</sup> (Cu  $K\alpha$ ). [The wavelength assumed for  $\lambda(\alpha_1)$  was 1.54050 Å.] The space group was determined by the systematic absences evident on Weissenberg and precession photographs.

The material supplied (Astra Pharmaceuticals Ltd.) was recrystallized from a solution in ethyl acetate and acetone, yielding colourless translucent prisms. These were generally of high mosaicity, and many were twinned. The nominal dimensions of the specimen used were  $0.42 \times 0.31 \times 0.45$  mm. Cell dimensions and relative intensities were measured with a four-circle diffractometer and scintillation counter, using nickel-filtered Cu  $K\alpha$  radiation with pulse-height discrimination. For the intensity measurements the specimen was mounted with  $c$  parallel to the  $\phi$  axis; the  $\theta$ - $2\theta$  scan mode was used (scans of 3° for  $2\theta \leq 50^\circ$ , 4° for  $50^\circ < 2\theta \leq 100^\circ$ , 4.6° for  $100^\circ < 2\theta \leq 130^\circ$ ) with background counts measured at the beginning and end of each scan. Reflexions for which the net count was less than 7 (deca-) counts or less than 10% of the corresponding background count were considered to be unobserved. The intensities were corrected for absorp-

tion, using a program of Ahmed (1970); the corrections ranged from 1.53 to 1.88.

### Structure determination

A trial structure was deduced routinely by symbolic addition procedures, and was refined by block-diagonal least-squares calculations. The programs used were those of Ahmed, Hall, Pippy & Huber (1966). The least-squares program minimizes  $\sum w\Delta F^2$ . The weighting scheme, chosen to ensure reasonable constancy of  $w\Delta F^2$  with  $F_o$  and with  $\sin^2 \theta$ , was  $w = w_1 w_2$  where

$$\begin{aligned} w_1 &= 1 \text{ for } F_o \leq 14 \\ &= (14/F_o)^{1/2} \text{ for } F_o > 14 \\ w_2 &= 2.86 \sin^2 \theta \text{ for } \sin^2 \theta < 0.35 \\ &= 1 \text{ for } \sin^2 \theta \geq 0.35 \end{aligned}$$

(The nominal minimum value of  $F_o$  was 3.5.)

The scattering-factor curves used for the non-hydrogen atoms were those of Hanson, Herman, Lea & Skillman (1964). For the chlorine atom (here assumed to be the neutral species) appropriate allowance was made for the real part of the anomalous scattering (*International Tables for X-ray Crystallography*, 1962). The curve used for the hydrogen atoms was that of Stewart, Davidson & Simpson (1965).

Refinement was initially rapid, but subsequently rather slow. A difference-Fourier synthesis, computed for the purpose of locating the hydrogen atoms, revealed some anomalous features, chief among which was a well-formed peak of height  $1.5 \text{ e.}\text{\AA}^{-3}$ , about  $1.5 \text{ \AA}$  from the nearest non-hydrogen atom. There was also a trough of  $-0.8 \text{ e.}\text{\AA}^{-3}$  at the position of the chlorine atom. (In a Fourier synthesis the density at the chlorine position was found to be  $31 \text{ e.}\text{\AA}^{-3}$ .) These features were considered to be consistent with the presence, at about 5% of all lattice sites, of an alternative structure in which the chlorine atom occupies the position of the anomalous peak. The remaining atoms of this structure would be represented by peaks no higher than  $0.5 \text{ e.}\text{\AA}^{-3}$ . None were identifiable as such, but many would not, of course, be resolved from the atoms of the predominant structure. Perhaps for this reason, it was not possible to identify and locate all the hydrogen atoms of the predominant structure.

Refinement was continued on the assumption that the structure was disordered. For the predominant structure the occupancy factor of the chlorine atom was assumed to be 0.95; those of the remaining atoms were not changed. For the alternative structure the occupancy factor of the chlorine atom was assumed to be 0.05; the remaining atoms were not considered.

Table 1. *Final parameters and their e.s.d.'s*

Parameters for which no e.s.d.'s are given have not been refined. The fractional coordinates are  $\times 10^4$  for non-hydrogen, and  $\times 10^3$  for hydrogen atoms. Anisotropic temperature parameters  $U_{ij}$  are  $\times 10^3$ ; the temperature factor is  $\exp[-2\pi^2(U_{11}a^{*2}h^2 + \dots + 2U_{12}a^*b^*hk + \dots)]$ . Isotropic temperature parameters  $B$  are Debye-Waller factors, in  $\text{\AA}^2$ . Cl(1) and Cl(2) have been assigned occupancy factors of 0.95 and 0.05, as explained in the text.

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{11}$	$U_{12}$	$U_{13}$	$U_{22}$	$U_{23}$	$U_{33}$
C(1)	7990 (6)	2598 (7)	373 (2)	40 (3)	-2 (2)	8 (2)	25 (2)	3 (2)	27 (2)
C(2)	6492 (7)	2476 (7)	8 (2)	44 (3)	-2 (2)	4 (2)	21 (2)	0 (2)	38 (3)
C(3)	6512 (9)	2262 (9)	-496 (2)	69 (4)	-4 (3)	5 (3)	41 (3)	3 (3)	36 (3)
C(4)	7933 (10)	2244 (10)	-625 (2)	80 (5)	-6 (4)	34 (3)	54 (4)	-2 (3)	41 (3)
C(5)	9435 (9)	2373 (10)	-248 (3)	61 (4)	0 (3)	36 (3)	55 (4)	6 (3)	58 (4)
C(6)	9470 (7)	2558 (8)	254 (2)	42 (3)	-3 (2)	16 (2)	37 (3)	2 (3)	44 (3)
C(7)	11093 (8)	2680 (13)	665 (3)	31 (3)	-3 (3)	14 (3)	78 (5)	0 (4)	80 (5)
C(8)	4875 (8)	2530 (10)	131 (2)	42 (3)	-3 (3)	4 (3)	46 (3)	-1 (3)	52 (4)
N(9)	8065 (6)	2854 (7)	900 (2)	45 (2)	-10 (2)	12 (2)	40 (3)	-3 (2)	26 (2)
C(10)	7792 (6)	1442 (8)	1185 (2)	33 (3)	-4 (2)	4 (2)	31 (3)	1 (2)	37 (3)
O(11)	7359 (6)	-127 (6)	1025 (2)	64 (3)	-12 (2)	9 (2)	40 (2)	-3 (2)	39 (2)
C(12)	8118 (7)	1984 (8)	1742 (2)	33 (3)	-6 (2)	4 (2)	46 (3)	1 (2)	35 (3)
N(13)	6732 (6)	1421 (8)	1952 (2)	40 (2)	-1 (2)	8 (2)	49 (3)	4 (2)	38 (2)
C(14)	5088 (8)	2269 (11)	1648 (2)	40 (3)	3 (3)	5 (2)	67 (4)	3 (3)	42 (3)
C(15)	5080 (10)	4314 (13)	1613 (3)	58 (4)	14 (4)	2 (3)	70 (5)	13 (4)	65 (5)
C(16)	6586 (8)	-613 (2)	2043 (2)	52 (3)	-9 (3)	15 (3)	40 (3)	-3 (3)	49 (3)
C(17)	8030 (10)	-1372 (10)	2453 (3)	72 (5)	9 (3)	18 (4)	47 (4)	19 (3)	64 (4)
Cl(1)	7827 (2)	3579 (2)	2960 (1)	48 (1)	11 (1)	9 (1)	56 (1)	-2 (1)	35 (1)
Cl(2)	7800 (39)	1511 (49)	2945 (10)	66 (16)	-8 (15)	12 (12)	77 (20)	20 (13)	41 (13)
O(W)	8985 (6)	6428 (7)	1366 (2)	68 (3)	11 (2)	13 (2)	42 (2)	12 (2)	72 (3)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>		<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(3)	550	218	-75	3.8	H(15A)	406	483	142	5.3
H(4)	794	212	-96	4.6	H(15B)	592	469	146	5.3
H(5)	1043	233	-34	4.9	H(15C)	537	481	195	5.3
H(9)	833	406	105	3.0	H(16A)	560	-84	214	3.8
H(12A)	910	136	194	3.1	H(16B)	649	-130	174	3.8
H(12B)	829	329	178	3.1	H(17A)	793	-270	252	5.0
H(13)	704	201	228	3.6	H(17B)	900	-118	236	5.0
H(14A)	427	188	180	3.9	H(17C)	812	-72	276	5.0
H(14B)	482	176	131	3.9	H(WA)	1177 (13)	254 (16)	375 (4)	6.7 (2.3)
					H(WB)	1009 (11)	209 (14)	336 (4)	5.7 (2.0)

Whenever possible the hydrogen atoms of the predominant structure were assigned reasonable parameters which were not refined. The hydrogen atoms of the methyl groups attached to the phenyl rings could

not be located in the difference map, nor could their positions be predicted. These atoms were subsequently disregarded. The aqueous hydrogen atoms were identified in the difference maps, and their parameters were

Table 2. Observed and calculated structure amplitudes, x 10

An asterisk indicates an unobserved reflexion; the value given for F<sub>0</sub> is the estimated threshold.

Table with columns for h, k, l, F<sub>o</sub>, F<sub>c</sub>, and various numerical values. The table is organized in a grid with multiple columns for different reflections. Asterisks are used to denote unobserved reflexions.

refined. Refinement appeared to be complete when no coordinate shift of a non-hydrogen atom exceeded 0.003 Å, or 43% of the corresponding nominal e.s.d. The final parameters are given in Table 1.

### Assessment of analysis

The final agreement residual ( $R = \sum |\Delta F| / \sum |F_o|$ ) is 0.11, for observed reflexions only. The overall agreement between observed and calculated structure amplitudes (Table 2) is reasonable but there are many minor discrepancies. Moreover, the difference-Fourier synthesis reveals residual features ranging in density from  $-0.5$  to  $0.8 \text{ e.Å}^{-3}$ . These circumstances would occasion some misgiving in respect of a nominally well ordered structure, but are perhaps not unreasonable for a disordered structure of the sort postulated. Further characterization of the alternative structure does not seem practicable, and we have not attempted it. We believe that the predominant structure has been sufficiently well determined to permit meaningful study. However, it is clear that the positions of some atoms must be perturbed by the overlap of the alternative structure, and that bond lengths and angles must therefore be regarded as unreliable. It is not surprising that there should be differences of as much as 0.05 Å between the lengths of chemically equivalent bonds, and it must be emphasized that the nominal e.s.d.'s (0.007 to 0.012 Å for bonds) are not, in this case, reliable indications of accuracy.

### Discussion

The structure is fully hydrogen bonded, utilizing all potential donor and acceptor groups. The lidocaine cation and the water molecule each donate two protons and accept one, while the chlorine anion accepts two. (The implied protonation of the amino nitrogen atom is not definitely proved by this analysis, because of uncertainty resulting from the disorder. It is, however, chemically reasonable and is consistent with the indications of the difference map.) Relevant distances and angles are given in Table 3, and the hydrogen bonding network is illustrated in Fig. 1. Lidocaine cations related by the  $b$  translation are linked by water molecules into endless chains. Adjacent chains related by the twofold screw axes are held together by chlorine ions, each of which accepts an aqueous proton from one chain and an amino proton from the other. The resulting double chains are not joined to their neighbours by any forces stronger than van der Waals.

Covalent bond lengths and angles are summarized in Table 4. These are generally consistent with expectation, but, as explained above, cannot be considered reliable.

The conformation of the lidocaine cation differs quite appreciably from that found in the hydrohexafluoroarsenate salt (I). Parameters are compared in Fig. 2. As in I the amide group is essentially planar

(Table 5) and is inclined at about the same angle to the phenyl ring. However, the conformation about C(12)–C(10), which was nearly eclipsed in I, is *gauche* in II.

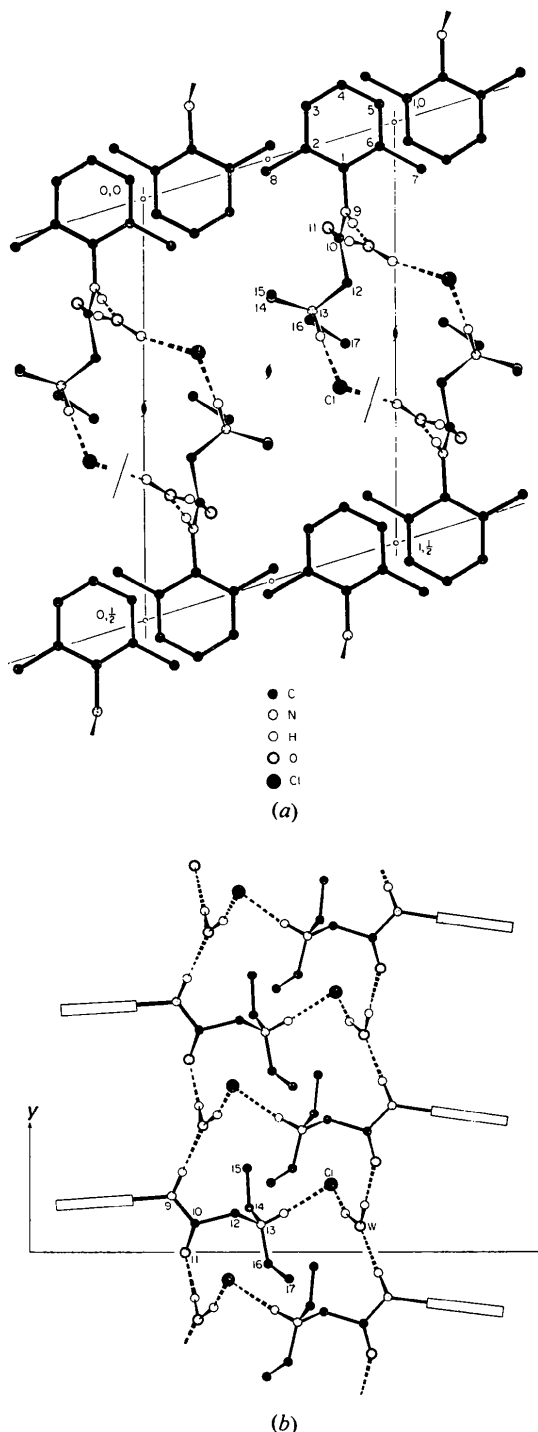


Fig. 1. (a) Part of the structure viewed along  $b$ . (b) Part of a hydrogen-bonded double chain viewed along  $a^*$ . (The phenyl rings are shown schematically.) Hydrogen bonds are shown as broken lines, and hydrogen atoms not involved in bonding are not shown.

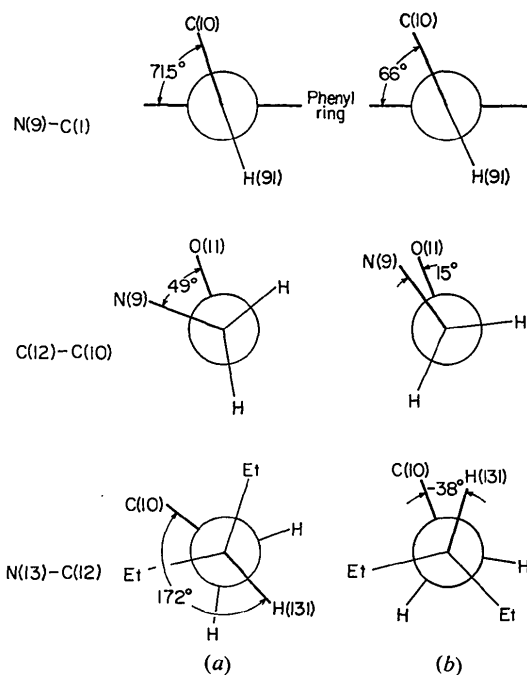


Fig. 2. Newman projections illustrating the torsion angles of certain bonds, defined according to Klyne & Prelog (1960). (a) Present compound. (b) Lidocaine hydrohexafluoroarsenate (II).

Table 3. Distances and angles involved in hydrogen bonding

Quantities in parentheses are based on assumed hydrogen positions.

N(9)·····O(W)	2.85 Å
H(9)·····O(W)	(1.90)
N(9)·····H(9)	(0.96)
∠N(9)—H(9)·····O(W)	(175°)
O(11)·····O(W)	2.84
O(11)·····H(WA)	1.84
O(W)·····H(WA)	1.01
∠O(11)·····H(WA)—O(W)	169°
O(W)·····Cl(1)	3.19
H(WB)·····Cl(1)	2.18
O(W)·····H(WB)	1.04
∠O(W)·····H(WB)·····Cl(1)	162°
N(13)·····Cl(1)	3.07
H(13)·····Cl(1)	(2.12)
N(13)—H(13)	(0.96)
∠N(13)—H(13)·····Cl(1)	(174°)
∠H(WB)·····Cl(1)·····H(13)	(101°)

This change results from the loss of the intramolecular N—H·····O bond inferred for (I) (Hanson, 1972). An even more drastic change is found for N(13)—C(12):

Table 4. A summary of covalent bond distances and angles

Nominal e.s.d.'s are about 0.01 Å and 0.6° for values not involving hydrogen.

Distances	
C—C (aromatic)	1.35 to 1.40 Å
C—CH <sub>3</sub>	1.46 to 1.51
C—N(13)	1.48 to 1.53
C(1)—N(9)	1.45
N(9)—C(10)	1.34
C(10)—O(11)	1.22
C(10)—C(12)	1.53
O(W)—H	1.0
Angles	
C—C—C(trigonal)	117 to 123°
C—C—C(tetrahedral)	113 to 115
C(1)—N(9)—C(10)	122
N(9)—C(10)—O(11)	124
N(9)—C(10)—C(12)	113
O(11)—C(10)—C(12)	123
C—N(13)—C	112 to 116
H—O(W)—H	99

*gauche* in I, and *trans* in II. The difference in conformation illustrates the manner in which the lidocaine cation responds to a more favourable hydrogen-bonding environment. This adaptability may be related to its effectiveness as a local anaesthetic.

Table 5. Distances (Å × 10<sup>2</sup>) of some atoms from certain mean planes

Atoms specified in bold type define the mean plane.

Phenyl ring	
C(1), 0; C(2), 1; C(3), -1; C(4), 1; C(5), 0;	
C(6), 0; C(7), -2; C(8), 2; N(9), 4.	
Amide group	
C(1), 4; N(9), 5; C(10), 2; O(11), 0;	
C(12), -3; N(13), 98.	

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