The Crystal Structure of (±)-1-Benzyl-5-phenyl-1-azacycloheptan-4-one Hydrochloride, $C_{19}H_{21}NO \cdot HCl$

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(Received December 6, 1973)

The crystal structure of (±)-1-benzyl-5-phenyl-1-azacycloheptan-4-one hydrochloride has been determined by the heavy-atom method from three-dimensional X-ray data. The crystals are monoclinic, space group $P2_1/c$, with four formula units in a unit cell of dimensions: $a=5.967(8)$, $b=11.20(1)$, $c=25.96(2)$ Å, and $\beta=93.8(3)°$. The structure was refined by the block-diagonal least-squares method to an R index of 0.076 for 1299 independent observed reflections. The benzyl and phenyl groups are bonded equatorially to the azacycloheptanone ring which takes a chair-like conformation. The chloride ion is hydrogen-bonded to the ring nitrogen atom at a distance of 3.075(4) Å.

The title compound $C_{19}H_{21}NO \cdot HCl$ has been prepared by Morosawa[1] at this Department as an intermediate material in the course of synthetic study of seven-membered azacyclic compounds. It is of our interest to compare the conformation of the azacycloheptanone ring with that of the azacyclic six-membered rings, say, piperidine[2] and piperazine.[3] The existence of N–H···Cl hydrogen bond is of additional interest in this work.

Experimental

The crystals supplied by Dr. Shiro Morosawa were thin transparent plates having well developed {001}. Cell constants were obtained from the rotation and Weissenberg photographs taken with Cu$K\alpha$ radiation ($\lambda=1.5418$ Å).

Crystal data:
(±)-1-Benzyl-5-phenyl-1-azacycloheptan-4-one hydrochloride $C_{19}H_{21}NO \cdot HCl$ F.W. 315.8, Mp 225 °C (decomposed)[1] Monoclinic, space group $P2_1/c$.

Systematic absences; $h0l$ when l odd, $0k0$ when k odd.

$a=5.967(8)$, $b=11.20(1)$, $c=25.96(2)$ Å, $\beta=93.8(3)°$

$V=1731$ Å^3, $Z=4$, $D_c=1.21$, $D_m=1.22$ g/cm^3 (by flotation)

μ (for Cu$K\alpha$) $=19.7$ cm^{-1}, $F(000)=672$.

The reflections were collected with Cu$K\alpha$ radiation by means of equi-inclination Weissenberg techniques for the layers from $0kl$ to $4kl$. The intensities of 1299 independent reflections were measured visually and corrected for the Lorentz and polarization factors and for spot shape. No corrections were made for absorption.

Structure Determination and Refinement

The coordinates of the chloride ion were deduced from a three-dimensional Patterson map. All the remaining non-hydrogen atoms were located in a subsequent heavy-atom Fourier map. The structure was refined by the block-diagonal least-squares method,[4] with anisotropic temperature factors for the chloride ion, to the conventional R index of 0.121. Excluding the reflections, 021, 111, 121, and 13$\bar{1}$, which were considered to suffer from extinction effect, the difference map revealed all the twenty-two hydrogen atoms.

Further least-squares refinement with anisotropic temperature factors for the non-hydrogen and with isotropic ones for the hydrogen atoms was carried out by using the weighting scheme:

$$w = 0.0 \quad \text{for } F_o < F_{min} \ (=3.6)$$
$$w = 1.0 \quad \text{for } F_{min} \leq F_o \leq F_{max} \ (=18.0)$$

and

$$w = (F_{max}/F_o)^2 \quad \text{for } F_{max} < F_o$$

The final R index was 0.076 for 1299 observed reflections.

The atomic scattering factors were taken from International Tables for X-Ray Crystallography.[5] The computations were performed on a NEAC 2200-700 computer at the Computation Center of Osaka University and on a NEAC 2200-500 computer at the Okayama University Computer Center.

Results and Discussion

The observed and calculated structure factors are given in Table 1. The final positional and thermal parameters together with their estimated standard deviations are given in Tables 2 and 3. Bond lengths and angles are shown in Fig. 1 and the stereoconfiguration drawn by the plotting program ORTEP[6] is illustrated in Fig. 2. The aromatic C–C bond lengths in the benzyl (B) and phenyl (C) groups are normal, their average values being 1.384 and 1.382 Å with maximum deviations of 0.020 and 0.038 Å, respectively. It should be noted that the bond angles of the C(sp^3) in the azacycloheptanone ring (A) range from 113.4 to 115.4° and are significantly larger than those found in piperidinium *p*-hydroxybenzoate (109.5 to 110.7°)[2] and in piperazinium terephthalate (110.1 to 111.0°).[3] The average C(sp^3)–C(sp^3) bond length in the ring A is 1.537 Å with maximum deviation of 0.005 Å. The C–N bond lengths, 1.494 and 1.506 Å, are close to those found in the piperidinium (1.494, 1.501 Å) and in the piperazinium (1.486, 1.494 Å) ions, but slightly differ from those in azacyclododecane hydrochloride (1.529, 1.536 Å)[7] and in 2,2,6,6-tetramethyl-4-piperidone hydrochloride (1.504, 1.533; 1.523, 1.526 Å).[8] Geometry of the carbonyl group is compared with that in some saturated cycloketones in Table 4. In the present compound, the C(4) atom deviates only by 0.02 Å from the plane through the C(3), C(5), and O(8) atoms and the C(3)–C(4)–C(5) bond angle is

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TABLE 1. OBSERVED AND CALCULATED STRUCTURE FACTORS ($\times 10$)

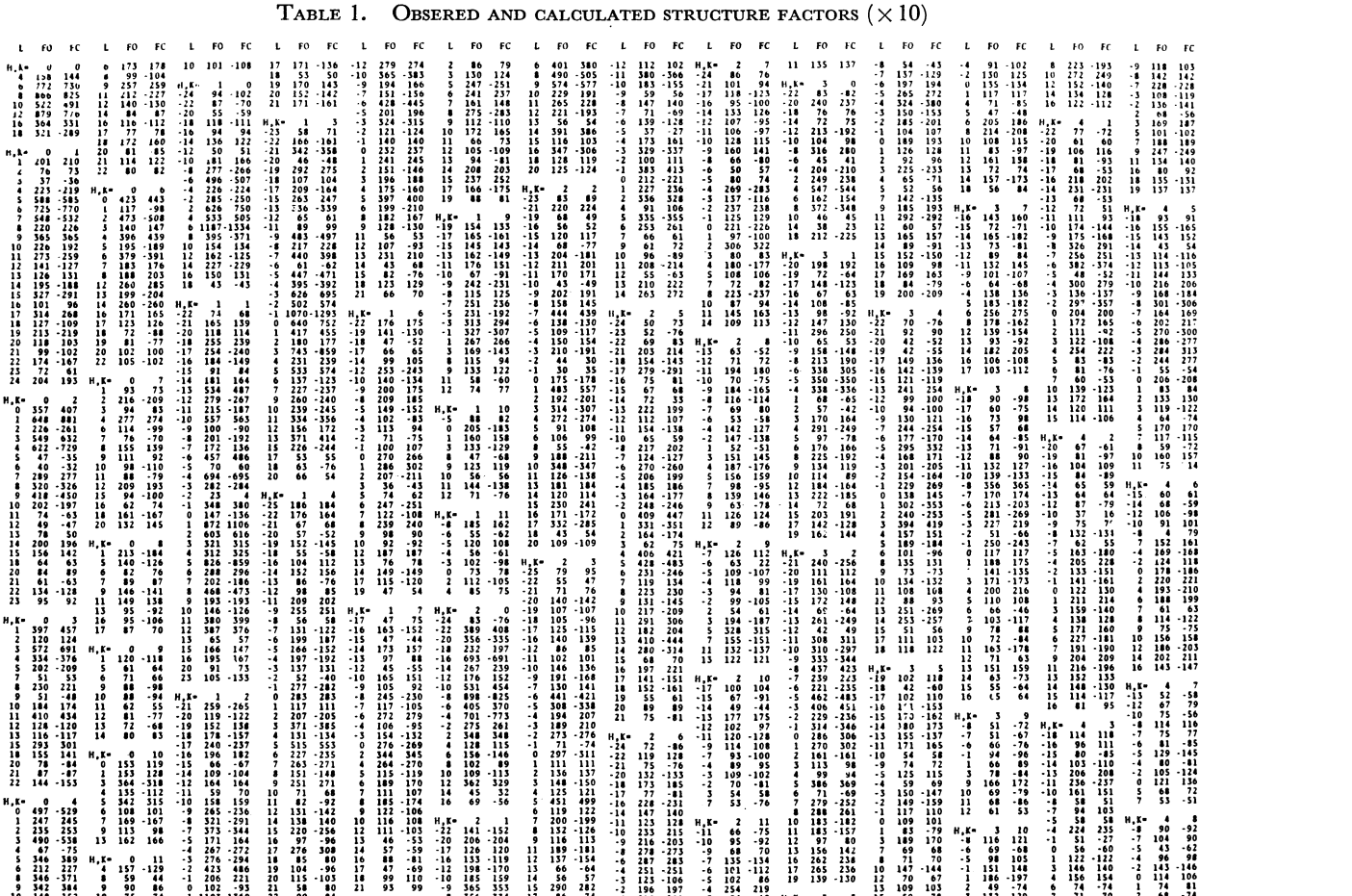

TABLE 2. FINAL ATOMIC PARAMETERS AND e.s.d.'s ($\times 10^4$) FOR NON-HYDROGEN ATOMS

The anisotropic temperature factor is defined as: $\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-\beta_{12}hk-\beta_{13}hl-\beta_{23}kl)$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	1561(2)	1696(1)	2404(1)	193(5)	58(1)	23(0)	−24(4)	12(2)	2(1)
N(1)	4586(6)	3828(3)	2725(1)	171(15)	61(3)	12(1)	15(10)	3(4)	3(2)
C(2)	3295(8)	4905(4)	2537(2)	195(19)	70(4)	15(1)	32(14)	9(6)	0(3)
C(3)	2328(8)	4802(5)	1974(2)	154(18)	83(5)	15(1)	42(14)	12(6)	2(3)
C(4)	3986(8)	5127(4)	1585(2)	298(21)	61(4)	13(1)	−2(14)	4(6)	−1(3)
C(5)	5953(9)	4305(4)	1496(2)	230(20)	75(5)	15(1)	−18(14)	15(6)	0(3)
C(6)	6246(8)	3252(4)	1875(2)	213(20)	69(4)	14(1)	34(14)	1(6)	3(3)
C(7)	6671(9)	3594(4)	2444(2)	223(21)	69(5)	18(1)	28(14)	−5(6)	2(3)
O(8)	3825(8)	6071(4)	1353(2)	640(21)	83(4)	22(1)	139(14)	81(6)	28(3)
C(9)	5275(9)	3929(5)	3301(2)	235(20)	103(5)	13(1)	−18(16)	−11(6)	9(4)
C(10)	3331(9)	4122(5)	3638(2)	275(21)	84(5)	12(1)	−2(15)	−5(6)	1(3)
C(11)	1857(9)	3206(5)	3724(2)	320(24)	112(6)	13(1)	−17(18)	2(7)	4(4)
C(12)	144(10)	3378(6)	4062(2)	339(25)	162(8)	15(1)	−22(21)	7(7)	17(5)
C(13)	−107(12)	4464(7)	4291(2)	440(30)	207(10)	14(1)	107(26)	18(8)	−8(5)
C(14)	1382(14)	5384(7)	4218(3)	738(39)	160(9)	20(1)	60(29)	69(11)	−35(5)
C(15)	3076(12)	5202(6)	3881(2)	549(30)	105(6)	20(1)	−51(21)	44(9)	−6(4)
C(16)	5747(9)	3862(5)	935(2)	269(22)	94(5)	14(1)	5(16)	32(6)	2(3)
C(17)	7362(11)	4165(6)	594(2)	399(28)	144(7)	17(1)	−2(21)	62(8)	1(4)
C(18)	7124(14)	3760(7)	83(3)	614(36)	190(10)	19(1)	113(29)	113(10)	8(6)
C(19)	5393(14)	3061(7)	−84(3)	625(36)	165(9)	18(1)	129(27)	50(10)	−3(5)
C(20)	3768(12)	2756(7)	251(3)	537(31)	141(8)	18(1)	−5(24)	−9(9)	−14(5)
C(21)	3964(10)	3159(6)	758(2)	347(25)	133(7)	15(1)	−17(20)	−2(7)	−15(4)

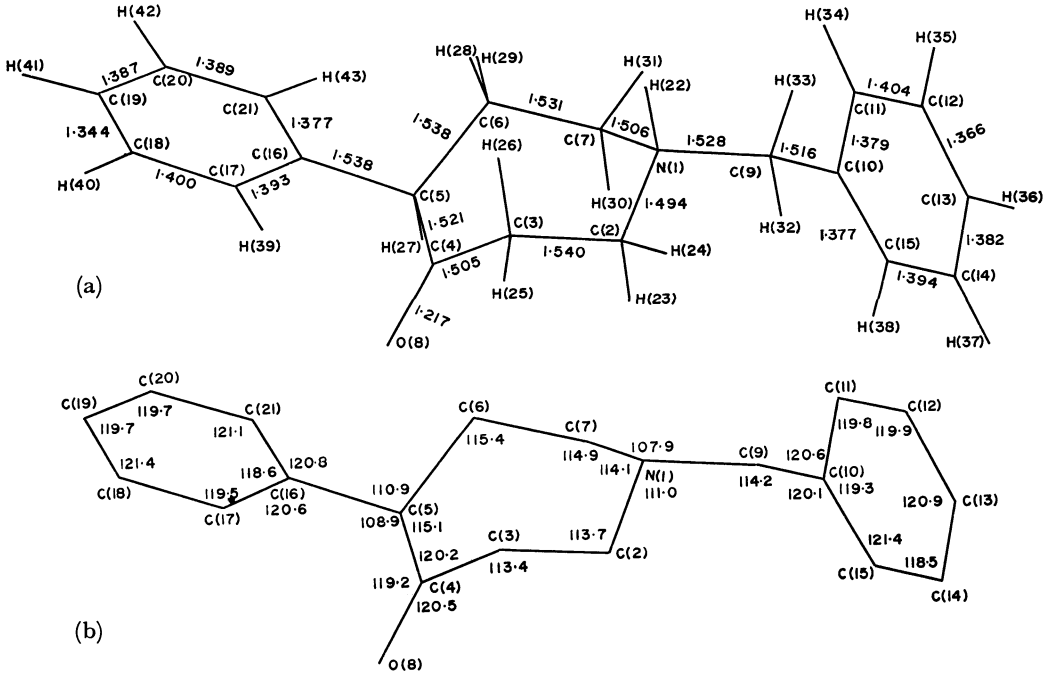

Fig. 1. (a) Bond lengths (Å) and numbering of atoms. (b) Bond angles (°). The estimated standard deviations for the bond lengths and angles are about 0.009 Å and 0.4°, respectively.

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

The e.s.d.'s are given in parentheses.

	x	y	z	B
H (22)	366 (9)	311 (5)	266 (2)	3.4 (1.3)
H (23)	435 (8)	562 (4)	258 (2)	2.2 (1.2)
H (24)	202 (8)	505 (5)	276 (2)	2.6 (1.2)
H (25)	107 (8)	533 (5)	194 (2)	2.1 (1.1)
H (26)	189 (9)	389 (5)	193 (2)	2.5 (1.2)
H (27)	722 (8)	481 (5)	155 (2)	2.7 (1.2)
H (28)	753 (10)	273 (5)	180 (2)	4.4 (1.4)
H (29)	487 (8)	270 (5)	181 (2)	2.1 (1.1)
H (30)	759 (9)	429 (5)	248 (2)	2.4 (1.2)
H (31)	749 (10)	291 (5)	265 (2)	4.2 (1.4)
H (32)	623 (9)	463 (5)	334 (2)	3.6 (1.3)
H (33)	614 (8)	317 (4)	342 (2)	1.6 (1.1)
H (34)	214 (9)	241 (5)	357 (2)	3.9 (1.4)
H (35)	−93 (11)	269 (6)	413 (2)	6.0 (1.7)
H (36)	−130 (14)	461 (7)	452 (3)	9.1 (2.3)
H (37)	108 (13)	619 (7)	439 (3)	7.5 (2.0)
H (38)	419 (9)	584 (5)	381 (2)	3.2 (1.3)
H (39)	866 (10)	469 (6)	73 (2)	5.5 (1.7)
H (40)	829 (13)	396 (7)	−14 (3)	7.4 (1.9)
H (41)	520 (12)	280 (7)	−47 (3)	7.0 (1.9)
H (42)	247 (12)	220 (6)	16 (3)	6.2 (1.7)
H (43)	280 (8)	293 (4)	102 (2)	1.3 (1.1)

120.2°, being closer to trigonal sp^2-hybrid angle than those in the six-membered cycloketones. The bond lengths of C(3)–C(4) and C(4)–C(5) are in accordance with the value, 1.505 Å, expected for C(sp^3)–C(sp^2) bond[13] and that of the C(4)=O(8) is close to the value of 1.216 Å found in acetaldehyde[14] from microwave spectra.

The least-squares planes through the ring atoms of

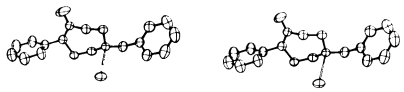

Fig. 2. Stereoconfiguration of (±)-1-benzyl-5-phenyl-1-azacycloheptan-4-one hydrochloride. The thermal ellipsoids are drawn at the 50% probability. Open bond represents hydrogen bond.

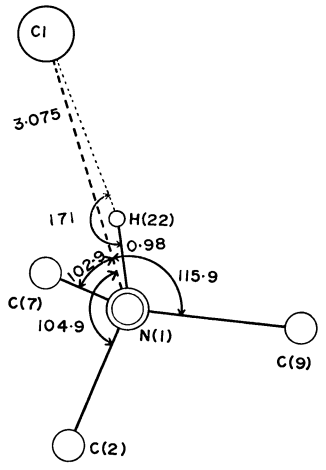

Fig. 3. Coordination of the N(1) atom.

the benzyl and phenyl groups are expressed as:

$$0.5544X - 0.3137Y + 0.7709Z + 6.5723 = 0 \quad (1)$$

and

$$0.5075X - 0.8186Y + 0.2689Z - 1.2316 = 0 \quad (2)$$

where X, Y, and Z are in Å with respect to the a, b, and c^* axes, respectively. The maximum deviations of the ring atoms from the planes (1) and (2) are 0.017 and 0.008 Å, respectively. The C(2), C(3), C(6), and C(7) atoms in the azacycloheptanone ring A give a plane,

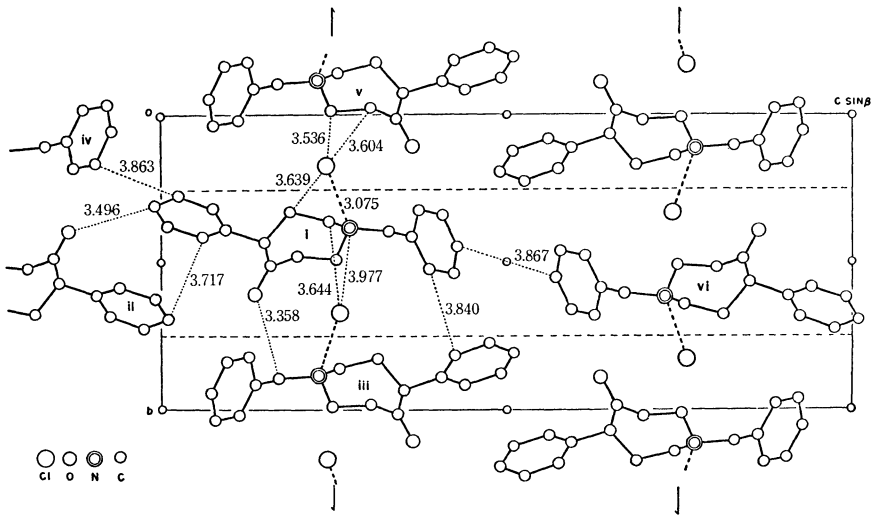

Fig. 4. The projection of the crystal structure viewed along the *a* axis. Hydrogen bonds are shown by broken lines and intermolecular contacts by dotted lines. Key to molecules; i: x, y, z. ii: $1-x, 1-y, -z$. iii: $1-x, 1/2+y, 1/2-z$. iv: $x, 1/2-y, -1/2+z$. v: $-x, -1/2+y, 1/2-z$. vi: $-x, 1-y, 1-z$.

TABLE 4. COMPARISON OF GEOMETRY OF THE CARBONYL GROUP OF THE RELATED COMPOUNDS

Compound	Bond length (Å)			Bond angle (°)
	C=O	C–C	C–C	C–C–C
1-Benzyl-5-phenyl-1-azacycloheptan-4-one[a)]	1.217	1.505	1.521	120.2
Delnudine hydrochloride[9)]	1.199	1.504	1.517	114.6
3-Chloro-2-decalone[10)]	1.20	1.50	1.52	112.8
2,2,6,6-Tetramethyl-4-piperidone hydrochloride[8)]	1.201	1.486	1.503	113.3
cis-2-Chloro-4-*t*-butylcyclohexanone[11)]	1.213	1.501	1.520	112.8
2,2,6,6-Tetramethyl-4-piperidone hydrochloride[8)]	1.221	1.490	1.508	113.3
3-Bromo-2-decalone[12)]	1.25	1.48	1.52	113.4

a) This work.

$$0.5517X + 0.7942Y - 0.2546Z + 3.5414 = 0 \quad (3)$$

with maximum deviation of 0.008 Å. The ring A takes a chair-like conformation, the N(1) atom deviating by +0.682 Å, C(5) −1.119 Å and C(4) −1.135 Å from the plane (3). The N(1) and C(5) atoms are bound equatorially to the benzyl and phenyl groups, respectively. The C(9) atom of benzyl group deviates by 0.068 Å out of the plane (1).

The chloride ion is hydrogen-bonded to the N(1) atom (N(1)···Cl=3.075(4) Å) which exhibits a nearly tetrahedral hybridization, as shown in Fig. 3. Such short hydrogen bonds have also been reported for methixene hydrochloride monohydrate (3.051 Å),[15)] azacyclododecane hydrochloride (3.061 and 3.069 Å),[7)] lidocaine hydrochloride monohydrate (3.07 Å),[16)] 1-(1-phenylcyclohexyl)piperidine hydrochloride (3.088 Å),[17)] 1-methylcytosine hydrochloride (3.1 Å),[18)] and triethylammonium tetrachlorocuprate (3.11 Å).[19)]

The projection of the crystal structure viewed along the a axis is shown in Fig. 4, together with some short contacts between the molecules. The enantiomorphs occur through the medial center of symmetry. The environment around the chloride ion is shown in Fig. 5, in which the C(12^{i})···C(9^{vii}) distance 3.460 Å is the shortest C···C contact. The bulky azacycloheptanone cations and the chloride anions may be held together mainly by Coulombic interactions and hydrogen bonding to form the sheets parallel to the *ab* plane. The sheets are stacked along the *c* axis by van der Waals forces. These are in accordance with relatively high melting point and morphology of the crystal.

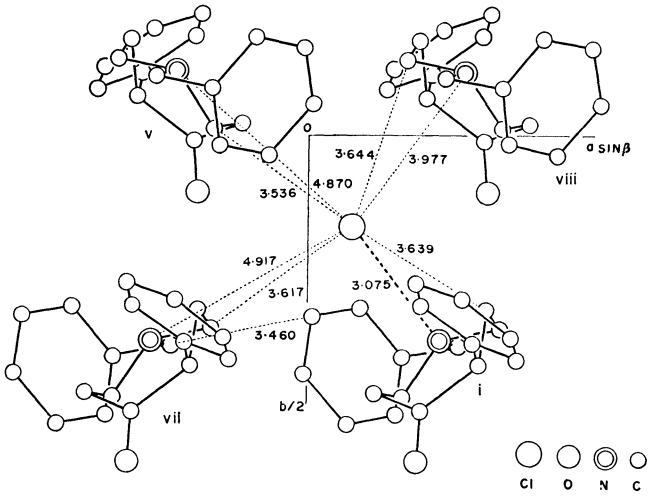

Fig. 5. The environments around the chloride ion. The estimated standard deviations of the distances are of the order of 0.005 Å.
Key to molecules. i: x, y, z. v: $-x, -1/2+y, 1/2-z$. vii: $-1+x, y, z$. viii: $1-x, -1/2+y, 1/2-z$.

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