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The Structures of the 3-Chloro- and 3-Iodopropyltrimethylammonium Cations in the Form of a Mixed Crystal of the Iodide Salt

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The crystal analysed was orthorhombic, space group *Pnma*, with $a = 10.905$, $b = 7.31$, $c = 13.22$ Å, $Z = 4$, and consists of *ca.* 48% of the chloro and 52% of the iodo salt. The cations adopt the extended conformation and possess crystallographic *m* (C_s) symmetry. The structure was determined by Patterson and Fourier methods from counter data and refined by least-squares and difference syntheses to R 7.1% for 1148 observed structure amplitudes.

Introduction

Muscarine and muscarone are highly specific agonists of acetylcholine at the parasympathetic post-ganglionic (muscarinic) receptor and they possess negligible agonistic activities at nicotinic receptors. Beckett (1967), by considering common structural features in numerous cholinergic agonists, delineated a muscarinic receptor surface. The groups involved in the binding are the onium nitrogen head, the ring oxygen of muscarine (and muscarone) or the ester oxygen atom of acetylcholine, and the 3-hydroxy substituent of muscarine, or the carbonyl oxygen atom of muscarone or acetylcholine. Chothia (1970) and Baker, Chothia, Pauling & Petcher (1971), however, emphasize the importance of the cationic head together with the 2-methyl substituent of muscarine or the acetoxy methyl group of acetylcholine. Bonding of these substituents with the receptor is formalized by the five-atom chain rule (Ing, 1949). According to this, maximal muscarinic activity in compounds of type R–N⁺Me₃ occurs when R contains a chain of five atoms, exclusive of hydrogens. When the third atom is oxygen a concomitant increase in activity is observed.

Notable exceptions to the five-atom rule are 3-halopropyltrimethylammonium salts, which have potencies of *ca.* 2–10% of that of acetylcholine itself (Friedman, 1967), and it is noteworthy that these compounds do not contain an oxygen atom. We now report the crystal structures of 3-chloro- and 3-iodopropyltrimethylammonium iodide in the form of a mixed crystal consisting of *ca.* 48% of the chloro and 52% of the iodo salt.

Experimental

3-Chloropropyldimethylammonium chloride (Kodak Ltd) was treated with aqueous ammonia at 0°C and the free base in ether solution (dried over anhydrous Na_2SO_4) reacted with methyl iodide. The methiodide was obtained as a white powder and recrystallization from hot ethanol yielded crystals suitable for X-ray analysis. At this stage we were under the impression that the crystals consisted of pure 3-chloropropyltrimethylammonium iodide. This was supported by elemental analysis of the powder: found 48.9% I; calculated 48.15%. Later, in the course of the analysis it became apparent that partial halogen exchange had occurred in the 3-position so that the crystals contained approximately 48% 3-chloro- and 52% 3-iodopropyltrimethylammonium iodide. The density of the crystals was not determined. However, a flotation test using ethyl iodide, density 1.93 g cm⁻³, indicated that

the crystal density was greater than this, consistent with a calculated density of 1·961 g cm^{-3} for crystals containing 48% chloro and 52% iodo salt. X-ray fluorescence analysis of the crystalline material indicated a chlorine:iodine ratio of 0·278:1, *i.e.* 43% chloro and 57% iodo salt. The exchange, therefore, presumably occurred during the crystallization from hot ethanol.

A crystal of dimensions 0·3 × 0·5 × 0·25 mm, mounted about the direction of elongation (**b**) was used for all the X-ray measurements. Oscillation and Weissenberg photographs indicated orthorhombic symmetry. Systematic absences corresponded to space group $Pn2_1a$ (C_{2v}^9) or $Pnma$ (D_{2h}^{16}). The final cell dimensions and intensity data were measured on a Stoe two-circle computer-controlled diffractometer with graphite-monochromated Mo $K\alpha$ radiation and a scintillation counter. The ω-scan technique was employed with a stepping interval of 0·01° and a step time of 1 s. For layers $h0l$–$h3l$ the scan range was 1·5°. For the higher layers (equi-inclination angle $\mu \geq 11\cdot21°$) a variable scan range given by $\Delta\omega = (A + B \sin \mu/\tan \theta')°$ with $A = 1\cdot2$ and $B = 0\cdot5$ was used, $2\theta'$ being the azimuth angle. Backgrounds were measured for 30 s at each end of the scan. From 1986 reflexions scanned within the range $5 \leq 2\theta' \leq 50°$, 1151, for which $I > 2\cdot5\sigma(I)$, were considered to be observed and were used in the structure analysis. Intensities were converted to structure amplitudes in the usual manner, but absorption corrections were not applied.

Crystal data

$(C_6H_{15}NCl_{0.48}I_{0.52})^+I^-$, $M = 311\cdot1$. Orthorhombic, $a = 10\cdot905$ (10), $b = 7\cdot31$ (1), $c = 13\cdot22$ (1) Å, $U = 1053\cdot8$ Å^3, $Z = 4$, $D_x = 1\cdot961$, $F(000) = 586\cdot9$. Systematic absences: $0kl$ when $k + l$ is odd, $hk0$ when h is odd. Space group $Pn2_1a$ (C_{2v}^9) or $Pnma$ (D_{2h}^{16}). $Pnma$ established as a result of the analysis. Molecular symmetry m (C_s). Mo $K\alpha$ radiation, $\lambda = 0\cdot71069$ Å. μ(Mo $K\alpha) = 46\cdot7$ cm^{-1}.

Determination of the structure

The coordinates of the iodide ion were determined from a Patterson synthesis. At this stage space group $Pn2_1a$ was assumed, structure factors were calculated (R 57%), and a Fourier synthesis, based on the calculated phases, was evaluated. In $Pn2_1a$ an electron density map phased on just the four iodide ions in the cell will exhibit pseudo-symmetry, since the symmetry of the arrangement of the iodide ions is higher than the true symmetry of the cell. Examination of the electron density map revealed that the organic cation lay in a pseudo-mirror plane, with only a pair of methyl groups situated above and below this plane. This indicated that the pseudo-mirror plane was probably a genuine symmetry plane and that the true space group was $Pnma$. Least-squares refinement of atomic parameters was initiated, however, on the basis of the

lower space group. At this stage it was still assumed that the covalently bound halogen atom was chlorine. The atomic positions refined to a close approximation of C_s symmetry, but R remained high (> 20%) even when the atoms were allowed to vibrate anisotropically. A difference synthesis was computed and revealed an electron density maximum of *ca.* 15 e Å^{-3} at the site of the chlorine atom. Re-examination of the initial heavy-atom phased electron density map showed that the maximum corresponding to the chlorine atom was approximately $\frac{2}{3}$ the height of the iodide ion maximum. It was now assumed that the halogen site was statistically occupied by half an atom of chlorine and half an atom of iodine and least-squares refinement was continued, varying the coordinates of the 'half-atoms' in alternate cycles. Starting coordinates for these atoms were calculated on the basis of C–Cl and C–I bond lengths of 1·77 and 2·20 Å (Sutton, 1965). For the iodide ion and the covalently linked half-iodine atom anisotropic thermal parameters were refined. The thermal parameters of the half chlorine atom were not refined, but were set equal to those of the half iodine atom after each cycle of refinement. The remaining atoms were refined isotropically. Hydrogen atoms were not considered. For the final cycles, the higher space group $Pnma$ was adopted, with all atoms lying in the mirror plane at $y = \pm\frac{1}{4}$, except methyl carbon atoms
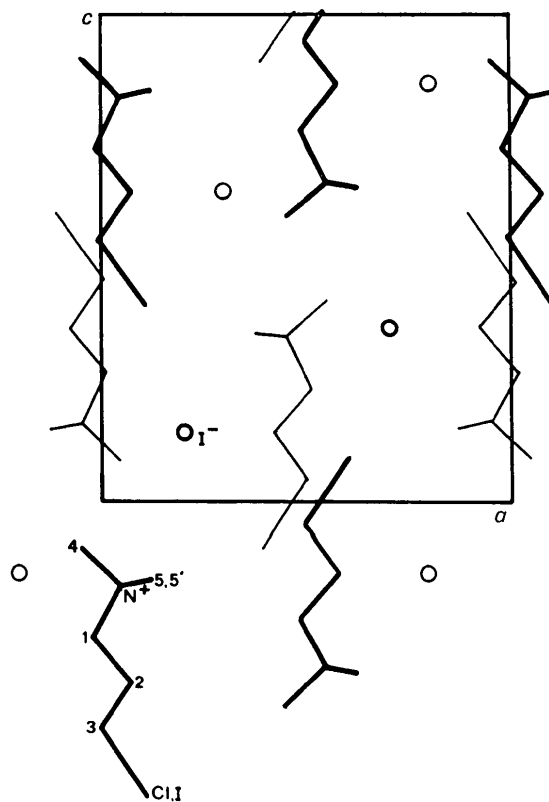

Fig. 1. The crystal structure of 3-chloro(iodo)propyltrimethyl-ammonium iodide projected along the y axis.

C(5) and C(5') which are related by the plane. Under these conditions, the refinement process proceeded smoothly and was terminated when the calculated shifts were all $<0.1\sigma$ and R 7·2%. A difference synthesis indicated some residual electron density at the (Cl,I) site, and the occupation factors were therefore adjusted until a difference map indicated only minimal electron density. This occurred when the occupation factors were 0·48 Cl, 0·52 I, and R 7·1% for 1148 structure amplitudes.* Three large, low-order reflexions (302, $|F_o| = 187.5$, $F_c = 208.4$; 004, $|F_o| = 234.1$, $F_c = -266.8$; 211, $|F_o| = 138.4$, $F_c = 155.0$) which appeared to be affected by extinction, were omitted from the final least-squares cycles. R for all 1151 observed amplitudes is 7·2%.

The weighting scheme was $w^{1/2} = 1.0$ if $|F_o| < 25.0$, and $w^{1/2} = 25.0/|F_o|$ if $|F_o| > 25.0$. Scattering factors were taken from Hanson, Herman, Lea & Skillman (1964).

Computations were carried out on the Birmingham University 1906A computer with local versions of *FORDAP*, the Zalkin Fourier program and *ORFLS* and *ORFFE*, the Busing, Martin & Levy full-matrix least-squares and function-and-error programs.

Final atomic coordinates and thermal parameters are listed in Table 1 and molecular dimensions in Table 2. The packing arrangement is illustrated in Fig. 1, which also indicates the atomic numbering scheme.

Table 1. *Fractional atomic coordinates and thermal parameters (both $\times 10^4$)*

Estimated standard deviations are in parentheses. Isotropic temperature factors are in the form $T = \exp[-2\pi^2 U(2\sin\theta/\lambda)^2]$. Anisotropic temperature factors are in the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{12}hka^*b^* + \ldots)]$.

	x	y	z	U
C(1)	−171 (13)	2500	−2690 (11)	494
C(2)	750 (16)	2500	−3612 (12)	583
C(3)	−40 (16)	2500	−4549 (14)	639
C(4)	−520 (15)	2500	−873 (12)	538
C(5)	1231 (12)	846 (18)	−1514 (9)	628
N	457 (10)	2500	−1647 (9)	438
Cl†	934	2500	−5756	‡
I†	1060	2500	−5943	‡
I⁻	2066 (1)	2500	1418 (1)	‡

† These sites are only partially occupied. Because of the additional uncertainty introduced by the disorder, standard deviations are not quoted.

‡ Anisotropic thermal parameters

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl, I	618	382	285	0	228	0
I⁻	707	532	427	0	−51	0

* A list of observed and calculated structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30584 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Molecular dimensions*

(a) Bond distances (Å) with standard deviations in parentheses

C(1)–C(2)	1·58 (2)	C(1)–N	1·54 (2)
C(2)–C(3)	1·51 (2)	C(4)–N	1·48 (2)
C(3)–Cl	1·92	C(5)–N	1·48 (2)
C(3)–I	2·20		

(b) Selected non-bonded distances (Å)

N·····C(3)	3·87	C(4)···Cl	6·65
N·····Cl	5·46	C(4)···I	6·92
N·····I	5·72	C(5)···Cl	5·75
C(5)···C(2)	3·07	C(5)···I	5·98

(c) Bond angles (°); mean standard deviation 1·2°

N——C(1)–C(2)	114	C(4)–N–C(1)	107
C(1)–C(2)–C(3)	106	C(5)–N–C(1)	111
C(2)–C(3)–Cl	112	C(4)–N–C(5)	109
C(2)–C(3)–I	112	C(5)–N–C(5')	109

(d) Torsion angles (°)

C(4)–N——C(1)–C(2)	180*	C(1)–C(2)–C(3)–Cl	180*
C(5)–N——C(1)–C(2)	−61	C(1)–C(2)–C(3)–I	180*
N——C(1)–C(2)–C(3)	180*		

* Required to be 180° by the C_s symmetry

The possibility that the structure only approximates to C_s symmetry and that the true space group is $Pn2_1a$ cannot be entirely excluded. However, any deviation from C_s symmetry must be very small and would not affect the results to any significant extent.

Discussion

Bond lengths and angles within the organic cation agree quite well with accepted values, but estimated standard deviations are high (averaging 0·02 Å for lengths and 1·2° for angles), probably due to the high proportion of iodine in the crystal and the effect of the disorder. The C(3)–Cl bond length, 1·92 Å, is ca. 0·15 Å longer than accepted values (Sutton, 1965), and it would appear that the chlorine atom has refined to a position too close to the iodine atom. The C(3)–I length, 2·20 Å, is normal for this type of bond.

The cation possesses crystallographic C_s symmetry and is in the extended all-*trans* conformation. A similar conformation occurs in the $-CH_2CH_2CH_2N^+Me_3$ moiety of the 3-acetoxypropyltrimethylammonium (acetylhomocholine) ion in crystals of the bromide salt (Craven & Hite, 1973). Here, however, the O–C(3)–C(2)–C(1) conformation is synclinal, in contrast to the antiplanar conformation of the Cl,I–C(3)–C(2)–C(1) group in the halogen compounds. In the crystal structures of acetylcholine bromide (Canepa, Pauling & Sörum, 1966) and acetylcholine chloride (Herdklotz & Sass, 1970) the O–C–C–N$^+$ conformation is synclinal and this is the conformation generally adopted by this grouping in a wide variety of molecules, with an N$^+$···O distance usually in the range 3·0–3·3 Å. Sundaralingam (1968) has suggested that the synclinal arrangement is due primarily to electrostatic attraction between the positively charged ammonium group and

the oxygen atom, and this conformation is also predicted by recent molecular orbital calculations (Radna, Beveridge & Bender, 1973; Port & Pullman, 1973). Calculations (Pullman, Courrière & Coubeils, 1971) indicate that the positive charge of the ammonium group is not localized on the nitrogen atom but is distributed among the neighbouring carbon and hydrogen atoms, and Craven & Hite (1973) attribute the synclinal conformation of the O–C(3)–C(2)–C(1) grouping in acetylhomocholine to a similar interaction between the oxygen atom and C(1). In the halogen compounds, electrostatic attraction between Cl, I and the cationic head is presumably weaker, so that a synclinal arrangement about C(2)–C(3) does not occur.

The $N^+\cdots Cl$ distance is 5·46 Å, but the chlorine position is probably affected by the disorder, and taking the C(3)–Cl bond length to be 1·77 Å, the generally accepted value (Sutton, 1965), rather than 1·92 Å as derived from the analysis, $N^+\cdots Cl$ becomes ca. 5·32 Å. The $N^+\cdots I$ distance is 5·72 Å and these distances may be compared with a separation of 5·4 Å between the nitrogen atom and the 2-methyl substituent in the crystal structure of L(+)-muscarine iodide (Jellinek, 1957), and with 5·1 and 5·38 Å for the $N^+\cdots$acetoxy methyl separations in acetylcholine bromide and acetylcholine chloride. The conformation adopted by acetylcholine in the crystal structure of the chloride salt is similar to that considered relevant to interaction with the muscarinic receptor (Chothia, 1970; Baker et al., 1971).

The distance between the nitrogen atom and the 3-hydroxy substituent of muscarine (5·65 Å) is also comparable with the $N^+\cdots$halogen distances. The $N^+\cdots$ring oxygen atom separation in muscarine and the $N^+\cdots O$ separations in acetylcholine bromide and chloride are, however, considerably shorter than the $N^+\cdots$halogen distances.

Intermolecular contact distances are listed in Table 3. The iodine$\cdots$iodide ion separation of 3·66 Å is significantly shorter than the sum of the van der Waals radii and may be indicative of a charge-transfer interaction. Other contact distances are normal.

Table 3. *Intermolecular contacts* ($<4\cdot0$ Å)

$I\cdots\cdots I^{-i}$	3·66	$C(3)\cdots I^{ii}$	3·88
$C(3)\cdots Cl^{ii}$	3·80	$C(5)\cdots I^{iii}$	3·91
$C(3)\cdots C(3^{ii})$	3·85	$Cl\cdots\cdots I^{-i}$	3·94

Symmetry code

(i)	$x,$	$y,$	$z-1$	(iii)	$\frac{1}{2}-x, -y, \frac{1}{2}+z$
(ii)	$-x, \frac{1}{2}+y, -z-1$				

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