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Structure of Trimethyl[(*cis*-4-methyl-1,3-dioxolan-2-yl)methyl]ammonium Iodide, $C_8H_{18}NO_2^+.I^-$

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Abstract. $M_r = 287\cdot1$, monoclinic, $P2_1/c$, $a = 14\cdot716$ (4), $b = 13\cdot002$ (4), $c = 14\cdot431$ (4) Å, $\beta = 116\cdot3$ (1)°, $Z = 8$, $U = 2475$ (2) Å^3, $D_m = 1\cdot54$, $D_x = 1\cdot541$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 2\cdot59$ mm^{-1}, $F(000) = 1144$. Final $R = 0\cdot069$ for 2334 observed reflections. The overall conformations of the cations, described by the torsion angles N—C—C—O, markedly differ from that found in many muscarinic agents.

Introduction. The solid-state conformation of a number of muscarinic agents is being studied in our laboratory to see if some correlation can be drawn between their molecular structure and pharmacological activity. In this paper we report on the crystal and molecular structure of the title compound (TMO2), derived from a single-crystal X-ray analysis.

Experimental. Single crystals obtained by slow evaporation of a solution in absolute ethanol, under reduced constant pressure in a dry atmosphere; D_m measured by flotation, approximate unit-cell parameters estimated from preliminary Weissenberg and precession photographs, crystal ~0·4 × 0·4 × 0·4 mm, Philips PW1100 four-circle diffractometer, graphite monochromator, $2\theta = 12\cdot16°$, accurate unit-cell parameters and crystal-orientation matrices (together with their estimated standard errors) obtained from least-squares refinement of 2θ, ω, χ and φ values of 20 carefully centered high-angle reflections; θ–2θ scan, scan speed 0·03°s^{-1}, scan width 1·20°, 2θ range 4–50°, two standard reflections ($2\bar{2}2$, $22\bar{2}$) every 180 min, 2498 data measured, 2334 with $I > 3\sigma(I)$, Lorentz and polarization corrections, intensities placed on an absolute scale by Wilson's method; trial structure obtained by heavy-atom method and refined by full-matrix least squares, H atoms not located, $\sum w(|F_o| - |F_c|)^2$ minimized, $w = 7\cdot3[\sigma^2(F_o) + 0\cdot000257F_o^2]^{-1}$, adequacy of weighting scheme confirmed by analysis of variation of mean $w(|F_o| - |F_c|)^2$ with $|F_o|$ and $\lambda^{-1}\sin\theta$, scattering factors from *International Tables for X-ray Crystallography* (1974), both real and imaginary components of anomalous dispersion included for I only (*International Tables for X-ray Crystallography,* 1974).

The refinement was carried out allowing both I$^-$ anions, along with all non-H atoms of a cation (hereinafter cation 1), to vibrate anisotropically. In contrast, all non-H atoms of the other cation (cation 2) were assigned isotropic thermal parameters because inspection of difference Fourier maps revealed remarkable disorder in the region of this cation. In addition, population parameters were applied to C(15) and C(17), and C(25) and C(27). Therefore cation 2 results from the overlap of four possible cations, quoted as cation 2(i) (i = 1,2,3,4). They have the same quaternary group, different methyl groups *i.e.* C(17) or C(27), and the five-membered rings differ owing to the presence of C(15) or C(25).

Final conventional $R = 0\cdot069$ ($R_w = 0\cdot070$) for 2334 observed reflections; calculations carried out on the CYBER 76 computer of CINECA with *SHELX* 76 (Sheldrick, 1976).

Discussion. The final positional parameters are given in Table 1† and interatomic distances and interbond angles with e.s.d.'s calculated from the full variance–covariance matrix are in Table 2.

A perspective view of cation 1 with the atom-numbering scheme and selected intramolecular non-bonding distances is presented in Fig. 1.

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† Lists of structure factors, anisotropic thermal parameters, least-squares-planes' data and all torsion angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38295 (19 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Table 1. *Final atomic coordinates* (× 10^4) *and isotropic thermal parameters* (Å^2 × 10^3) *with e.s.d.'s in parentheses*

Anions	x	y	z	U_{eq}/U	
I(1)	8138 (1)	8105 (1)	8854 (1)	80·4 (7)*	
I(2)	6464 (1)	2385 (1)	5575 (1)	85·5 (7)*	
Cation 1					
O(1)	4820 (10)	135 (10)	7074 (11)	114 (9)*	
O(2)	3133 (9)	35 (9)	6417 (12)	118 (10)*	
N(1)	3301 (9)	1323 (9)	4578 (11)	73 (8)*	
C(1)	3777 (11)	789 (12)	3983 (11)	85 (10)*	
C(2)	2204 (11)	937 (13)	4245 (13)	92 (11)*	
C(3)	3247 (12)	2457 (11)	4328 (14)	86 (11)*	
C(4)	3919 (13)	1227 (14)	5747 (16)	93 (13)*	
C(5)	3937 (13)	180 (13)	6147 (15)	90 (12)*	
C(6)	4573 (18)	−522 (16)	7730 (18)	129 (16)*	
C(7)	5332 (17)	−283 (19)	8834 (19)	163 (18)*	
C(8)	3496 (17)	−159 (17)	7492 (18)	140 (17)*	
Cation 2					p†
O(11)	9760 (10)	447 (12)	7756 (12)	138 (5)	1
O(12)	9662 (10)	2184 (10)	7922 (11)	112 (4)	1
N(11)	8287 (9)	1485 (9)	9004 (9)	77 (8)*	1
C(11)	8697 (13)	1107 (15)	10083 (15)	101 (13)*	1
C(12)	8443 (15)	2659 (14)	9022 (18)	125 (15)*	1
C(13)	7162 (12)	1239 (14)	8436 (13)	89 (12)*	1
C(14)	8754 (16)	971 (17)	8376 (18)	127 (7)	1
C(15)	9703 (28)	1226 (27)	8585 (30)	113 (11)	0·6
C(16)	10366 (18)	989 (20)	7262 (19)	142 (7)	1
C(17)	10386 (33)	324 (32)	6540 (36)	151 (14)	0·6
C(18)	10176 (18)	1999 (20)	7381 (20)	155 (8)	1
C(25)	8920 (27)	1277 (28)	7672 (32)	68 (10)	0·4
C(27)	10978 (45)	261 (45)	7338 (51)	126 (18)	0·4

*$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.
†p is the population parameter.

Table 2. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

	Cation 1	Cation 2	
N(1)–C(1)	1·50 (2)	1·48 (2)	
N(1)–C(2)	1·55 (2)	1·54 (2)	
N(1)–C(3)	1·51 (2)	1·52 (2)	
N(1)–C(4)	1·53 (2)	1·51 (3)	
C(4)–C(5)	1·47 (3)	1·33 (5)	1·21 (6)
C(5)–O(1)	1·39 (2)	1·60 (5)	1·60 (4)
C(5)–O(2)	1·41 (3)	1·55 (4)	1·54 (4)
O(2)–C(8)	1·42 (3)	1·33 (4)	
C(6)–C(8)	1·54 (4)	1·37 (4)	
C(6)–O(1)	1·44 (3)	1·54 (4)	
C(6)–C(7)	1·52 (3)	1·36 (6)	1·28 (7)
C(1)–N(1)–C(2)	111 (1)	109 (1)	
C(1)–N(1)–C(3)	108 (1)	110 (1)	
C(1)–N(1)–C(4)	113 (1)	114 (1)	
C(2)–N(1)–C(3)	108 (1)	110 (1)	
C(2)–N(1)–C(4)	110 (1)	110 (1)	
C(3)–N(1)–C(4)	107 (1)	105 (1)	
N(1)–C(4)–C(5)	114 (1)	117 (2)	132 (2)
C(4)–C(5)–O(1)	105 (2)	94 (3)	99 (3)
C(4)–C(5)–O(2)	111 (2)	108 (3)	116 (3)
C(5)–O(2)–C(8)	112 (2)	110 (2)	105 (2)
C(6)–C(8)–O(2)	99 (2)	117 (2)	
C(8)–C(6)–O(1)	102 (2)	101 (2)	
C(6)–O(1)–C(5)	105 (2)	107 (2)	104 (2)
O(1)–C(5)–O(2)	105 (1)	93 (2)	93 (2)
C(8)–C(6)–C(7)	112 (2)	141 (3)	151 (4)
C(7)–C(6)–O(1)	107 (2)	106 (3)	99 (3)

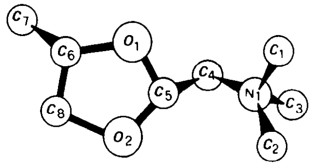


Fig. 1. Perspective view of cation 1 with the atom-numbering scheme. Selected intramolecular non-bonding distances are: C(1)···O(1) 4·11 (2), N(1)···O(1) 3·64 (2) and N(1)···C(7) 5·89 (3) Å.

The high values of the e.s.d.'s and the unusual value of some bond lengths, caused mainly by the presence of disorder in the crystal, mean that the precise values of bond lengths and angles do no warrant further discussion.

Because the most relevant aspect of the structure of the molecule is the orientation of the dioxolane ring with respect to the tetrahedral ammonium N we express the conformational parameters of cation 1 of TMO2 in terms of the torsion angles τ\{C(3)[C(1),C(2)]–N$^+$(1)–C(4)–C(5)\}, τ[N$^+$(1)–C(4)–C(5)–O(1)], τ[C(4)–C(5)–O(1)–C(6)] and τ[C(5)–O(1)–C(6)–C(7)]. As is commonly observed in similar structures (Baker, Chothia, Pauling & Petcher, 1971), steric hindrance between C(5) and the methyl groups on N forces the value of τ[C(3)–N$^+$(1)–C(4)–C(5)] to be antiperiplanar. The τ[C(4)–C(5)–O(1)–C(6)] and τ[C(5)–O(1)–C(6)–C(7)] torsion angles will be discussed together. In cholinergic compounds the observed value of the former angle varies between +76 and −148° and/or between −76 and +148°. The observed value depends upon intramolecular steric strain, the substituents on C(4) and C(5) and crystal-packing forces (Baker *et al.*, 1971). Therefore the value of 146° observed in TMO2 agrees with these contentions. The theoretical value of τ[C(5)–O(1)–C(6)–C(7)] in cholinergic agents would be 180° on the basis of steric hindrance and van der Waals interactions; the departure from this value observed in TMO2 is certainly attributed to the intramolecular steric strain typical of the five-membered rings.

The most relevant difference between the conformation of TMO2 and that found in many cholinergic agonists involves the value of τ[N$^+$(1)–C(4)–C(5)–O(1)]; this is 156° in TMO2 and in the range of 60–85° for many agonists (Chothia & Pauling, 1968). Therefore the C(1)···O(1) and N(1)···O(1) distances of 4·11 (2) and 3·64 (2) Å, observed in TMO2, greatly differ from those in L-(+)-muscarine (2·87 and 3·07 Å) (Jellinek, 1957) and in acetylcholine (3·02 and 3·29 Å) (Canepa, Pauling & Sörum, 1966). It is our contention that the crystal-packing forces cannot be responsible for these differences. Nevertheless, these unusual values can be justified by the presence in TMO2 of two electronegative O atoms which tend to be equidistant from the positively charged N. Therefore the value of

τ[N$^+$(1)—C(4)—C(5)—O(1)] is mainly determined by the competitive electrostatic interactions N(1)···O(1) and N(1)···O(2). Table 3 suggests that the conformations of cation 2(i) (i = 1,2,3,4) differ from that found in cation 1 and none of these is that which has been suggested to be necessary for muscarinic activity in acetylcholine and its analogues (Baker *et al.*, 1971).

It is evident that the five-membered rings C(5)—O(1)—C(6)—C(8)—O(2), C(15)—O(11)—C(16)—C(18)—O(12) and C(25)—O(11)—C(16)—C(18)—O(12) (hereinafter rings *a*, *b* and *c*, respectively) cannot be planar. The total puckering amplitudes Q (Cremer & Pople, 1975) are quoted in Fig. 2. In addition, within ring (*a*) there is a pseudo mirror plane through C(6) and C(5)—O(2) and a pseudo twofold axis through O(2) and C(6)—O(1). From Fig. 2(*a*) and the asymmetry parameters of Duax, Weeks & Rohrer (1976), it appears that the 'envelope' (C_s) conformation is predominant. The asymmetry parameters of rings (*b*) and (*c*), shown in Fig. 2(*b,c*), indicate that the conformation of these rings is twisted between 'half-chair' (C_2) and 'envelope' (C_s).

The crystal packing, as viewed down **b**, is depicted in Fig. 3 and is mainly determined by Coulombic and van der Waals forces. The intermolecular non-bonding distances are those expected for standard van der Waals values. The environment of the I$^-$ anions is approximately tetrahedral with I$^-$···N$^+$ distances ranging from 4·4 to 4·8 Å.

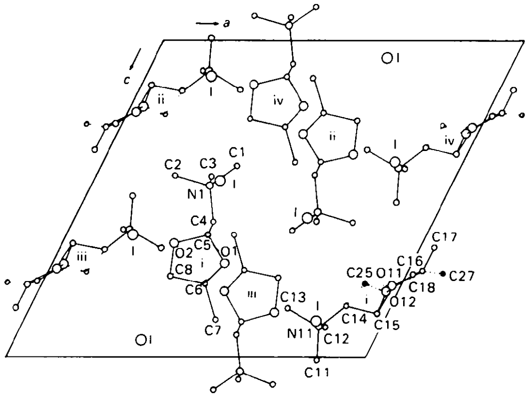
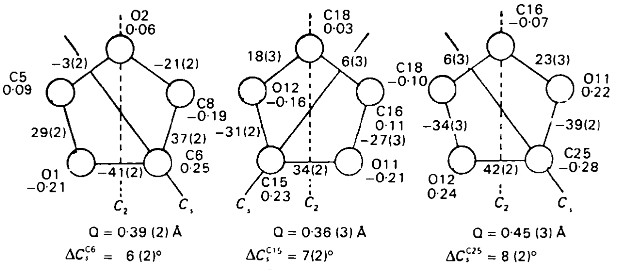


Fig. 3. The crystal structure projected down **b**. The symbols inside the ring represent the equivalent positions in space group $P2_1/c$ (No. 14) [*i.e.* (i) x,y,z; (ii) $1-x,\bar{y},1-z$; (iii) $1-x,\frac{1}{2}+y,\frac{3}{2}-z$; (iv) $x,\frac{1}{2}-y,z-\frac{1}{2}$].

Table 3. *Some relevant torsion angles* (°)

Cation 1				
C(3)—N(1)—C(4)—C(5)	172 (1)		C(4)—C(5)—O(1)—C(6)	146 (2)
N(1)—C(4)—C(5)—O(1)	156 (1)		C(5)—O(1)—C(6)—C(7)	−159 (2)
Cation 2 (1)			Cation 2 (2)	
C(13)—N(11)—C(14)—C(15)	167 (3)		C(13)—N(11)—C(14)—C(15)	
N(11)—C(14)—C(15)—O(11)	178 (2)		N(11)—C(14)—C(15)—O(11)	
C(14)—C(15)—O(11)—C(16)	142 (2)		C(14)—C(15)—O(11)—C(16)	
C(15)—O(11)—C(16)—C(17)	−179 (3)	132 (4)	C(15)—O(11)—C(16)—C(27)	
Cation 2 (3)			Cation 2 (4)	
C(13)—N(11)—C(14)—C(25)	91 (4)		C(13)—N(11)—C(14)—C(25)	
N(11)—C(14)—C(25)—O(11)	160 (2)		N(11)—C(14)—C(25)—O(11)	
C(14)—C(25)—O(11)—C(16)	−156 (2)		C(14) C(25) O(11) C(16)	
C(25)—O(11)—C(16)—C(17)	−128 (3)	−178 (4)	C(25)—O(11)—C(16)—C(27)	



Q = 0·39 (2) Å
ΔC_s^{C6} = 6 (2)°
ΔC_2^{O2} = 14 (2)°
(*a*)

Q = 0·36 (3) Å
ΔC_s^{C15} = 7(2)°
ΔC_2^{C18} = 9(2)°
(*b*)

Q = 0·45 (3) Å
ΔC_s^{C25} = 8 (2)°
ΔC_2^{C16} = 12 (2)°
(*c*)

Fig. 2. The puckering of the five-membered rings. Near the circles are the perpendicular displacements of the corresponding atoms out of the mean plane through the ring (Å, e.s.d.'s 0·01 Å). Torsion angles in°.

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