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Structure of (2-Ethoxyethyl)trimethylammonium Iodide, C₇H₁₈NO⁺.I⁻

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Abstract. $M_r = 259.1$, monoclinic, $P2_1/n$, $a = 16.060$ (7), $b = 13.231$ (6), $c = 10.610$ (6) Å, $\beta = 94.8$ (1)°, $Z = 8$, $U = 2247$ (2) Å³, $D_m = 1.53$, $D_x = 1.532$ Mg m⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 2.84$ mm⁻¹, $F(000) = 1024$, $T = 298$ K. Final $R = 0.070$ for 2477 observed reflections. The overall conformation of the cations, described by the torsion angles N–C–C–O, does not markedly differ from that found in many muscarinic agents.

Introduction. We have performed the single-crystal X-ray analysis of the structure of the title ethoxy substituted choline iodide, as a part of an investigation into the conformational properties of some muscarinic agents, which we are examining in an attempt to correlate molecular conformation and biological activity. The title compound, which possesses remarkable muscarinic activity, has been considered in an extensive structure–activity analysis (Pratesi, Villa & Grana, 1968; Pratesi, Villa, Ferri, De Micheli, Grana, Santagostino Barbone, Silipo & Vittoria, 1981).

Experimental. Compound obtained by condensation of potassium ethoxide with (dimethylamino)ethyl chloride hydrochloride, distillation of resulting product and subsequent quaternization (Pratesi *et al.*, 1968); 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. Prismatic crystal $\sim 0.3 \times 0.3 \times 0.5$ mm. Philips PW 1100 four-circle diffractometer, graphite monochromator. 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 (θ range 15–20°) reflections. θ – 2θ scan, scan speed 0.03° s⁻¹, 2θ range 4–50° ($-18 \leq h \leq 18$, $0 \leq k \leq 15$, $0 \leq l \leq 11$). Two standard reflections ($\bar{3}11$, $3\bar{1}\bar{1}$) every 180 min with no significant intensity variation during data collection. 3902 data measured, 2477 with $I \geq 3\sigma(I)$, R_{int} for 216 equivalent reflections (only $hk0$) being 0.062. Lorentz and polarization corrections, intensities placed on an absolute scale by Wilson's method, experimental

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absorption correction applied (max. and min. values 1.5 and 0.8 respectively) (North, Phillips & Mathews, 1968). No secondary-extinction correction. Trial structure obtained by heavy-atom method and refined by full-matrix least-squares procedure. $\sum w(|F_o| - |F_c|)^2$ minimized, $w = 4.007[\sigma^2(F_o) + 0.0005F_o^2]^{-1}$, adequacy of weighting scheme confirmed by analysis of variance 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), C(17), C(25) and C(27) respectively. Therefore cation 2 results from the overlap of four possible cations, quoted as cation 2(*i*) (*i* = 1,2,3,4). H atoms were located in calculated idealized positions (C-H = 1.0 Å) and not varied for cation 1, but were not located owing to the disorder for cation 2.

Final conventional $R = 0.070$, $R_w = 0.074$ for 2477 observed reflections. Max. least-squares shift/error < 0.4. Max. and min. heights in final difference Fourier synthesis $\pm 0.8 \text{ e } \text{Å}^{-3}$ (close to I⁻). Calculations carried out on the CYBER76 computer of 'CINECA' with *SHELX76* (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.

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 not warrant further discussion.

The conformational parameters of the ethoxy substituted choline cation 1 can be expressed in terms of the torsion angles $\tau\{C(3)[C(1),C(2)]-N^+(1)-C(4)-C(5)\}$, $\tau\{N^+(1)-C(4)-C(5)-O(1)\}$, $\tau\{C(4)-C(5)-O(1)-C(6)\}$ and $\tau\{C(5)-O(1)-C(6)-C(7)\}$ (Table 3).

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates for cation 1 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38647 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($\text{Å}^2 \times 10^3$) with e.s.d.'s in parentheses

| | x | y | z | U_{eq}/U | |
|-----------------|-----------|-----------|-----------|------------|-----|
| Anions | | | | | |
| I(1) | 1230 (1) | 1176 (1) | 2326 (1) | 86 (1)* | |
| I(2) | 6637 (1) | 556 (1) | 2128 (1) | 80 (1)* | |
| Cation 1 | | | | | |
| O(1) | 1088 (8) | 6114 (10) | 732 (11) | 130 (9)* | |
| N(1) | 1089 (6) | 4514 (7) | 2949 (10) | 71 (5)* | |
| C(1) | 1049 (12) | 5591 (9) | 3439 (19) | 105 (9)* | |
| C(2) | 1939 (9) | 4094 (11) | 3338 (19) | 98 (8)* | |
| C(3) | 462 (8) | 3889 (10) | 3613 (14) | 83 (9)* | |
| C(4) | 844 (12) | 4426 (12) | 1609 (16) | 107 (9)* | |
| C(5) | 1372 (15) | 5035 (19) | 766 (18) | 149 (12)* | |
| C(6) | 1681 (15) | 6612 (23) | -17 (25) | 179 (12)* | |
| C(7) | 1374 (15) | 7431 (18) | -581 (32) | 187 (17)* | |
| Cation 2 | | | | | |
| O(11) | 4727 (8) | 3007 (10) | 1010 (12) | 132 (4) | p† |
| N(11) | 6049 (7) | 3752 (8) | 3106 (11) | 85 (3) | 1 |
| C(11) | 5335 (10) | 3090 (12) | 3495 (15) | 106 (5) | 1 |
| C(12) | 6004 (8) | 4830 (10) | 3630 (12) | 80 (3) | 1 |
| C(13) | 6833 (11) | 3277 (13) | 3728 (16) | 112 (5) | 1 |
| C(14) | 6155 (13) | 3693 (14) | 1689 (20) | 130 (6) | 1 |
| C(15) | 5397 (26) | 3821 (28) | 948 (36) | 132 (12) | 0.5 |
| C(16) | 4033 (24) | 3519 (30) | 63 (38) | 267 (17) | 1 |
| C(17) | 3535 (24) | 3202 (30) | 380 (37) | 116 (11) | 0.5 |
| C(25) | 4517 (23) | 3259 (27) | 2505 (33) | 117 (11) | 0.5 |
| C(27) | 3706 (24) | 2919 (29) | -801 (36) | 127 (11) | 0.5 |

* $U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$.

† 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) | 1.52 (2) | 1.53 (2) | |
| N(1)—C(2) | 1.50 (2) | 1.53 (2) | |
| N(1)—C(3) | 1.52 (2) | 1.51 (2) | |
| N(1)—C(4) | 1.45 (2) | 1.53 (2) | |
| C(4)—C(5) | 1.51 (3) | 1.40 (4) | C(11)—C(25) 1.63 (4) |
| C(5)—O(1) | 1.50 (3) | 1.53 (4) | O(11)—C(25) 1.68 (4) |
| O(1)—C(6) | 1.45 (3) | 1.59 (4) | |
| C(6)—C(7) | 1.31 (4) | 0.99 (6) | C(16)—C(27) 1.29 (5) |
| C(1)—N(1)—C(2) | 108 (1) | 112 (1) | |
| C(1)—N(1)—C(3) | 108 (1) | 105 (1) | |
| C(1)—N(1)—C(4) | 113 (1) | 113 (1) | |
| C(2)—N(1)—C(3) | 107 (1) | 107 (1) | |
| C(2)—N(1)—C(4) | 114 (1) | 115 (1) | |
| C(3)—N(1)—C(4) | 106 (1) | 105 (1) | |
| N(1)—C(4)—C(5) | 115 (1) | 112 (2) | N(11)—C(11)—C(25) 109 (2) |
| C(4)—C(5)—O(1) | 110 (2) | 118 (3) | C(11)—C(25)—O(11) 112 (2) |
| C(5)—O(1)—C(6) | 103 (2) | 97 (2) | C(25)—O(11)—C(16) 109 (2) |
| O(1)—C(6)—C(7) | 113 (2) | 99 (4) | C(27)—C(16)—O(11) 114 (3) |

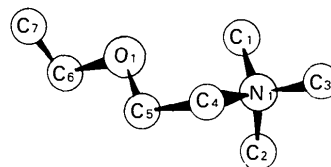


Fig. 1. Perspective view of cation 1 with the atom-numbering scheme. Selected intramolecular non-bonding distances are: C(1)···O(1) 2.96 (2), N(1)···O(1) 3.16 (2) and N(1)···C(7) 5.42 (3) Å.

As is commonly observed in similar structures, steric hindrance between C(5) and the methyl groups on N forces the value of $\tau[C(3)-N^+(1)-C(4)-C(5)]$ to be antiperiplanar (Baker, Chothia, Pauling & Petcher, 1971). In this structure, $\tau[N^+(1)-C(4)-C(5)-O(1)]$ is $-81(2)^\circ$ and $C(1)\cdots O(1)$ is $2.96(2)$ Å. The synclinal value for this torsion angle is generally found in $N^+-C-C-O$ systems (Sundaralingam, 1968). A careful X-ray structure analysis of xylocholine (Coggon, McPhail & Roe, 1969) has shown that none of the H atoms on C(1) are in positions to form hydrogen bonds with O(1) and therefore the stability of synclinal $N^+-C-C-O$ conformations is a result of electrostatic attraction between the positively charged quaternary group and the electronegative O atom. A similar conclusion was reached in the neutron diffraction study of *erythro*-acetyl- α,β -dimethylcholine (Brennan, Ross, Hamilton & Shefter, 1970). The value of the $\tau[C(4)-C(5)-O(1)-C(6)]$ torsion angle observed in the title compound is 176° . In cholinergic compounds the observed value of this 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). The theoretical value of $\tau[C(5)-O(1)-C(6)-C(7)]$ in cholinergic agents would be 180° on the basis of steric hindrance and van der Waals interactions; the departure from this value, which is low, may be attributed to intermolecular interactions. Recently, Jagner & Jensen (1977) have compiled structural data for a number of crystals of choline esters (see their Fig. 3). The data for all ions, except some of the unmodified and modified carbamoylcholine ions, clearly cluster around two main conformations, often called *trans-gauche* and *gauche-gauche*. The cations 1 in the crystals of the title compound are seen to belong to the former group. Finally, the terminal methyl atom C(7) is at a distance of $5.43(3)$ Å from the ammonium tetrahedral N(1). $N^+\cdots$ methyl distances in the range $5-6$ Å are typical of acetylcholine-like molecules (Baker *et al.*, 1971).

The conformational features of cations 2(*i*) (*i* = 1,2,3,4), owing to disorder in the crystal, do not warrant discussion. Nevertheless, the conformation adopted by these cations is similar to that found in cation 1.

The crystal packing, as viewed down **b**, is depicted in Fig. 2 and it is mainly determined by Coulombic and van der Waals interactions. All intermolecular non-bonding contacts agree with those predicted from radii-sum values. The environment of the I^- ions is approximately tetrahedral with $I^-\cdots N^+$ distances ranging from 4.4 to 4.9 Å.

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Table 3. Torsion angles ($^\circ$) with *e.s.d.*'s in parentheses

Cation 1

| | | | |
|---------------------|--------|---------------------|--------|
| C(1)-N(1)-C(4)-C(5) | 60(2) | N(1)-C(4)-C(5)-O(1) | -81(2) |
| C(2)-N(1)-C(4)-C(5) | -65(2) | C(4)-C(5)-O(1)-C(6) | 176(2) |
| C(3)-N(1)-C(4)-C(5) | 178(1) | C(5)-O(1)-C(6)-C(7) | 154(2) |

Cation 2(1) and 2(2)

| | | | |
|-------------------------|--------|-------------------------|---------|
| C(11)-N(11)-C(14)-C(15) | 49(2) | C(14)-C(15)-O(11)-C(16) | 179(3) |
| C(12)-N(11)-C(14)-C(15) | -81(2) | C(15)-O(11)-C(16)-C(17) | -155(3) |
| C(13)-N(11)-C(14)-C(15) | 162(2) | C(15)-O(11)-C(16)-C(27) | 131(3) |
| N(11)-C(14)-C(15)-O(11) | -67(3) | | |

Cation 2(3) and 2(4)

| | | | |
|-------------------------|---------|-------------------------|---------|
| C(14)-N(11)-C(11)-C(25) | -46(2) | C(11)-C(25)-O(11)-C(16) | -161(2) |
| C(12)-N(11)-C(11)-C(25) | 85(2) | C(25)-O(11)-C(16)-C(17) | -56(4) |
| C(13)-N(11)-C(11)-C(25) | -159(2) | C(25)-O(11)-C(16)-C(27) | -130(3) |
| N(11)-C(11)-C(25)-O(11) | 57(2) | | |

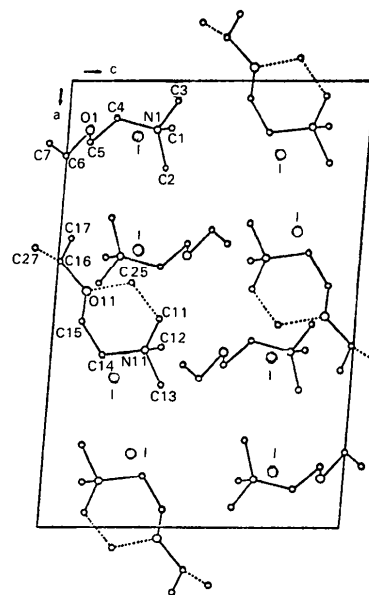


Fig. 2. The crystal structure of the title compound projected along **b**.

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