Structure Investigations of Agonists of the Natural Neurotransmitter Acetylcholine, III [1]
X-Ray Structure Analysis of (2-Ethoxyethyl)trimethylammonium Chloride

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X-Ray Structure Analysis, Neurotransmitter, Conformational Flexibility, Structure-Activity Correlation

To elucidate the structure-activity correlations we have performed an X-ray structure analysis of the title compound (**1**), which is a muscarinic agonist of the natural neurotransmitter acetylcholine. **1** crystallizes in the monoclinic space group $P2_1/n$ with 2 molecules per asymmetric unit. Lattice parameters are: $a = 10.375(6)$, $b = 12.468(5)$, $c = 15.274(17)$ Å; $\beta = 95.32(7)°$. The structure was solved by direct methods and refined to an R-value of 0.14 for 1828 observed reflections. Both cations in the asymmetric unit are disordered. In the crystal structure at least four conformations of the cation occur, indicating a pronounced conformational flexibility of the neurotransmitter cation. The anions are arranged stereospecifically with respect to the quaternary trimethylammonio methyl group. The geometry of triangles which are defined by a nitrogen of the quaternary ammonium group and an ether oxygen on one hand and an anion occupying a specific type of tetrahedral faces of a $(CH_3)_3N^+-CH_2$ group on the other hand, is characteristic for muscarinic agonists if they contain an ether or ester oxygen in the analogous position to the ester oxygen of acetylcholine.

Introduction

In the course of systematic X-ray investigations of cholinergic agonists [1 – 4] we have carried out a single crystal X-ray structure analysis of (2-ethoxyethyl)trimethylammonium chloride (O-ethylcholine chloride) (**1**). The cation of **1** ($[C_7H_{18}NO]^+Cl^-$) is derived from the natural neurotransmitter acetylcholine by replacement of the carbonyl group in the latter with a CH_2 group. **1** is a muscarinic agonist with an activity of about 1/10 that of acetylcholine [5]. The nicotinc activity of **1** is negligible [6].

$$\mathbf{1}\quad (H_3C)_3\overset{+}{N}-CH_2-CH_2-O-CH_2-CH_3\ Cl^- .$$

Experimental

Compound **1** was synthesized in analogy to specifications given in the literature [5, 7]. By recrystallization from absolute ethanol colourless crystals of a quality suitable for an X-ray structure analysis were obtained. Because the substance is sensitive to moisture, a crystal of dimensions 0.11×0.13×0.71 mm was sealed under dried Ar as protecting gas in a glass capillary. Photographs recorded by aid of the Weissenberg and precession technique showed the Laue diffraction symmetry 2/m and together with systematic extinctions for h0l, h + l odd, and 0k0, k odd, the monoclinic space group $P2_1/n$ with the b-axis as unique axis was deduced. The lattice parameters were determined by an automatic punch tape controlled single-crystal diffractometer (Siemens-AED, Mo K_α-radiation, Nb-Filter). The lattice constants are: $a = 10.375(6)$, $b = 12.468(5)$, $c = 15.274(17)$ Å, $\beta = 95.32(7)°$. The unit cell of the volume 1967.3 Å^3 contains 8 formula units, *i.e.* two formula units per asymmetric unit ($D_c = 1.13$ gcm^{-3}, $D_m = 1.13$ gcm^{-3}).

Using the diffractometer mentioned above with Mo K_α-radiation 3672 independent reflection intensities up to a maximum Θ angle of 26.35 ° were collected (5-point measurement, $\Theta - 2\Theta$ scan). 1844 reflections with $I < 2\sigma_I$ were classified as unobserved. To those reflections an intensity of $I = 2\sigma_I$ was assigned.

Structure solution and refinement

The reflection intensities were corrected for Lorentz and polarization effects in the usual way. No absorption correction was applied (μ(Mo K_α) = 3.4

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cm^{-1}). The statistics of E-values clearly showed a centrosymmetric space group. The scattering factors for O, N, C and Cl^- were taken from International Tables for X-Ray Crystallography [8]. The scattering factors for H are given by Stewart, Davidson, and Simpson [9]. Most of the computer calculations were performed with a special version [10] of the X-ray 67 program system [11]. For this work a Siemens 4004, an IBM 360/91 and an Amdahl 470 computer were employed.

The phase problem was solved using direct methods by aid of the PHASDT program [12]. For the determination of the signs 198 reflections with the largest E-values were used ($3.2 \geqq E \geqq 1.5$). The starting set of phases was composed of the signs of 7 reflections with large E-values. Three of them were used for origin definition, the signs of 4 reflections were varied (16 solutions). The correct solution, which was recognized by the Q-criterion of consistency [12, 13], yielded the signs of 197 reflections. From an E-Fourier synthesis phased with these reflections a partial structure could be obtained. A following Fourier synthesis with all reflections showed the correct number of positions of nonhydrogen atoms which could be expected due to the chemical composition. But already in this Fourier synthesis additional peaks were an indication for a partial disorder, which was confirmed by the following refinement of the structure. The least squares refinement (full matrix, unit weights) showed too large temperature parameters for some atomic positions and furthermore there occurred chemically meaningless bond lengths and angles.

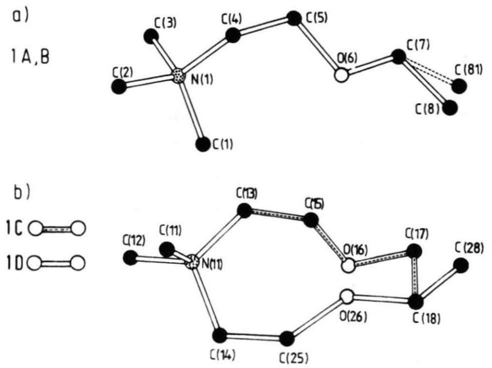

Fig. 1. Disorder in the crystal structure of **1**. a) Disorder of the first cation of the asymmetric unit: Conformations **1A** (with C(8)) and **1B** (with C(81)). b) Disorder of the second cation of the asymmetric unit: Conformations **1C** and **1D**.

By way of difference Fourier syntheses in course of successive refinement, a crystallographic disorder for both cations of the asymmetric unit became evident (Fig. 1). For one cation of the asymmetric unit the C atom of the CH_3 group of the O-ethyl group splitted into two atomic positions (C(8) and C(81); conformations **1A** and **1B**). The second cation of the asymmetric unit was found to be more strongly disordered. Instead of the expected four atomic positions of the C and O atoms for the $CH_2-O-CH_2-CH_3$ fragment seven were found by difference Fourier maps. These seven positions describe two different conformations of the cation of **1** (conformation **1C** and **1D**). The disorder occurs in such a way that the $CH_2-O-C_2H_5$ chain originates from two different C atoms of the quaternary ammonium group. The $CH_2-O-C_2H_5$ groups of both conformations **1C** and **1D** have one C atom (C18) in common. – This C atom, however, is disordered to some extent, what is indicated by its high temperature parameter ($B = 10$ Å^2). – Some of the remaining electron densities in the difference Fourier syntheses could be assigned to hydrogen atoms. But hydrogens were not included in the refinement because of the partial disorder of the structure. Thus the hydrogen atoms represented in the following figures are in calculated positions.

In the first stages of refinement the isotropic temperature parameters of the disordered, statistically occupied atomic positions of the most disordered cation wer set equal to the mean value of the remaining "not" disordered nonhydrogen atoms and were held fixed. Besides the scale factor, the positional parameters and the anisotropic temperature parameters of the "not" disordered atoms, the occupancy parameters of the disordered atoms were refined. Because of the electron density distribution derived from difference Fourier syntheses the occupancy factor of these atoms was given a starting value of 0.5. Taking into account, that the sum of the occupation densities of the atoms with double positions should in every case be one and also that the occupation densities of the disordered atoms should be equal for each conformation, **1C** or **1D** respectively, the isotropic temperature parameters of the disordered atoms were corrected "by hand" until the occupancy factors converged under the given constraints. The occupancy densities of C-positions C(8) and C(81) were estimated from a difference Fourier map. In the following steps of re-

Table I. Fractional atomic coordinates, thermal parameters and occupation densities (M). Standard deviations in terms of the least significant digits are given in parentheses. Isotropic and anisotropic thermal parameters are defined as $T = \exp(-B \sin^2 \Theta/\lambda^2)$ and
$T = \exp[-1/4(B_{11}\, h^2 a^{*2} + B_{22}\, k^2 b^{*2} + B_{33}\, l^2 c^{*2} + 2B_{12}\, h\, k\, a^* b^* + 2B_{13}\, h\, l\, a^* c^* + 2B_{23}\, k\, l\, b^* c^*)]$.

Atom	x	y	z	M	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl (1)	0.7034 (2)	0.0549 (2)	0.1630 (2)	1.00	5.0 (1)	5.3 (1)	6.5 (1)	0.0 (1)	0.1 (1)	0.3 (1)
Cl (11)	0.2270 (3)	0.3794 (3)	0.1207 (2)	1.00	6.9 (2)	6.5 (2)	11.0 (2)	0.6 (1)	0.3 (1)	−0.4 (2)
O (6)	0.0571 (7)	−0.0960 (7)	0.1123 (5)	1.00	6.2 (4)	8.1 (4)	7.1 (4)	−1.4 (3)	1.1 (3)	0.9 (4)
O (16)	0.5782 (21)	0.2969 (20)	−0.0079 (15)	0.45	6.3 (11)	7.7 (12)	7.1 (14)	−0.9 (9)	1.0 (9)	1.5 (10)
O (26)	0.6257 (14)	0.3095 (13)	−0.0462 (10)	0.55	5.2 (8)	5.7 (7)	4.9 (8)	0.0 (6)	−0.6 (6)	0.2 (6)
N (1)	0.3064 (6)	0.0536 (6)	0.1078 (5)	1.00	4.3 (3)	4.6 (3)	5.7 (4)	−0.2 (3)	0.6 (3)	−0.1 (3)
N (11)	0.8251 (7)	0.3694 (6)	0.1114 (5)	1.00	5.5 (4)	5.6 (4)	5.4 (4)	0.8 (3)	0.1 (3)	−0.9 (3)
C (1)	0.3467 (10)	−0.0606 (8)	0.1026 (8)	1.00	5.9 (5)	4.4 (5)	10.0 (7)	0.7 (4)	1.6 (5)	−0.1 (5)
C (2)	0.3769 (10)	0.1185 (9)	0.0404 (8)	1.00	5.9 (5)	6.5 (6)	7.9 (6)	−0.8 (5)	2.1 (5)	0.6 (5)
C (3)	0.3465 (10)	0.0974 (10)	0.1973 (7)	1.00	7.0 (6)	8.0 (7)	6.0 (6)	0.6 (5)	0.4 (5)	−0.8 (5)
C (4)	0.1614 (9)	0.0679 (8)	0.0823 (8)	1.00	4.4 (4)	5.8 (5)	10.0 (8)	−0.5 (4)	−0.5 (5)	1.3 (5)
C (5)	0.0758 (11)	0.0156 (10)	0.1383 (9)	1.00	5.8 (6)	7.3 (7)	10.4 (9)	−0.8 (5)	2.2 (6)	−1.2 (6)
C (7)	−0.0200 (13)	−0.1466 (12)	0.1761 (9)	1.00	8.8 (8)	11.0 (10)	7.6 (7)	−3.8 (7)	0.6 (6)	0.6 (7)
C (11)	0.8809 (12)	0.4799 (9)	0.1024 (8)	1.00	10.0 (8)	4.6 (5)	8.6 (7)	0.6 (5)	2.0 (6)	0.9 (5)
C (12)	0.8913 (11)	0.3208 (9)	0.1931 (7)	1.00	7.3 (6)	6.2 (6)	6.3 (6)	0.0 (5)	−0.6 (5)	1.5 (5)
C (13)	0.6797 (13)	0.3707 (14)	0.1183 (9)	1.00	7.3 (7)	13.7 (12)	8.0 (8)	2.2 (7)	0.4 (6)	−1.9 (8)
C (14)	0.8578 (13)	0.2984 (11)	0.0346 (8)	1.00	9.5 (8)	11.0 (9)	5.7 (6)	3.5 (7)	0.1 (6)	−1.3 (6)
C (15)	0.6001 (21)	0.3834 (23)	0.0406 (20)	0.45	4.4 (10)	8.7 (16)	10.2 (18)	1.2 (11)	−1.6 (11)	−5.7 (14)
C (25)	0.7757 (25)	0.3347 (23)	−0.0474 (16)	0.55	9.3 (15)	11.3 (18)	7.5 (14)	1.1 (13)	2.4 (12)	0.5 (13)
C (18)	0.5466 (16)	0.3519 (12)	−0.1330 (11)	1.00	10.5 (10)	9.3 (9)	10.2 (11)	−0.4 (8)	2.4 (8)	−1.3 (7)
C (28)	0.4237 (22)	0.3232 (17)	−0.1228 (14)	0.55	7.3 (12)	7.2 (11)	5.0 (10)	−0.7 (9)	0.0 (9)	−0.9 (9)

Atom	x	y	z	M	B
C (8)	−0.0517 (25)	−0.2527 (20)	0.1468 (17)	0.60	7.2 (6)
C (81)	−0.0942 (37)	−0.2297 (33)	0.1436 (26)	0.40	7.4 (9)
C (17)	0.4769 (50)	0.3348 (39)	−0.0696 (34)	0.45	12.5 (13)

finement the occupancy factors were not further refined but instead the temperature parameters of the disordered atoms. With exception of the temperature parameters of positions C(8), C(81) and C(17) all temperature parameters were refined anisotropically. A refinement of these statistically occupied atomic positions with anisotropic temperature parameters turned out to be not useful. During the last cycles of refinement 17 reflections with $|\Delta F| = ||F_o| - |F_c|| > 12$ were not included in the calculation of the parameter shifts. The unobserved reflections were only included if $|F_o| = 4\sigma_F < |F_c|$. The refinement converged to a residual of 0.140 ($R = \sum ||F_o| - |F_c|| / \sum |F_o|$).

The final atomic coordinates of nonhydrogen atoms, their temperature parameters and the occupancy factors are included in Table I. The listings of observed and calculated structure factors can be obtained by request from the authors.

The high R-value is a result of the structural disorder. Besides the statistically occupied atomic positions to some extent a disorder of atoms with the occupancy factor 1 should also be assumed, as it can be conluded from the relatively high temperature parameters. All isotropic temperature factors (B_{equ}) are not smaller than 4.9 Å^2 and most of them significantly larger. The smearing of the electron densities coupled with high temperature parameters is also responsible for the large amount of unobserved reflections. The very high temperature factor of C(18) has already been discussed. The atom C(7) of the less disorded cation of the asymmetric unit, which is bound to the disordered C atom of the CH_3 group exhibits a B_{equ} of 9.1 Å^2, which is significantly larger than those of the other nonhydrogen atoms of this cation. The C atoms C(13) and C(14) of the quaternary ammonium group of the second cation of the asymmetric unit, from which each of the disordered $CH_2{-}O{-}CH_2{-}CH_3$ groups originates, have on the average a temperature factor 2 Å^2 larger in comparison with both the other C atoms (CH_3 groups) of this quaternary ammonium group. The high temperature parameters of the statistically occupied atomic positons C(17) and C(25) (12.5 Å^2 and 9.4 Å^2) also clearly indicate, that the disorder which is induced by the conformational flexibility of the cations can be described only in a first approximation by the parameters gained from the structure refinement.

The relatively high isotropic temperature parameters of the Cl anions (B_{equ} = 5.6, and 8.1 Å^2) also are a consequence of the cationic flexibility and of the disorder induced by that. For comparison in the crystal structures of trimethyl(4-oxopentyl)ammonium chloride [1] and trimethyl(3-pyridyl-methyl)-ammonium chloride hydrochloride · H_2O [14], where we found no strong and no crystallographic disorder, respectively, the isotropic temperature parameters of chlorine anions are significantly smaller (3.6 and 3.7 Å^2, respectively). On the other hand in the crystal structure of trimethylpentylammonium chloride [14], which also contains a strongly disordered cation, a similarly large temperature parameter for the Cl anion (B = 8.1 Å^2) was found.

Though in space group P2$_1$/n there are only two formula units per asymmetric unit, at least four different conformations of the cation were found. This finding aroused the suspicion that a superstructure of space group P2$_1$ or Pn might be existent because these space groups allow four formula units per asymmetric unit. Though no significant violation of the conditions for systematical extinctions of reflections concerning space group P2$_1$/n could be found, we tested all possible models in these alternative space groups. But even after the refinement of the parameters of the superstructures – *i.e.* the parameters of statistically occupied atomic positions in space group P2$_1$/n – there was no evidence of space groups P2$_1$ or Pn. The triclinic space group P$\bar{1}$ was excluded, too, because we couldn't find any deviations from the 2/m Laue diffraction symmetry in the photographs.

Description and discussion of the structure of the neurotransmitter cation

The four distinct conformations of the cation found in the crystal structure of **1** are shown in Fig. 2. Although the bond lengths (Fig. 2) do partially not correspond even under consideration of the very high standard deviations to the expected values, this however is not reliable for due to the disorder the atomic positions are no more defined exactly. The same is also valid for the deviations of the bond angles (Table II) from the expected values. The conformational flexibility manifested in the

Table II. Bond angles defined by nonhydrogen atoms in the cation of **1**. In parentheses standard deviations in the least significant digits.

C (1)−N (1)−C (2)	108.2 (8)
C (1)−N (1)−C (3)	110.0 (8)
C (1)−N (1)−C (4)	111.9 (7)
C (2)−N (1)−C (3)	108.0 (7)
C (2)−N (1)−C (4)	106.5 (7)
C (3)−N (1)−C (4)	112.0 (8)
N (1)−C (4)−C (5)	116.2 (9)
C (4)−C (5)−O (6)	110.1 (10)
C (5)−O (6)−C (7)	107.4 (9)
O (6)−C (7)−C (8)	108.5 (14)
O (6)−C (7)−C (81)	114.5 (20)
C (11)−N (11)−C (12)	107.2 (8)
C (11)−N (11)−C (13)	112.9 (9)
C (11)−N (11)−C (14)	110.2 (9)
C (12)−N (11)−C (13)	109.1 (8)
C (12)−N (11)−C (14)	106.7 (8)
C (13)−N (11)−C (14)	110.6 (9)
N (11)−C (13)−C (15)	117 (1)
C (13)−C (15)−O (16)	116 (2)
C (15)−O (16)−C (17)	100 (3)
O (16)−C (17)−C (18)	97 (4)
N (11)−C (14)−C (25)	108 (1)
C (14)−C (25)−O (26)	114 (2)
C (25)−O (26)−C (18)	111 (1)
O (26)−C (18)−C (28)	104 (1)

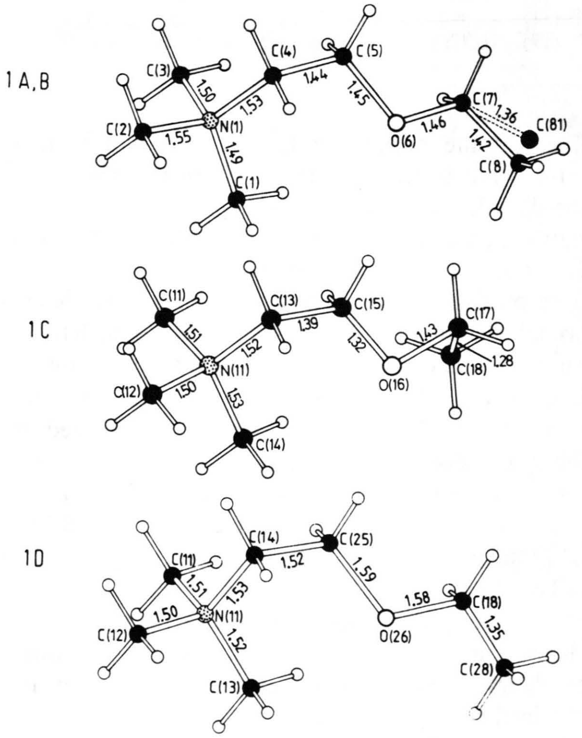

Fig. 2. Conformations **1A–1D** of the cation in **1**. The conformation **1C** is the mirror image with respect to the atomic coordinates given in Table I. The standard deviations of the bond lengths (Å) given are in the region 0.01–0.06 Å.

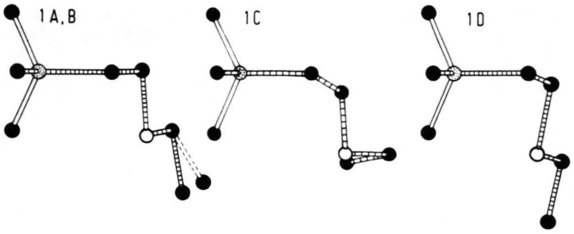

Fig. 3. Comparison of the conformations **1A–1D** of the cation in **1**. The conformation of **1C** is the mirror image with respect to the coordinates given in Table I.

crystal structure of **1** is of special interest because it has been discussed [15–18] with respect to the physiological activity.

In Fig. 3 the four distinct conformations of the O-ethylcholine ion in **1** are compared in projections which show clearly these differences. For this purpose the H-atoms are omitted and the $\overset{+}{N}C_4$ groups are orientated in the same way. The conformations of the O-ethylcholine cation can be described by the four torsion angles $\tau_1 - \tau_4$, which are defined in Fig. 4 for conformation **1D**. These torsion angles are compared in Table III with the equivalent torsion angles of acetylcholine salts [19–23]. τ_1 and τ_2 are in agreement with the neurotransmitter cations taken for comparison, however remarkable differences occur at τ_3 and τ_4. Due to the nearly equal torsion angles τ_1 and τ_2 in **1** and the salts of acetylcholine, the intramolecular N^+---O (ether or ester oxygen) contact distances are almost the same (Fig. 5). This intramolecular contact distance is noteworthy with respect to the physiological activity of the cation, because it is generally assumed, that the neurotransmitter-receptor interaction occurs not only by an interaction of the ammonium group but also by an interaction of a second polar group, in the case of **1** the ether oxygen. In the structure of **1** we found intramolecular N^+---O distances of 3.12–3.19 Å. As can be demonstrated by Fig. 5, in the cations of **1** also relatively short intramolecular contact distances can be found between the ether oxygen and that methyl group of the trimethylammonio methyl group, which is directed towards the ether oxygen. These contact distances are analogous those between an ester oxygen and a CH_3 group of the quaternary ammonium group in the structures of acetylcholine [19–23].

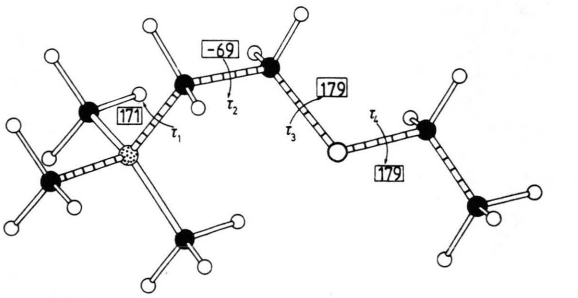

Fig. 4. Definition of the torsion angles $\tau_1 - \tau_4$ in the cation of **1** with conformation **1D** as an example.

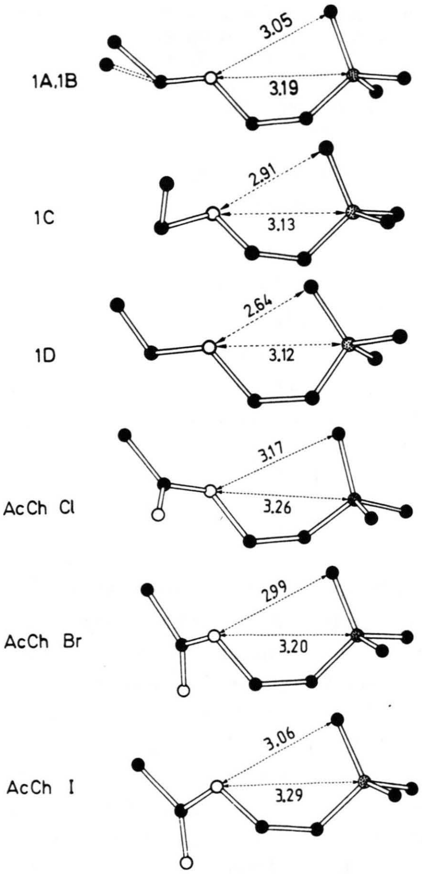

Fig. 5. Short intramolecular contact distances between nitrogen and a methyl group of the quaternary ammonium group on one hand and the ether or ester oxygen in **1** and the halides of acetylcholine.

Crystal structure and correlation to pharmacological activity

The arrangement of the cations and anions in the crystal structure is demonstrated in Fig. 6. By com-

Table III. Torsion angles $\tau_1 - \tau_4$ for the four conformations of O-ethylcholine chloride in comparison with those of acetylcholine in the structures of the chloride (AcCh Cl) [19], bromide (AcCh Br) [20] and iodide (AcCh I) [21], perchlorate (AcCh ClO_4) [22] and *β*-resorcylate [23]. With exception of the structures of **1 A, B, D,** AcCh ClO_4, and the first molecule of AcCh $C_7H_5O_4$ all others are mirror images with respect to the coordinates given in this paper and the literature, respectively. ac = anticlinol.

	τ_1 (°)	τ_2 (°)	τ_3 (°)	τ_4 (°)
1 A, B	− 179 (*trans*)	− 84 (*gauche*)	175 (*trans*)	$\frac{174}{151}$ (*trans*)
1 C	162 (*trans*)	− 81 (*gauche*)	− 169 (*trans*)	− 101 (*ac*)
1 D	171 (*trans*)	− 69 (*gauche*)	179 (*trans*)	179 (*trans*)
AcCh Cl	− 171 (*trans*)	− 85 (*gauche*)	167 (*trans*)	175 (*trans*)
AcCh Br	175 (*trans*)	− 78 (*gauche*)	− 79 (*gauche*)	174 (*trans*)
AcCh I	174 (*trans*)	− 89 (*gauche*)	− 83 (*gauche*)	180 (*trans*)
AcCh ClO_4	− 168 (*trans*)	− 74 (*gauche*)	180 (*trans*)	− 178 (*trans*)
AcCh $C_7H_5O_4$	180 175 (*trans*)	− 84 − 77 (*gauche*)	− 159 − 163 (*trans*)	178 180 (*trans*)

parison of the atomic coordinates given in Table I one can see, that applying appropriate symmetry operations there is approximately a translation vector between the following pairs of atoms: Cl(1), Cl(11); N(1), N(11); C(1), C(11); C(2), C(14); C(3), C(12) and C(4), C(13). This translation vector has in a crude approximation the form (0, 0, 0.5), which transforms partially one formula unit of the asymmetric unit into the other (Fig. 6). Those atoms are transformed, which are not splitted into two positions by disorder in both formula units of the asymmetric unit. The combination of this vector with the symmetry elements of the space group leads to additional pseudo symmetry centres, screw axes and glide planes respectively, which allow to describe the crystal structure as a superstructure of a substructure of space group $P2_1/a$ with half the *c*-axis length. But on the other hand the deviations from the additional symmetry are as large that no obvious reflection extinctions of type $hkl: l = 2n + 1$ occur and no serious correlations of the parameters between both formula units of the asymmetric unit could be observed.

With respect to the crystal packing and also in relation to the physiological activity the arrangement of the anions relative to the quaternary ammonium groups is of interest. In Table IV the shortest

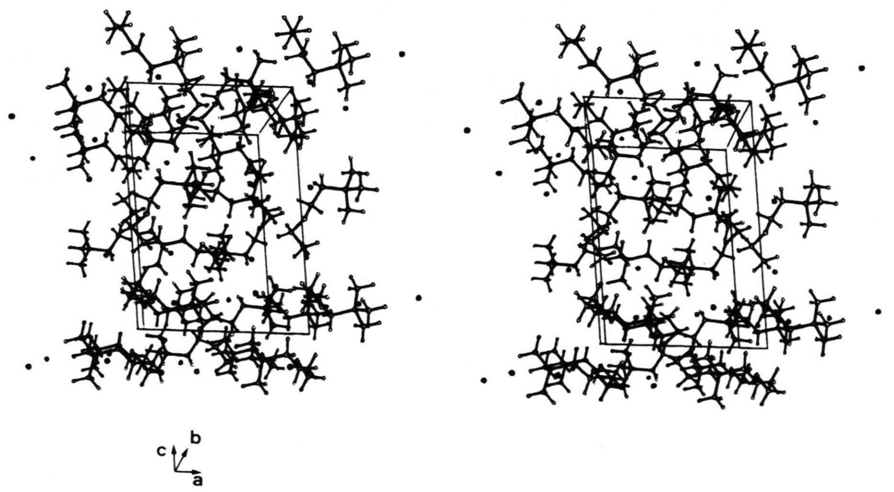

Fig. 6. Stereoscopic representation of the crystal structure of **1**. For reasons of clarity only the cations of conformations **1 A** and **1 C** are plotted.

Table IV. Coordination of the N^+C_4 tetrahedron by the Cl anions. The letters A, B, C give the face type of the tetrahedron of the $(CH_3)_3N^+$-CH_2-group, which is occupied by a Cl anion as defined in [1]. In the case of two letters the first is related to conformation **1 C** and the second to **1 D**.

	N → Cl	N → C				
		N(1)–C(1)	N(1)–C(2)	N(1)–C(3)	N(1)–C(4)	d_{N-Cl} [Å]
A	N(1)–Cl(1)	75°	67°	68°	172°	4.127(7)
B	N(1)–Cl(11)	175°	68°	69°	73°	4.153(8)
B	N(1)–Cl(1)*	68°	60°	165°	82°	4.344(8)
C	N(1)–Cl(11)*	70°	155°	53°	97°	4.721(8)
	N → Cl	N → C				
		N(11)–C(11)	N(11)–C(12)	N(1)–C(13)	N(11)–C(14)	d_{N-Cl} [Å]
A, B	N(11)–Cl(11)**	65°	67°	174°	76°	4.161(8)
B, A	N(11)–Cl(1)**	68°	66°	78°	171°	4.184(6)
B	N(11)–Cl(1)	173°	66°	71°	72°	4.216(8)
C	N(11)–Cl(11)***	49°	155°	90°	80°	4.724(9)

Symmetry code: Cl(1)*: $-x+1, -y, -z$; Cl(1)**: $-x+1.5, y+0.5, -z+0.5$; Cl(11)*: $-x+0.5, y-0.5, -z+0.5$; Cl(11)**: $x+1, y, z$; Cl(11)***: $-x+1, -y+1, -z$.

distances between the nitrogen atoms and the Cl anions are summarized. The orientation of the anions with respect to the quaternary ammonium group can be described by the angles which are formed by the N^+-Cl^- vectors and the N^+-C vectors (Table IV). Each cation is surrounded by four anions and each anion by four cations in the first coordination sphere. The coordination polyhedron is in both cases a distorted tetrahedron. The anions are arranged with respect to the quaternary ammonium groups in such a way, that the N^+-Cl^- vector is nearly perpendicular to a tetrahedral face of the N^+C_4 group and is directed in the opposite direction of the N^+-C vector of the *trans* positioned CH_3 or CH_2 group respectively, cutting the face of the N^+C_4 tetrahedron in its centre of gravity. In the case of the tetrahedron of a quaternary trimethylammonio methyl group there is to be differenciated between three geometrically distinct face types (A, B, C), wereby the B-face due to a local mirror plane appears doubled. For definition of the face types A, B, and C there is refered to reference [1]. An ideal tetrahedral coordination of the cations by halide anions is given under the condition that the N → Cl and N → C vectors given in Table IV in every case include three angles of 70.5° and one of 180°. As can be extracted from Table IV this is well fulfilled for the occupation of face types A and B of the N^+C_4 tetrahedron by anions. In the case of the C faces however significant deviations from the ideal angles occur. Furthermore the N^+-Cl^- distances of anions which occupy faces of type C are significantly longer.

As we could find out by way of our own structure investigations [1–4] of cholinergic neurotransmitters and by comparison with the literature, the anions, which occupy faces of type B show a relation to the pharmacological activity. These anions can be used as a model for the anionic binding site of the receptor [1–4]. Furthermore we

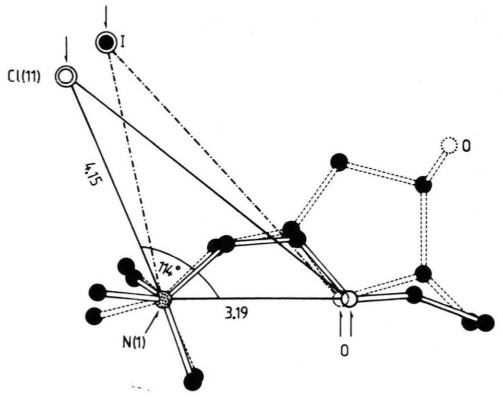

Fig. 7. An "activity triangle" (N(1), O(6), Cl(11)) with the conformation **1 A** in the crystal structure of **1** in comparison with an analogous triangle in the crystal structure of L(+)-muscarine iodide. The cations are in both cases projected on the corners (atoms marked by arrows) of the triangles. For calculation of the plot of the muscarine iodide the coordinates given in the literature [24] were used.

found that the triangles formed by the nitrogen of the quaternary ammonium group, a second polar group of the cation – in **1** the ether oxygen – and an anion occupying a B face of the $(H_3C)_3\overset{+}{N}-CH_2$ group allow a differentiation between the muscarinic and nicotinic activity mode of cholinergic neurotransmitters. Such an "activity triangle" is represented in Fig. 7 in comparison with an analogous triangle in the crystal structure of L(+)-muscarine iodide [24]. Both triangles shown in Fig. 7 are geometrically very similar and are characteristic for muscarinic activity. The triangles in Fig. 7 are so named "activity triangles" of the second type for muscarinic activity [3]. All conformations of O-ethylcholine found in the crystal structure of **1** form with anions occupying faces of type B almost the same triangles as that shown in Fig. 7, independently of conformational differences at τ_3 and τ_4.

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