Two Conformations of the Cholinergic Agonist Acetyl-α-methylcholine: a New Conformation of Cholinergic Molecules

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ACETYL-α-METHYLCHOLINE is a cholinergic agonist: a potent stimulant at nicotinic nerve junctions,[1] less potent at muscarinic junctions,[2] and is hydrolysed rapidly by acetylcholinesterase.[2] Crystals of D(+)-acetyl-α-methylcholine iodide are monoclinic, Laue group $P2/m$, space-group $C_2^2 - P2_1$, $a = 12{\cdot}01 \pm 0{\cdot}01$, $b = 7{\cdot}490 \pm 0{\cdot}004$, $c = 13{\cdot}79 \pm 0{\cdot}01$ Å, $\beta = 105{\cdot}12 \pm 0{\cdot}05°$, $Z = 4$, 3730 single-crystal X-ray diffraction data measured with Mo-K_α radiation on a computer-controlled Stoe four-circle diffractometer resulted in 1395 independent observations ($I > 3\sigma(I)$). The data were not corrected for absorption but were standardized and scaled by linear interpolation between periodic measurements of a normalized standard diffraction maximum. The crystal structure was analysed by heavy-atom Patterson and Fourier methods and refined by full-matrix least-squares with anisotropic thermal parameters for the iodine atom and isotropic thermal parameters for the light atoms, neglecting the hydrogen atoms. The residual at the present stage of the refinement with 24 atoms is 0·10. Bond distances are within 2σ of expected values.

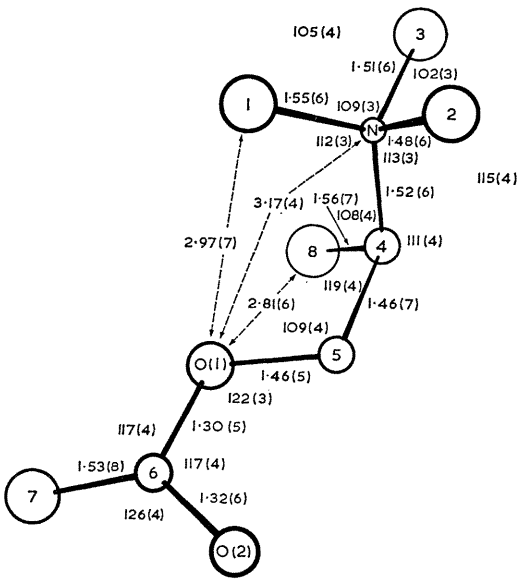

FIGURE 1. *One conformation* (A) *of the molecule* D(+)*-acetyl-α-methylcholine found in crystals of the iodide. Some interatomic distances and angles are given in* Å *and degrees, with statistical standard deviations in parentheses in units of the least significant digit given.*

Crystals of D(+)-acetyl-α-methylcholine iodide have two separate molecules with different conformations in the crystalline asymmetric unit. The two conformations of the D(+)-enantiomer studied are shown with certain interatomic distances and angles in Figures 1 and 2. The major difference between the two conformations is that the torsion angle 0(1)–C(5)–C(4)–N of molecule A (Figure 1) is +90° and that of molecule B (Figure 2) is −148°. The two molecules in the asymmetric unit are related approximately by inversion centres at the positions (0,0,0; 0,½,0) + 0,0,¼; 0,0,¾; ½,0,¼; ½,0,¾. These inversion centres are equivalent to c glide planes at $y = \frac{1}{4}$ and $y = \frac{3}{4}$. The displacement of the atoms from positions exactly related by inversion centres varies from 0·11 Å for the iodine atoms to 0·55 Å for C(4) and C(14), the α-carbon atom; the mean displacement is 0·29 Å. The crystal has pseudo-symmetry of space-group $P2_1/c$. Of the 198 observed ($h0l$) maxima, the intensities of the 57 with $l = 2n + 1$, systematic absences of space-group $P2_1/c$, are weak.

Several torsion angles of the different conformations of D(+)-acetyl-α-methylcholine iodide are given in the Table. One conformation (A) found of the acetyl-α-methylcholine molecule is similar to those of most acetylcholine-like cholinergic molecules such as lactoylcholine,[3] 2-methyl-4-trimethylammoniummethyl-1,3-dioxolan[4], and acetyl-β-methylcholine.[5] The O(1)–C(5)–C(4)–N torsion angles are all approximately +85°. The value of +90° for molecule

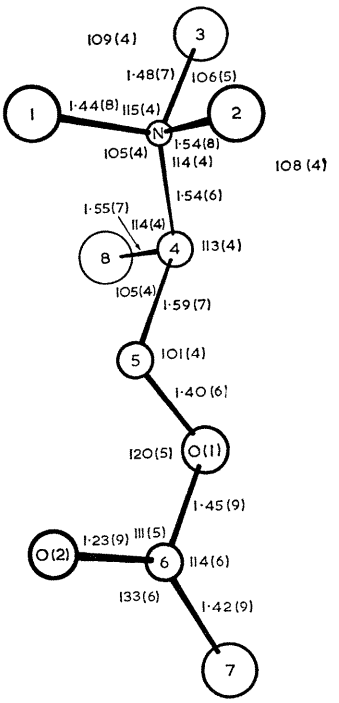

FIGURE 2. *The other conformation* (B) *of the molecule* D(+)*-acetyl-α-methylcholine found in crystals of the iodide.*

A of acetyl-α-methylcholine is the largest found so far for this conformation, and the ester oxygen atom O(1) is midway between the C(1) methyl group and the C(8) α-methyl group. The C(6)–O(1)–C(5)–C(4) torsion angles

are all approximately +160°. The O(2)–C(6)–O(1)–C(5) torsion angles are all nearly 0°, due to the partial double-bond character of the C(6)–O(1) bond.[3,6]

Torsion angles of the two conformations of D(+)*-acetyl-α-methylcholine iodide*

Conformation	A	B
O(1)–C(5)–C(4)–C(8)	− 35°	+ 93°
O(1)–C(5)–C(4)–N	+ 90	−148
C(6)–O(1)–C(5)–C(4)	+170	176
O(2)–C(6)–O(1)–C(5)	0	− 10
C(7)–C(6)–O(1)–C(5)	175	177

The other conformation, B, of acetyl-α-methylcholine with an O(1)–C(5)–C(4)–N torsion angle of −148° is the first reported example of a nearly *trans* or anti-planar[7] N^+–C–C–O– group,[6,8] though Shefter[9] has found that the more crowded molecule (*RR*)-*threo*-αβ-dimethyl acetylcholine iodide has the same conformation (B) with τ O(1)–C(5)–C(4)–N = − 143°. Conformation B is midway between anti-clinal and anti-planar.

The presence of two conformations of this cholinergic molecule in a single crystal, one syn-clinal and one midway between anti-clinal and anti-planar, is evidence of the lability of these molecules and their property of multiple stable conformations.

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