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Short Communications

The Crystal Structure of Methoxycarbonylcholine Iodide, an Acetylcholine Analogue with Extended Conformation

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As part of an investigation of the properties of choline esters the methoxy- and ethoxycarbonylcholine iodides have been synthesized and the crystal structure of methoxycarbonylcholine iodide has been determined. Bond lengths and angles calculated from the final parameters (Table 1) are shown in Fig. 1. The methoxycarbonylcholine ion is situated in a mirror plane (Fig. 2) and it thus has the fully extended conformation. In all choline esters with the exception of carbamoylcholine the O−C−C−N$^+$ moiety was found in a "*gauche*" conformation in the crystal structures investigated.[1] In solution all choline esters, including carbamoylcholine [2] and methoxycarbonylcholine,[3] are found to prefer the *gauche* conformation. Theoretical calculations performed for models of a variety of choline esters indicate [4] that the *gauche* O−C−C−N$^+$ conformation is hardly less energetically favourable for carbamoylcholine and methoxycarbonylcholine than for other choline esters. Thus crystal forces alone seem to be responsible for the observed extended conformation. In contrast to the situation in crystals of salts of carbamoylcholine, no hydrogen bonds can be formed in crystals of methoxycarbonylcholine iodide. It can be seen (Table 2) that the distance between the methoxycarbon atom and an iodide ion is rather short, probably due to electrostatic attraction. The partial positive charge of the methyl group in a methoxy group is definitely greater than that of the methyl group in an acetoxy group.[4] The structure seems, however, to be stabilized by a number of weak contacts (Table 2) rather than to be dominated by a single strong contact.

A detailed examination of the biological activity of ethoxy- and methoxycarbonylcholine is in progress.[3] The latter shows muscarinic activity [3,5] and acts as an acetylcholine esterase inhibitor.[3]

Table 1. Final positional and thermal parameters. The estimated standard deviations, referring to the last figure, are given in parentheses. Thermal parameters are $\times 10^2$. The temperature factor is defined by: $\exp[-2\pi^2(U_{11}h^2a^{*2}+\ldots+2U_{12}hka^*b^*\ldots)]$.

Atom	x/A	y/B	z/C	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C11	.0134(10)	.4069(6)	.25	5.5(6)	3.6(5)	6.5(7)	−0.2(5)	0.0	0.0
O1	−.0199(7)	.4979(5)	.25	3.7(4)	3.9(3)	8.3(6)	−0.2(3)	0.0	0.0
C2	.0790(10)	.5519(6)	.25	4.1(6)	4.5(5)	3.3(5)	−0.3(5)	0.0	0.0
O3	.1911(7)	.5330(5)	.25	3.4(4)	5.0(4)	10.5(7)	0.4(4)	0.0	0.0
O4	.0311(6)	.6323(4)	.25	3.9(4)	3.4(4)	6.6(5)	0.1(3)	0.0	0.0
C5	.1240(9)	.7024(6)	.25	3.5(5)	3.9(5)	5.3(6)	−0.4(4)	0.0	0.0
C6	.0375(9)	.7799(6)	.25	3.5(5)	3.8(5)	3.9(5)	−0.3(4)	0.0	0.0
N7	.1054(7)	.8671(5)	.25	3.1(4)	3.5(4)	3.9(4)	0.2(3)	0.0	0.0
C8	−.0028(11)	.9343(6)	.25	4.7(6)	3.9(5)	5.5(6)	1.0(4)	0.0	0.0
C9	.1847(7)	.8792(5)	.074(1)	4.9(4)	6.0(4)	5.4(5)	−0.9(3)	1.8(4)	0.4(4)
I$^-$	.14693(6)	.17857(4)	.25	4.52(4)	4.81(4)	3.67(4)	−0.49(3)	0.0	0.0

Atom	x/A	y/B	z/C	Atom	x/A	y/B	z/C	Atom	x/A	y/B	z/C
H111	.067	.395	.133	H6	−.018	.777	.133	H91	.250	.832	.067
H113	−.061	.366	.25	H81	−.059	.928	.133	H92	.127	.876	−.041
H5	.179	.701	.133	H83	.040	.992	.25	H93	.229	.937	.074

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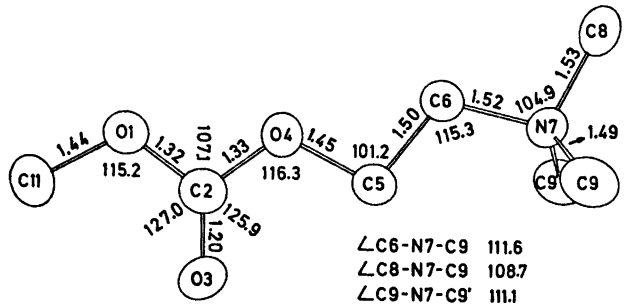

Fig. 1. The dimensions of the methoxycarbonylcholine ion. The estimated standard deviations on bond lengths and angles are about 0.01 Å and 0.6 – 0.8°, respectively. The drawings were produced by ORTEP.[10]

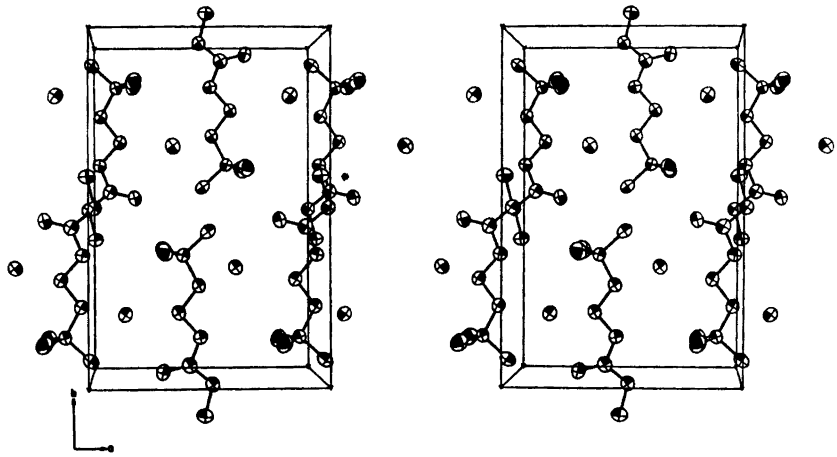

Fig. 2. A stereo view of the packing of methoxycarbonylcholine iodide.

Experimental. Methoxy- and ethoxycarbonylcholine iodide were synthesized by reacting *N,N*-dimethylaminoethanol with methyl- and ethylchloroformate, respectively,[6] followed by methylation with methyl iodide. M.p. 145 and 109 °C for methoxy- and ethoxycarbonylcholine iodide, respectively. Single crystals were grown by diffusion of dimethoxymethane into aqueous ethanolic solutions of the compounds.

Table 2. All interionic distances (Å) shorter than the sum of the van der Waals' radii.

C8---I⁻	$(x,y+1,z)$	4.07(1)
C11---I⁻	(x,y,z)	3.78(1)
C6---I⁻	$(-x,1-y,-z)$	4.04(1)
C8---I⁻	$(-x,1-y,-z)$	4.18(1)
C11---C2	$(-x,1-y,-z)$	3.68(1)
O3---C8	$(x+\frac{1}{2},1\frac{1}{2}-y,z)$	3.22(1)
C11---I⁻	$(x-\frac{1}{2},\frac{1}{2}-y,z)$	4.03(1)
C11---C9	$(\frac{1}{2}-x,y-\frac{1}{2},-z)$	3.89(1)

Crystal data. Methoxycarbonylcholine iodide, $C_7H_{16}NO_3I$. $M=289.12$. Space group *Pnam*, $a=10.388(6)$, $b=15.404(6)$, $c=6.988(2)$ Å, $V=1118.2$ Å^3, $D_m=1.72$ g cm^{-3}, $Z=4$, $D_c=1.72$ g cm^{-3}, $\mu(\text{Mo}K\alpha)=28.9$ cm^{-1}. $F(000)=568$. The unit cell parameters were refined by least-squares techniques from the θ angles measured for 48 reflections on a NONIUS CAD-3 diffractometer. The density was measured by flotation. The melting point was determined on a Leitz hot stage microscope.

Intensity data were collected on the diffractometer from a crystal with dimensions $0.16\times0.2\times0.4$ mm using Mo$K\alpha$ radiation and omega scan. Out of the 1080 independent reflections measured in the range $3.0°\leq\theta\leq25.0°$,

798 had $I_{net} \geq 2.0\ \sigma(I)$, where σ is the standard deviation from counting statistics. No absorption corrections have been made.

The structure was solved by the heavy atom method and refined by full matrix least-squares techniques to a final R value of 0.041, using the X-Ray System.[7] The final cycles of refinement included positional and anisotropic thermal parameters for all non-hydrogen atoms while the hydrogen atoms were fixed in their calculated positions (C−H equal to 1.0 Å) with a common thermal parameter (B = 4.0). The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = 1$ for $F_o \leq 40$ and $(40/F_o)^2$ for $F_o \geq 40$. The X-ray atomic scattering factors used for hydrogen were those of Stewart, Davidson and Simpson [8] and for all other atoms those listed in International Tables for X-Ray Crystallography.[9] All atoms but I^- were treated as uncharged. The final list of structure factors is available from the author on request.

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