Crystal Structure of the Reversed Carboxy-analogue of Acetylcholine [Methyl 3-(dimethylamino)propionate Methiodide]

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The crystal structure of the title compound has been determined by *X*-ray diffraction. Crystals are orthorhombic with $a = 10.948(5)$, $b = 13.803(6)$, $c = 7.101(2)$ Å, $Z = 4$, space group *Pnam*. The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares to *R* 0.047 for 952 three-dimensional diffractometer data. The iodide and methyl 3-(trimethylammonio)propionate ions are situated on the mirror plane at $z = \frac{1}{4}$, and the crystal structure therefore consists of layers parallel to (001).

METHYL 3-(dimethylamino)propionate methiodide (1), $\mathrm{Me_3\overset{+}{N}\cdot[CH_2]_2\cdot CO_2MeI^-}$, is the reversed carboxy-analogue of acetylcholine (2), $\mathrm{Me_3\overset{+}{N}\cdot[CH_2]_2\cdot O\cdot COMe}$, a chemical transmitter substance in the peripheral nervous system. The pharmacological activity of methyl 3-(dimethyl amino)propionate methiodide was first investigated by Schueler and Keasling,[1] and has recently been re-examined by Biggs *et al.*[2] who showed that the compound is almost equipotent with acetylcholine when acting at the nicotinic receptor but is only about one-third as active at the muscarinic receptor. We have determined the crystal structure of methyl 3-(dimethylamino)propionate methiodide by *X*-ray diffraction as part of an investigation [3,4] of structure-activity relationships among compounds related to acetylcholine.

EXPERIMENTAL

Crystals of (1) from methanol exhibited the forms {010}, {320}, {101}, and {011}. Under polarised light, crystals gave straight extinction in three mutually perpendicular directions, and yielded biaxial interference figures.

Crystal Data.—$\mathrm{C_7H_{16}NO_2I}$, $M = 273.1$, Orthorhombic, $a = 10.948(5)$, $b = 13.803(6)$, $c = 7.101(2)$ Å, $U = 1\,073.1$ Å^3, $D_m = 1.69$ g cm^{-3} (by flotation), $Z = 4$, $D_c = 1.69$ g cm^{-3}. Mo-K_α radiation, $\lambda = 0.7107$ Å; $\mu(\text{Mo-}K_\alpha) = 31.6$ cm^{-1}. Systematic absences: $h0l$ for $h = 2n + 1$, $0kl$ for $k + l = 2n + 1$, ($h00$ for $h = 2n + 1$), ($0k0$ for $k = 2n + 1$), ($00l$ for $l = 2n + 1$). Space group $Pna2_1$ or *Pnam*, shown to be the latter by successful refinement.

Intensity Measurement.—Intensities were measured by use of a computer-controlled [5] automatic four-circle *X*-ray diffractometer with graphite-monochromated Mo-K_α radiation. Reflections were integrated over a peakwidth of 1.6° by the θ—2θ scan technique with steps of 0.04° in 2θ and a counting time of 5 s per step. Within the range $5° \leqslant 2\theta \leqslant 55°$, 1 518 reflections were measured, of which 952 having $I \geqslant 3\sigma(I)$ were considered observed. Data were corrected for Lorentz-polarisation effects, but not for absorption or extinction. Only observed reflections were used for structure determination.

Structure Solution and Refinement.—The space group ambiguity between $Pna2_1$ and *Pnam* could not be satisfactorily resolved until the later stages of structure refinement, as these space groups differ only by a centre of symmetry. Solution and refinement procedures were therefore carried out independently for each space group with 650 data having $2\theta \leqslant 45°$. In the non-centrosymmetric space group $Pna2_1$ all atoms in the structure lie in general positions, and, excluding hydrogen atoms, there are 32 co-ordinate and 66 anisotropic thermal parameters to be determined, but for the centrosymmetric space group *Pnam* these figures reduce to 21 and 42 respectively because the iodide and methyl 3-(trimethylammonio)propionate ions lie on a mirror plane at $z = \frac{1}{4}$.

The iodide ion, and carbon, nitrogen, and oxygen atoms were located by Patterson and Fourier methods and their parameters refined by full-matrix least-squares. The function minimised was $\Sigma\omega(|F_o| - |F_c|)^2$ with $\omega = 1$ for all data. Atomic scattering factors for iodide ion, carbon, nitrogen, and oxygen were taken from ref. 6 and for hydrogen from ref. 7.

The initial solution to the structure was the same for both space groups and yielded *R* 0.30. However, prior to refinement of the structure in space group $Pna2_1$, the light atoms had to be shifted slightly from $z = \frac{1}{4}$ to destroy the pseudomirror plane present in the structure. In the absence of this modification, a singular least-squares matrix resulted. Refinement of scale factors, co-ordinates other than those fixed by symmetry, and eventually isotropic thermal parameters reduced *R* to 0.126 for both space groups, at which point the iodide ion was assigned an anisotropic temperature factor.

Subsequent refinement reduced *R* to 0.055, and the introduction of anisotropic thermal parameters for the light atoms gave *R* 0.045 for both possible space groups. Bond lengths and angles were essentially the same for both structures. Thus, the 35 extra parameters required by the noncentrosymmetric space group did not lead to an improved fit between the structure and the data and therefore this space group was rejected in favour of the centrosymmetric *Pnam*. Indeed, on the basis of the *R*-factor

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[5] W. R. Busing, R. D. Ellison, H. A. Levy, S. P. King, and R. T. Roseberry, 'The Oak Ridge Computer-controlled *X*-Ray Diffractometer,' Oak Ridge National Laboratory Report ORNL 4143, 1968.

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significance test,[8] it is impossible to reject the hypothesis that *Pnam* is the true space group at even a 50% level of significance. Final refinement was therefore carried out with this space group alone.

The reflections with $45° < 2\theta \leqslant 55°$ were included in the data set, and two cycles of refinement of all parameters gave R 0.061. A difference-Fourier synthesis revealed the positions of all the hydrogen atoms, and these were included in the structure-factor calculation, but their parameters were not refined. Further refinement of the parameters of the non-hydrogen atoms reduced R to the final value of 0.047.

TABLE 1

Fractional co-ordinates * and thermal parameters † ($\times 10^4$) for non-hydrogen atoms, with estimated standard deviations in parentheses

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	13 994(8)	18 971(5)	25 000	680(4)	495(3)	352(3)	−82(4)	0	0
C(1)	−105(11)	9 150(9)	2 500	689(81)	586(74)	471(65)	−36(65)	0	0
C(2)	1 766(9)	8 905(7)	4 242(12)	851(69)	758(57)	515(48)	14(51)	−112(49)	1(45)
C(3)	691(15)	7 555(10)	2 500	1 031(107)	514(76)	798(91)	132(81)	0	0
C(4)	1 705(14)	6 883(12)	2 500	790(103)	838(95)	825(97)	−2(90)	0	0
C(5)	1 388(18)	5 805(10)	2 500	920(110)	555(79)	506(65)	−32(87)	0	0
C(6)	−156(16)	4 540(12)	2 500	835(118)	868(120)	849(116)	−53(98)	0	0
N	1 093(10)	8 626(6)	2 500	785(77)	368(45)	439(49)	23(46)	0	0
O(1)	163(12)	5 602(7)	2 500	1 310(96)	656(56)	705(62)	494(62)	0	0
O(2)	2 079(12)	5 246(9)	2 500	1 071(97)	858(82)	1 066(91)	−97(74)	0	0

* Fractional co-ordinates $\times 10^5$ for iodide and $\times 10^4$ for other atoms. † The anisotropic thermal parameter is in the form: $\exp[-2\pi^2(h^2a^{*2}U_{11} \cdots + 2hka^*b^*U_{12} \cdots)]$.

TABLE 2

Fractional co-ordinates ($\times 10^3$) for hydrogen * atoms

Atom	x	y	z	Atom	x	y	z
H(1,1)	−35	897	367	H(3)	15	740	376
H(1,2)	14	990	250	H(4)	225	705	376
H(2,1)	190	953	417	H(6,1)	27	432	343
H(2,2)	252	890	385	H(6,2)	−123	457	250
H(2,3)	122	882	528				

* U_{iso} 0.0760 Å^2.

TABLE 3

Interatomic distances (Å) and angles (°), with estimated standard deviations in parentheses

(*a*) Distances

C(1)–N	1.499(16)	C(6)–O(1)	1.506(18)
C(2)–N	1.491(10)	I ··· C(1^{I})	4.087(6)
C(3)–N	1.542(16)	I ··· C(1^{II})	4.134(13)
C(3)–C(4)	1.447(21)	I ··· C(2^{III})	4.132(9)
C(4)–C(5)	1.528(20)	I ··· C(2^{IV})	4.132(9)
C(5)–O(1)	1.370(18)	I ··· C(4^{V})	4.113(8)
C(5)–O(2)	1.080(17)	I ··· C(6)	4.026(17)

Bond distances to hydrogen are in the range 0.86—1.18 Å

(*b*) Angles

C(1)–N–C(2)	107.9(6)	C(3)–C(4)–C(5)	116.8(14)
C(1)–N–C(3)	102.3(10)	C(4)–C(5)–O(1)	114.9(14)
C(2)–N–C(2^{VI})	112.2(10)	C(4)–C(5)–O(2)	122.4(17)
C(2)–N–C(3)	112.9(6)	O(1)–C(5)–O(2)	122.6(14)
N–C(3)–C(4)	113.3(13)	C(5)–O(1)–C(6)	115.2(11)

Symmetry operators:

I $\bar{x}, 1 - y, z \pm \frac{1}{2}$ II $x, y - 1, z$
III $\frac{1}{2} - x, y - \frac{1}{2}, z - \frac{1}{2}$ IV $\frac{1}{2} - x, y - \frac{1}{2}, 1 - z$
IV $\frac{1}{2} - x, y - \frac{1}{2}, z \pm \frac{1}{2}$ VI $x, y, \frac{1}{2} - z$

Final parameters are given for the non-hydrogen atoms in Table 1, for hydrogen atoms in Table 2, and interatomic distances and angles [9] in Table 3. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21342 (5 pp., 1 microfiche).

DISCUSSION

In the crystal, the iodide and methyl 3-(trimethylammonio)propionate ions are situated on the mirror plane at $z = \frac{1}{4}$. The light-atom part of the asymmetric unit is shown in Figure 1, and the complete methyl 3-(trimethylammonio)propionate ion is generated from it by reflection in the plane of the page.

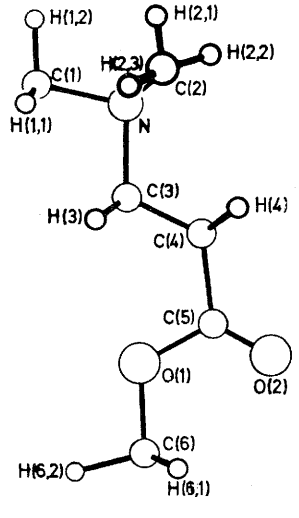

FIGURE 1 The asymmetric unit excluding the iodide ion. The complete molecule is generated *via* reflection in the plane of the page

Comparison with the crystal structures of acetyl-

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[8] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

[9] W. R. Busing, K. O. Martin, and H. A. Levy, 'ORFFE, a FORTRAN Crystallographic Function and Error Program,' Oak Ridge National Laboratory, Report ORNL TM 306, 1964.

choline chloride,[10] carbamoylcholine bromide,[11] and erythro-α(*S*),β(*R*)-dimethylacetylcholine iodide [12] indicates that in the present structure bond lengths C(3)–C(4) (1.45 Å) and C(5)–O(2) (1.08 Å) are rather short, that the bond angle C(3)–C(4)–C(5) (117°) is large, and that the angle C(1)–N–C(3) (102°) is small. Whilst there is no definite cause for the short bond lengths, the large and small bond angles may arise from interactions between non-bonded groups of atoms. The zero value for τ [C(3)–C(4)–C(5)–O(1)] results in a short intramolecular contact of 2.76 Å between atoms C(3) and O(1) which tends to enlarge angles C(3)–C(4)–C(5) and C(4)–C(5)–O(1). The former is significantly enlarged, and the latter (115°) is just larger than the range of values (108—113°) found previously.[10-12] Atom C(1) is in van der Waals contact with the iodide ion [C(1) · · · I at $x,y+1,z$ 4.13 Å], but the attached hydrogen H(1,2) is even closer [H(1,2) · · · I at $x,y+1,z$ 3.08 Å] and C–H–I is 168°. It is probable that the bond angle C(1)–N–C(3) is decreased through the effect of these contacts, since even after this decrease, the H · · · I contact is still 0.27 Å less than the formal van der Waals distance of 3.35 Å.

The mirror symmetry of the methyl 3-(trimethylammonio)propionate ion constrains all but one of the torsion angles between the non-hydrogen atoms to be 0° or 180°, the exception being τ [C(2)–N–C(3)–C(4)] −64.3(7)°. It is not therefore meaningful to compare directly the observed conformation of the methyl 3-(trimethylammonio)propionate ion with that found [3] for other nicotinic agonists.

The crystal structure is depicted in Figure 2, and consists of layers of iodide and methyl 3-(trimethylammonio)propionate ions at $z=\frac{1}{4}$ and $\frac{3}{4}$. The iodide ion is surrounded by six methyl 3-(trimethylammonio)propionate ions and makes several van der Waals contacts with them (Table 3). The chemical constitution of the compound precludes the possibility of hydrogen bonding.

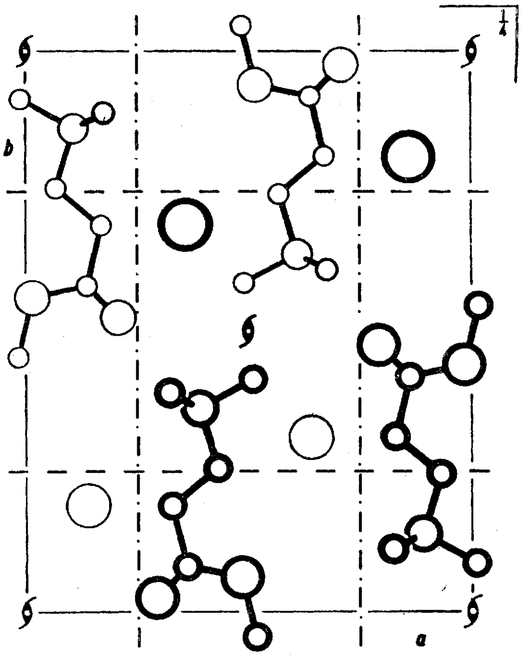

FIGURE 2 The crystal structure viewed normal to (001)

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