Acta Cryst. (1978). B**34**, 2986–2989

The Crystal and Molecular Structure of 1,1-Dimethyl-4-phenylpiperazinium Iodide

BY CYRUS CHOTHIA AND PETER PAULING

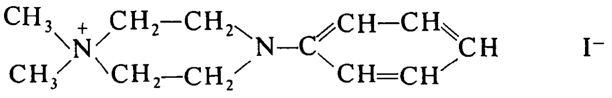
William Ramsay, Ralph Forster and Christopher Ingold Laboratories, University College London, Gower Street, London WC1, England

(*Received* 4 *April* 1977; *accepted* 3 *November* 1977)

Crystals of the cholinergic ganglion stimulant 1,1-dimethyl-4-phenylpiperazinium iodide are monoclinic, space group $P2_1/c$ (C_{2h}^5), $a = 6.264$ (2), $b = 7.741$ (2), $c = 27.897$ (8) Å, $\beta = 96.01$ (2)°, $Z = 4$. Using 2117 unique, observed [$I \geq 3\sigma(I)$] diffraction data, the structure was solved by Patterson and Fourier methods and refined by least squares to a residual $R = 0.042$. H atom positions were determined from a difference synthesis. The plane of the phenyl ring is observed to be coplanar with the plane of the C atoms of the piperazinium ring, although this conformation is sterically unstable. The stabilization of this conformation is interpreted in terms of a partial double bond between N(4) and the aromatic ring. The structure provides information about the required conformation of nerve ganglion stimulants and the differences between ganglion stimulants and motor-end-plate stimulants, both of which are classified as nicotinic.

Introduction

1,1-Dimethyl-4-phenylpiperazine (DMPP) mimics the action of acetylcholine at nicotinic nerve receptors in the nerve ganglia. It has no activity at muscarinic receptors and little activity at the nerve–muscle junction (Chen, Portman & Wickel, 1951; Barlow, 1968). We describe here the crystal structure of DMPP iodide.



Experimental results

DMPP iodide, from the Aldrich Chemical Co. Inc., was in the form of small crystals which were used without further recrystallization. The crystals are colourless, monoclinic, square or rectangular plates with developed faces (110) and are elongated along the *a* axis. Optical extinction occurred parallel to the plate edges and an acute interference figure suggested that crystals are biaxial and positive.

Crystal data

1,1-Dimethyl-4-phenylpiperazinium iodide, $C_{12}H_{19}IN_2$, $M_r = 318.21$, $a = 6.264$ (2), $b = 7.741$ (2), $c = 27.897$ (8) Å, $\beta = 96.01$ (2)°, $Z = 4$, $d_c = 1.57$ g cm^{-3}, Laue symmetry $2/m$, systematic absences: $0k0$, $k = 2n + 1$; $h0l$, $l = 2n + 1$, space group $P2_1/c$ (C_{2h}^5).

The diffraction data were collected on a computer-controlled Stoe four-circle diffractometer with a crystal $0.35 \times 0.30 \times 0.15$ mm, coated in Formvar. The X-ray counter was centred on 12 diffraction maxima and the values of the three angular coordinates for each maximum were used to calculate a least-squares refinement of the unit-cell parameters. Diffraction data were measured using Mo radiation and consisted of a hemisphere defined by $2\theta = 1 - 45°$ and the *h* index positive (two unique data sets). The effect of absorption of the crystal was determined by rotating the φ axis by 5° intervals, centring the X-ray counter on the 200 reflection and measuring intensity. Corrections to the data for absorption were made by the empirical technique of North, Phillips & Mathews (1968). The symmetry-related reflections of the 3989 diffraction maxima measured were averaged to give 2117 intensities [$I \geq 3\sigma(I)$] and these were used for the analysis of the structure. The stochastic *R* factor of the data $\sum \sigma(F^2)/\sum F^2_{\rm mean}$ is 0·071 and the value of $\sum [2(F_{hkl} - F_{h\bar{k}l})/(F_{hkl} - F_{h\bar{k}l})]/n$ for maxima measured more than once (n) is 0·043.

Structure analysis

A three-dimensional Patterson synthesis gave the position of the I atom, and a Fourier synthesis phased on this atom clearly showed all the non-hydrogen atoms. The structure was refined by full-matrix least squares on London University's ATLAS computer using a program written by Dr Shearing. The weighting scheme used for each diffraction maximum was $4I_{hkl}/\sigma(I)$, $\sigma(I)$ being the square root of the sum of the total count measured. The atomic scattering factors used were those of Cromer & Waber (1965) except for that of H which was taken from *International Tables for X-ray Crystallography* (1962).

Table 1. *Final positional parameters* ($\times 10^4$, *for* H $\times 10^3$) *and their standard deviations*

Hydrogen atoms are numbered (i) H(*Cnm*) for those bonded to C atom C(*n*); or (ii) H(*n*) for those bonded to the phenyl ring.

	x	*y*	*z*
I(1)	9166 (1)	7515 (2)	621 (0)
N(1)	5330 (15)	2430 (23)	744 (3)
C(2)	6835 (18)	2319 (27)	1203 (5)
C(3)	5716 (21)	2230 (25)	1652 (5)
N(4)	4190 (17)	3631 (14)	1690 (5)
C(5)	2736 (21)	3846 (18)	1252 (5)
C(6)	3887 (26)	3942 (21)	804 (6)
C(8)	6568 (19)	2605 (28)	321 (5)
C(7)	3976 (29)	776 (22)	645 (7)
C(10)	3210 (23)	3631 (18)	2118 (6)
C(11)	1291 (24)	4476 (18)	2150 (6)
C(12)	362 (26)	4485 (20)	2570 (8)
C(13)	1260 (29)	3646 (21)	2994 (6)
C(14)	3182 (27)	2868 (20)	2965 (6)
C(15)	4154 (21)	2866 (19)	2543 (6)
H(C61)	500	487	80
H(C62)	275	396	48
H(C71)	485	42	80
H(C72)	315	100	32
H(C73)	325	104	95
H(C81)	590	271	2
H(C82)	770	571	36
H(C83)	775	133	42
H(C21)	785	113	115
H(C22)	765	354	119
H(C31)	680	229	199
H(C32)	515	125	163
H(C51)	175	508	127
H(C52)	175	292	119
H(11)	65	500	186
H(12)	−85	471	259
H(13)	35	363	326
H(14)	425	250	333
H(15)	565	238	252

Table 2. 1,1-*Dimethyl*-4-*phenylpiperazinium iodide: deviations of atoms from least-squares planes* (Å $\times 10^2$)

Atoms used to define the planes are indicated by daggers. The equations of the planes relative to the orthogonal axes *a*, *b* and *c** are:

(1) $0·455x + 0·847y + 0·274z = 7·667$
(2) $0·456x + 0·847y + 0·273z = 7·670$
(3) $0·408x + 0·853y + 0·325z = 4·928$
(4) $0·707x - 0·545y + 0·450z = 4·967$.

	(1)	(2)	(3)	(4)
N(1)	−107	−106	−67	0
C(7)	−260	−259	−219	−1†
C(8)	−86	−85	−57	+3†
N(4)	−1	0†	+57	−3†
C(6)	−45	−44	0†	−122
C(2)	−42	−41	0†	+119
C(3)	−52	−51	0†	+120
C(5)	−56	−55	0†	−122
C(10)	−2†	−2†	+65	−2†
C(13)	−2†	−2†	+85	+3†
C(11)	+1†	+1†	+75	−119
C(15)	+1†	+1†	+72	+117
C(12)	+1†	+1†	+84	−117
C(14)	0†	0†	+80	+118

Table 3. *Torsion angles* (°) *about* N(4)—C(10) *of* 1,1-*dimethyl*-4-*phenylpiperazinium in crystals of the iodide for one of the two enantomeric molecules*

C(5)–N(4)–C(10)–C(11)	−27
C(3)–N(4)–C(10)–C(15)	+25
C(5)–N(4)–C(10)–C(15)	+157
C(3)–N(4)–C(10)–C(11)	−159

Table 4. 1,1-*Dimethyl*-4-*phenylpiperazinium iodide: intermolecular distances less than* 4 Å

		Symmetry and translation of second atom		
C(2)–C(5)	3·86 Å	(I)	+*a*	
C(2)–C(11)	3·96	(I)	+*a*	
C(2)–C(13)	3·72	(II)	+*a*	
C(3)–C(12)	3·74	(II)	+*a*	
C(3)–C(13)	3·43	(II)	+*a*	−*b*
C(3)–C(14)	3·58	(II)	+*a*	−*b*
N(4)–C(14)	3·74	(II)	+*a*	
N(4)–C(15)	3·98	(II)	+*a*	
C(11)–C(15)	3·90	(II)	+*a*	
C(10)–C(15)	3·74	(II)	+*a*	
C(11)–C(13)	3·60	(II)		
C(11)–C(14)	3·83	(II)		
C(12)–C(12)	3·91	(II)		
C(12)–C(13)	3·67	(II)		
C(12)–C(14)	3·63	(II)		
C(12)–C(15)	3·84	(II)		
C(8)–C(7)	3·74	(III)	+*a*	
C(12)–C(12)	3·91	(II)		−*b*

Symmetry code

(I) x,y,z (II) $x,\frac{1}{2}+y,\frac{1}{2}-z$ (III) $-x,-y,-z$

The structure was refined using an anisotropic thermal parameter for the iodide ion and isotropic thermal parameters for all other atoms to a residual of 0·056. The positions of all 19 H atoms of the molecule were then determined from the difference synthesis. All non-hydrogen atom positions were then further refined with anisotropic thermal parameters to the point where $R =$ 0·042 and the weighted $R =$ 0·041. Hamilton's (1965) test showed that this R factor was significant at the 0·005 level. The parameters given by the last refinement were taken as the final coordinates (Table 1) and thermal parameters of the atoms.* Table 2 gives the deviations of atoms from various least-squares planes. None of the atoms used to calculate least-squares planes of the various groups deviate a significant distance from the calculated plane. The molecular torsion angles are listed in Table 3. The presence of the iodide ion means that the standard deviations of the

---

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33638 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

positional parameters are not small. Therefore the bond lengths were not corrected for the effect of thermal vibration. Intermolecular distances are given in Table 4.

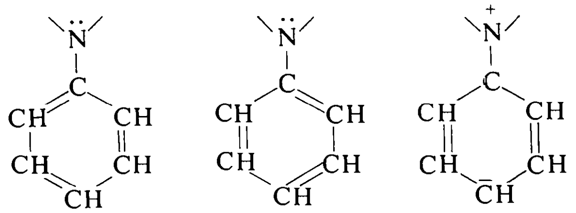
Discussion

Molecular structure

The intramolecular bond lengths (Fig. 1) do not differ significantly from expected values. The normal value of the C(sp^3)—N$^+$(alkyl)$_3$ bond length is 1·51 (1) Å (Singh & Ahmed, 1969). In this structure analysis the four C—N$^+$ bond lengths are within two standard deviations of this value. The C—C single-bond lengths of the piperazinium ring [1·52 (2) and 1·51 (2) Å] are shorter than the normal single-bond value of 1·54 Å by an amount that is not significant. Potter (1966) found, however, a value of 1·51 (1) Å for these bond lengths in 1,4-piperazine-γ,γ-dibutyric acid, and Rérat (1960) gives a value of 1·527 Å (no e.s.d.) for these bond lengths in piperazine dihydrochloride monohydrate.

The normal C(sp^3)—N bond length is 1·47 Å. The values observed here are 1·44 (2) and 1·46 (2) Å. The value of the N—C(benzene) bond length is 1·41 (2) Å. These are two or three standard deviations more than the equivalent values in 4-nitroaniline (Trueblood, Goldish & Donohue, 1961) and *N*,*N*-dimethyl-4-nitroaniline (Mak & Trotter, 1965) (1·37 and 1·36 Å respectively). In these structures the nitro group facilitates delocalization of the lone pair of electrons on the N atom. The N—C(benzene) length is closer to the value found in compounds in which less delocalization occurs, such as 2,5-dichloroaniline (Sakurai, Sundaralingam & Jeffrey, 1963) in which the bond length is 1·41 Å.

The C—C bond lengths of the aromatic ring are within one standard deviation of the equivalent bond lengths in benzene (1·393 Å) and biphenyl (1·379, 1·398 Å) (Cox, Cruickshank & Smith, 1958; Robertson, 1961). No bond angles differ significantly from the expected values except for C(15)—C(10)—C(11) and C(12)—C(13)—C(14) which at 115·6 (1·4) and 115·0 (1·5)° are significantly less than the trigonal value of 120°. A similar decrease is found in the equivalent bond angles of biphenyl (Robertson, 1961) (117·4 and 119·5°) and triphenyl (Rietveld, Maslen & Clews, 1970). This effect is probably due to a delocalization of the lone pair of electrons on the N atom.



The H atoms bonded to C atoms in the piperazinium ring have bond lengths of 0·80 to 1·10 Å and bond angles close to the expected tetrahedral value of 109·5°. The C—H bond lengths of the benzene ring vary between 0·8 and 1·2 Å and bond angles vary between 109 and 124°. The H atoms on the methyl groups were indicated by peaks of poor definition and their positions are approximate.

The values of the torsion angles about C(10)—N(4) are unexpected as they make the distances between H(C61) and H(15) and between H(C31) and H(11) ~ 1·8 Å. This value is shorter than the minimum usually given for the H—H contact distance [2·34 Å

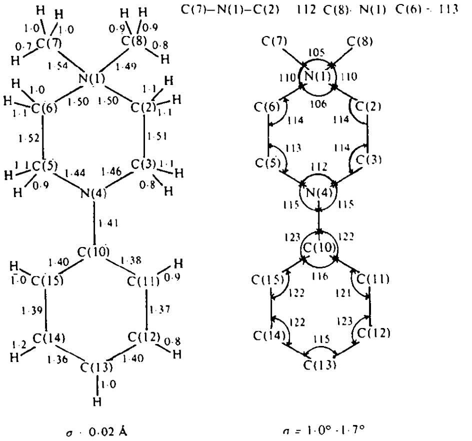


Fig. 1. Bond lengths (Å) and angles (°).

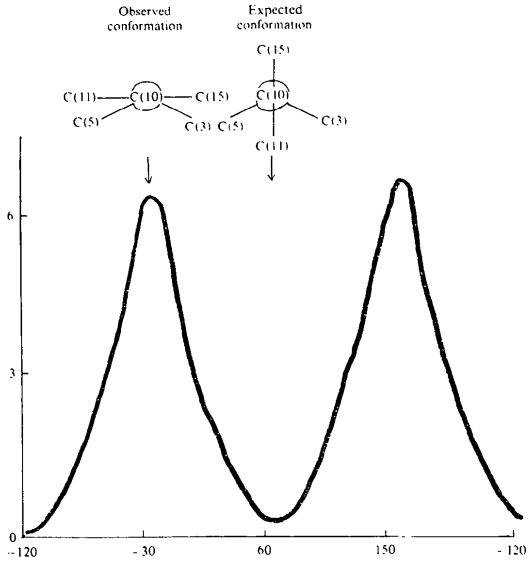


Fig. 2. Energy of DMPP as a function of the torsion angle about C(4)—C(10). The energies are calculated by the methods of Giglio (1969). Relaxation of bond angles and bond lengths will reduce the amount of strain but not the shape of the curve (Gelin & Karplus, 1975).

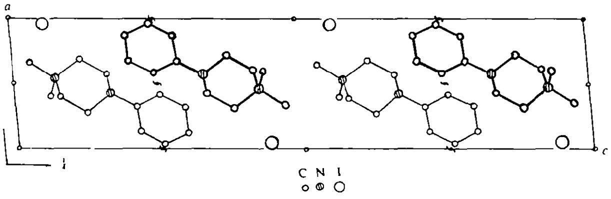


Fig. 3. A view of the unit cell in the **b** direction.

(Kitaigorodskii, 1961), and 2·40 Å (Pauling, 1960)] and causes steric strain (Fig. 2). Considered in isolation, these H—H distances are certainly not significant but consideration of the structure as a whole and the steric-energy curve (Fig. 2) indicate that some factor other than steric energy is stabilizing the observed conformation.

Pauling (1960) has described the partial delocalization of the lone pair of electrons on N(4) over the benzene ring. This gives the N(4)—C(10) bond some double-bond character and a resonance energy of about 7 kcal mol^{-1}. For delocalization of the electrons to occur the plane of the benzene ring must be normal to the lone pair of electrons on N(4). Thus the gain in resonance energy that occurs in the observed conformation easily compensates for the steric strain due to the repulsion between the H atoms.

Molecular packing

The molecular packing of DMPP in crystals of the iodide can be described in terms of a bilayer structure (Fig. 3). On the 'interior', benzene rings from DMPP molecules on the two sides of the bilayer interpenetrate. Each benzene ring is surrounded by six others, two from its own layer (at $\pm b$) and four from the other side of the bilayer.

The quaternary groups and iodide ions are on the 'exterior' of the bilayer and adjacent bilayers are held together by the ionic attraction. The iodide ions sit in ridges that run parallel to the b axis (Fig. 3). Each iodide ion is coordinated by four quaternary groups from its own layer. These form an approximate square-planar arrangement about I$^-$ in the ab plane. The close approaches are I—C(8) = 4·18 Å for the origin molecule, I—C(6) = 4·04 Å for the molecule at $+a$, I—C(7) = 4·12 Å for the molecule at $+b$ and I—C(7) = 3·93 Å for the molecule at $+a$ $+b$. The iodide ion is also near two quaternary groups from the adjacent bilayer, with close approaches of I—C(8) = 3·96 Å to one and I—C(7) = 4·04 Å to the other.

The structure of this specific ganglion stimulant adds appreciably to the arguments for the required conformation of such substances (Chothia & Pauling, 1970).

We are grateful to the Medical Research Council for support, Mr John Cresswell for the drawings, and Mrs Patricia Breen for assistance.

References

Barlow, R. B. (1968). *Introduction to Chemical Pharmacology*. London: Methuen.

Chen, G., Portman, R. & Wickel, A. (1951). *J. Pharmacol.* **103**, 330.

Chothia, C. H. & Pauling, P. J. (1970). *Proc. Natl Acad. Sci. USA*, **65**, 477–482.

Cox, E. G., Cruickshank, D. W. J. & Smith, J. A. S. (1958). *Proc. R. Soc. London Ser. A*, **247**, 1.

Cromer, D. T. & Waber, J. T. (1965). *Acta Cryst.* **18**, 104–109.

Gelin, B. R. & Karplus, M. (1975). *J. Am. Chem. Soc.* **97**, 6996–7006.

Giglio, E. (1969). *Nature (London)*, **222**, 339–341.

Hamilton, W. C. (1965). *Acta Cryst.* **18**, 502–510.

International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.

Kitaigorodskii, A. I. (1961). *Organic Chemical Crystallography*. New York: Consultants Bureau.

Mak, T. C. W. & Trotter, J. (1965). *Acta Cryst.* **18**, 68–74.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

Pauling, L. (1960). *The Nature of the Chemical Bond*, 3rd edition. Ithaca: Cornell Univ. Press.

Potter, N. (1966). *Acta Cryst.* **20**, 54–59.

Rérat, C. (1960). *Acta Cryst.* **13**, 459–468.

Rietveld, H. M., Maslen, E. N. & Clews, C. J. B. (1970). *Acta Cryst.* B**26**, 693–706.

Robertson, G. B. (1961). *Nature (London)*, **191**, 593–594.

Sakurai, T., Sundaralingam, M. & Jeffrey, G. A. (1963). *Acta Cryst.* **16**, 354–363.

Singh, P. & Ahmed, F. R. (1969). *Acta Cryst.* B**25**, 1901–1910.

Trueblood, K. N., Goldish, E. & Donohue, J. (1961). *Acta Cryst.* **14**, 1009–1017.