An MPP+ Analog: the 2:1 N-Cyclopentyl-4-phenylpyridinium Bromide–4-Phenyl-pyridine Complex

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Abstract

The molecular structure and cohesion in the solid state of the title addition compound between N-cyclopentyl-4-phenylpyridinium (CPPP) bromide, 4-phenylpyridine (PP), hydrogen bromide and water [bis(N-cyclopentyl-4-phenylpyridinium) 4-phenylpyridinium tribromide monohydrate, $2C_{16}H_{18}N^+.C_{11}H_{10}N^+.3Br^-.H_2O$], is discussed. The 4-phenylpyridine molecule, which is protonated, the bromide ions and the water molecule all lie on a mirror plane. Cohesion of the 2:1 CPPP:PP compound is achieved mainly through hydrogen bonds and salt bridges. No charge-transfer interaction between the two molecules was found. The phenyl ring is essentially coplanar with the pyridine ring in the PP molecule, while in the CPPP ion these two rings are rotated with respect to one another. The conformations of these two molecules are compared with theoretical data (conformational analysis) and with structures of phenylpyridinium analogs retrieved from the Cambridge Structural Database. As a result, this study allows the identification of stable conformers for phenylpyridinium analogs and could lead to the definition of active conformers for the neurotoxin MPP+ and some of its derivatives.

Comment

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is highly neurotoxic in humans and certain animals, causing effects similar to those observed in Parkinson's disease. The toxication route involves oxidation of this compound in the brain by type B monoamine oxidase to a dihydropyridinium intermediate which spontaneously oxidizes to form the 1-methyl-4-phenylpyridinium ion (MPP+), the neurotoxin which causes cell death (Singer & Ramsay, 1990; Singer, Trevor & Castagnoli, 1987; Chiba, Trevor & Castagnoli, 1984; Langston, Ballard, Tetrud & Irwin, 1983). MPTP and some analogs have also been found to inhibit monoamine oxidase (Singer,

Salach & Crabtree, 1985; Salach, Singer, Castagnoli & Trevor, 1984).

A series of synthetic studies designed to investigate structural parameters associated with monoamine oxidase catalysis have led to the synthesis of a variety of tetrahydropyridine derivatives by way of the corresponding pyridinium compounds. One of these compounds, N-cyclopentyl-4-phenylpyridinium (CPPP) bromide, crystallized from the reaction mixture as a ternary addition compound with 4-phenylpyridine (PP) (Kalgutkar, Castagnoli, Hall & Castagnoli, 1994). This 2:1 compound was isolated and fully characterized by NMR and elemental analysis. This unusual interaction between the pyridinium and pyridine species has prompted us to examine the structural features of this molecule by single-crystal X-ray analysis. This work is complementary to some recent structure–activity studies of MPTP (Altomare et al., 1992; Efrange & Boudreau, 1991) and MPP+ (Altomare, Carrupt, El Tayar & Testa, 1991) analogs, which have provided some insight into the stereo-electronic parameters underlying the properties of those molecules.

(CPPP)   (PP)

The 4-phenylpyridine (PP) molecule lies on a mirror plane together with the bromide ions and a water molecule of crystallization. The pyridine N atom in the PP molecule, N18, is protonated and implied in a hydrogen bond with Br3 (Table 3). The phenyl ring in this molecule is coplanar with the pyridine ring, as a consequence of the position of the molecule on the mirror plane at $x = 0$. The C21—C24 intercyclic bond [1.48 (2) Å] is longer than the the intracyclic C_{ar}—C_{ar} bonds in the molecule, implying that it has lower aromatic character (Table 2).

The molecular conformation of the N-cyclopentyl-4-phenylpyridinium (CPPP) ion differs from that of the phenylpyridine molecule. The phenyl and the pyridine rings in the CPPP ion are rotated with respect to each other, the torsion angle between the two rings being close to 30° [C3—C4—C7—C8 −30.1 (13)°]. Despite this twist, which leads to a less favorable overlap between the p_z atomic orbitals, the intercyclic C4—C7 bond [1.452 (10) Å] is significantly shorter than in the

PP molecule, indicating more electronic delocalization between the two rings. It appears, therefore, that the positive charge introduced at the pyridinium cation influences the delocalization of the electrons more deeply than the conformation of the phenyl and the pyridine rings. The differences in electronic delocalization in the N-alkyl pyridinium ion and the pyridine molecule is also reflected by the C_{ar}—N bond lengths, which are significantly shorter in PP than in CPPP (Table 2). The cyclopentyl ring in CPPP adopts an envelope conformation (Table 4) and is perpendicular to the pyridinium moiety [C2—N1—C13—C14 125.4 (8) Å].

Cohesion of the 2:1 CPPP:PP compound is achieved by hydrogen bonds, electrostatic interactions and van der Waals forces, and does not occur *via* a charge-transfer process. Each molecule of 4-phenylpyridine is flanked by two N-cyclopentyl-4-phenylpyridinium ions.

The bromide counterions lie in the same plane as the planar PP molecule (Fig. 1).

Conformational analysis of MPP+ analogs has been carried out previously and has shown that the rotation barrier around the inter-ring bond is less than $2.5\,\text{kcal mol}^{-1}$ for 4-phenylpyridine derivatives, allowing free rotation and coplanarity of the two rings (Altomare, Carrupt, El Tayar & Testa, 1991). The minimum-energy structures correspond to inter-ring torsion angles of 30 and 150°, in good agreement with the structure of CPPP we report here. A systematic search of molecular structures included in version 5.08 of the Cambridge Structural Database (Allen, Kennard & Taylor, 1983) yielded nine structures containing a non-hindered 4-phenylpyridinium motif. In all of these, the phenyl and the pyridinium rings are rotated with respect to each other (Fig. 3). The influence of non-coplanarity on the electronic delocalization between the two aromatic rings is not obvious, as there is no correlation between the torsion angle $T1$ and the length of the inter-ring bond.

Fig. 1. The molecular structure and conformation of the title compound. Non-H atoms are represented by displacement ellipsoids at the 50% probability level.
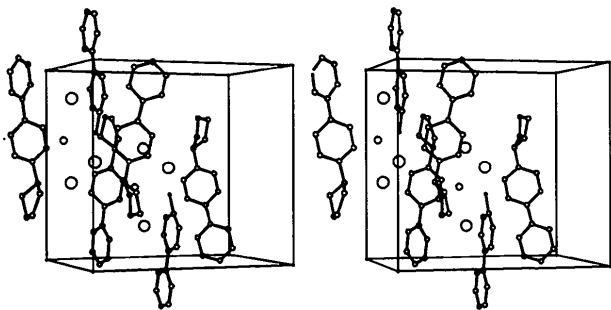
Fig. 2. Stereoview of the crystal packing and molecular conformation of the title compound.
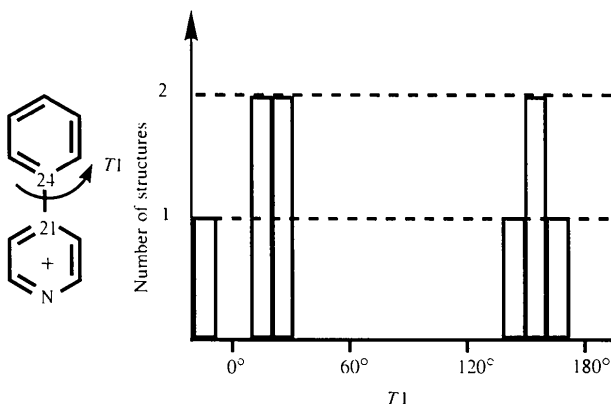
Fig. 3. The distribution of the torsion angle $T1$ between the phenyl and the pyridinium rings in nine structures containing the 4-phenyl-pyridinium motif.

In conclusion, although free rotation of the phenyl ring is predicted from theoretical calculations, all the structures reported in the literature and the structure of the N-cyclopentyl-4-phenylpyridinium ion reported here have a non-coplanar conformation in the solid state with a torsion angle between the two rings of around 30°. It is not possible to draw conclusions about the conjugation between the two rings. Nevertheless, this work establishes a stable (non-coplanar) conformation for phenyl-pyridinium analogs and leads to the identification of an active conformer for the neurotoxin MPP+ and its derivatives.

Experimental

The compound was prepared as described by Kalgutkar, Castagnoli, Hall & Castagnoli (1994).

Crystal data

$2C_{16}H_{18}N^+.C_{11}H_{10}N^+.3Br^-.-$
H_2O
$M_r = 861.7$
Orthorhombic
$Pmn2_1$
$a = 14.692\,(2)$ Å
$b = 13.880\,(1)$ Å
$c = 9.759\,(1)$ Å
$V = 1990.1\,(4)$ Å^3
$Z = 2$
$D_x = 1.438$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25
reflections
$\theta = 11-25°$
$\mu = 4.032$ mm^{-1}
$T = 293\,(2)$ K
Small prism
$0.29 \times 0.16 \times 0.01$ mm
Colorless

Data collection

Enraf–Nonius CAD-4
diffractometer
$\omega/2\theta$ scans
Absorption correction:
refined from ΔF
(*DIFABS*; Walker &
Stuart, 1983)
$T_{min} = 0.362$, $T_{max} = 1.000$
3539 measured reflections
2154 independent reflections

1701 observed reflections
$[I > 2\sigma(I)]$
$R_{int} = 0.0256$
$\theta_{max} = 71.8°$
$h = -18 \rightarrow 15$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 12$
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0447$
$wR(F^2) = 0.0997$
$S = 1.104$
2154 reflections
250 parameters
All H-atom parameters
refined
$w = 1/[\sigma^2(F_o^2) + (0.0378P)^2 + 0.3537P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.251$

$\Delta\rho_{max} = 0.411$ e Å^{-3}
$\Delta\rho_{min} = -0.407$ e Å^{-3}
Extinction correction: none
Atomic scattering factors
from *International Tables
for Crystallography* (1992,
Vol. C, Tables 4.2.6.8 and
6.1.1.4)
Absolute configuration:
Flack (1983) parameter
$= 0.19\,(4)$

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	U_{eq}
Br1	0	0.82827(9)	0.58183(13)	0.0595(3)
Br2	0	0.41252(10)	0.5645(2)	0.0753(4)
Br3	0	0.51515(9)	0.0396(2)	0.0751(5)
N1	0.2315(4)	0.5180(4)	0.7783(7)	0.049(2)
C2	0.1632(5)	0.5812(5)	0.7621(9)	0.057(2)
C3	0.1807(5)	0.6791(5)	0.7682(9)	0.053(2)
C4	0.2699(5)	0.7132(5)	0.7983(9)	0.050(2)
C5	0.3382(6)	0.6432(5)	0.8065(9)	0.064(2)
C6	0.3188(5)	0.5471(6)	0.8006(10)	0.063(2)
C7	0.2881(5)	0.8143(5)	0.8248(10)	0.052(2)
C8	0.2365(6)	0.8872(5)	0.7651(12)	0.075(3)
C9	0.2540(9)	0.9834(6)	0.7959(18)	0.101(4)
C10	0.3189(7)	1.0058(6)	0.8933(14)	0.095(4)
C11	0.3689(6)	0.9375(5)	0.9515(10)	0.073(2)
C12	0.3555(6)	0.8396(5)	0.9203(10)	0.066(2)
C13	0.2087(6)	0.4137(5)	0.7852(9)	0.054(2)
C14	0.2610(7)	0.3521(5)	0.6800(11)	0.072(3)
C15	0.2494(7)	0.2521(7)	0.7387(13)	0.090(4)
C16	0.2549(8)	0.2644(6)	0.8919(11)	0.080(3)
C17	0.2274(7)	0.3688(5)	0.9230(11)	0.070(3)
N18	0	0.7477(9)	1.1270(14)	0.074(4)
C19	0	0.7697(13)	0.9996(19)	0.118(7)
C20	0	0.8613(9)	0.9497(17)	0.101(6)
C21	0	0.9374(8)	1.0384(12)	0.058(3)
C22	0	0.9114(10)	1.1766(16)	0.083(4)
C23	0	0.8146(12)	1.2185(15)	0.086(5)
C24	0	1.0396(9)	0.9941(14)	0.061(3)
C25	0	1.0601(9)	0.8534(15)	0.076(4)
C26	0	1.1566(9)	0.8104(19)	0.087(4)
C27	0	1.2300(12)	0.902(2)	0.104(7)
C28	0	1.2097(11)	1.036(3)	0.119(7)
C29	0	1.1142(11)	1.085(3)	0.103(5)
O1*W*	0	0.6228(7)	0.3999(12)	0.111(4)

Table 2. *Selected geometric parameters (Å, °)*

N1—C2	1.343(8)	C14—C15	1.512(12)
N1—C6	1.361(9)	C15—C16	1.51(2)
N1—C13	1.488(8)	C16—C17	1.534(11)
C2—C3	1.384(9)	N18—C19	1.28(2)
C3—C4	1.424(10)	N18—C23	1.29(2)
C4—C5	1.400(10)	C19—C20	1.36(2)
C4—C7	1.452(10)	C20—C21	1.37(2)
C5—C6	1.365(10)	C21—C22	1.40(2)
C7—C8	1.392(10)	C21—C24	1.48(2)
C7—C12	1.404(11)	C22—C23	1.40(2)
C8—C9	1.393(12)	C24—C29	1.36(2)
C9—C10	1.38(2)	C24—C25	1.40(2)
C10—C11	1.326(12)	C25—C26	1.40(2)
C11—C12	1.407(10)	C26—C27	1.35(2)
C13—C17	1.508(12)	C27—C28	1.34(2)
C13—C14	1.541(11)	C28—C29	1.41(2)
C2—N1—C6	122.0(6)	C15—C14—C13	101.6(8)
C2—N1—C13	118.2(6)	C16—C15—C14	105.4(9)
C6—N1—C13	119.5(6)	C15—C16—C17	106.8(8)
N1—C2—C3	119.8(7)	C13—C17—C16	105.2(7)
C2—C3—C4	120.4(7)	C19—N18—C23	120.0(16)
C5—C4—C3	116.2(6)	N18—C19—C20	124.8(17)
C5—C4—C7	121.9(7)	C19—C20—C21	119.7(15)
C3—C4—C7	121.9(7)	C20—C21—C22	114.4(12)
C6—C5—C4	121.7(7)	C20—C21—C24	123.7(12)
C5—C6—N1	119.5(7)	C22—C21—C24	121.9(11)
C8—C7—C12	118.7(7)	C21—C22—C23	121.9(13)
C8—C7—C4	121.8(8)	N18—C23—C22	119.2(14)
C12—C7—C4	119.4(7)	C29—C24—C25	118.9(15)
C7—C8—C9	120.4(10)	C29—C24—C21	122.4(14)
C10—C9—C8	119.4(10)	C25—C24—C21	118.6(12)
C11—C10—C9	121.0(8)	C26—C25—C24	119.1(14)
C10—C11—C12	121.4(9)	C27—C26—C25	121.4(17)
C7—C12—C11	118.9(8)	C28—C27—C26	119.0(17)
N1—C13—C17	113.7(6)	C27—C28—C29	122(2)
N1—C13—C14	113.4(7)	C24—C29—C28	120(2)
C17—C13—C14	105.9(7)		

C6—N1—C2—C3	−0.1(14)
C13—N1—C2—C3	173.9(8)
C2—C3—C4—C7	−171.0(8)
C7—C4—C5—C6	170.6(9)
C13—N1—C6—C5	−174.1(8)
C5—C4—C7—C8	152.7(10)
C3—C4—C7—C8	−30.1(13)
C5—C4—C7—C12	−31.8(12)
C3—C4—C7—C12	145.5(9)
C4—C7—C8—C9	178.1(11)
C4—C7—C12—C11	−176.2(8)
C2—N1—C13—C17	−113.5(9)
C6—N1—C13—C17	60.7(10)
C2—N1—C13—C14	125.4(8)
C6—N1—C13—C14	−60.4(11)
N1—C13—C14—C15	162.3(7)
C17—C13—C14—C15	36.9(9)
C13—C14—C15—C16	−37.4(10)
C14—C15—C16—C17	24.6(12)
N1—C13—C17—C16	−147.5(8)
C14—C13—C17—C16	−22.3(10)
C15—C16—C17—C13	−1.2(12)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H· · ·*A*	*D*—H	*D*· · ·*A*	*D*—H· · ·*A*
N18—HBr3· · ·Br3[i]	1.503	3.341 (10)	160.3
O1*W*—HBr1· · ·Br1	1.036	3.360 (10)	155.3

Symmetry code: (i) $\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$.

Table 4. *Least-squares-planes data*

The equations of the planes can be expressed as $PX + QY + RZ = S$ in direct space with $P = 11.7$, $Q = 8.2$, $R = 1.1$ and $S = 6.7$ for plane *A* and $P = 14.5$, $Q = 1.3$, $R = 1.2$ and $S = 5.0$ for plane *B*.

	Δ (Å)
Plane *A*	
C13*	0.0
C14*	0.0
C17*	0.0
C15	−0.890
C16	−0.561
Plane *B*	
C14*	0.086
C15*	−0.141
C16*	0.141
C17*	−0.086
C13	−0.464

* Atom included in the definition of the least-squares plane.

Data collection, cell refinement and data reduction were performed using *CAD-4 EXPRESS* (Enraf–Nonius, 1993) and *NONIUS*93 (Baudoux & Evrard, 1993). Corrections for background, decay, Lorentz and polarization factors, and absorption effects were included in the data reduction. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1990), resulting in reliable positions for all the non-H atoms. The initial model was refined with *SHELXL*93 (Sheldrick, 1993). One H atom in the water molecule was not found. *PLATON*93 (Spek, 1990) was used for the generation of the CIF and geometry analysis. The structures retrieved from the Cambridge Structural Database were BIGTEQ, CORXUC, FOYWAR, FUTXEX, FUTXIB, HACDUK, PDZNCP and VUKBEI. The structural statistics display package *VISTA-3D* (Allen, Kennard & Taylor, 1983) was used for the statistical analysis. Diagrams were prepared using *ORTEP* (Johnson, 1965) and *VISTA-3D*.

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4-[(1-Cyclohexenyl)nitromethyl]-2-(3,4-methylenedioxyphenyl)-3-nitro-3,4-dihydro-2H-1-benzopyran

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Abstract

The crystal structure determination of $C_{23}H_{22}N_2O_7$ shows that the mutual dispositions of the H atoms attached to the four successive chiral centres are *gauche*, *gauche* and *trans*.

Comment

The present study owes its origin to the need for ascertaining the relative stereochemistry in products obtained in the reaction of 1-(1-nitrophenyl)cyclo-

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