C(1)	0.8409 (6)	0.4850 (5)	0.8339 (5)	0.079 (2)
C(2)	0.7483 (5)	0.6929 (5)	0.7665 (4)	0.061 (2)
C(3)	0.6675 (4)	0.7501 (4)	0.5920 (4)	0.050 (1)
C(4)	0.7665 (4)	0.8418 (4)	0.3888 (4)	0.046 (1)
C(5)	0.6765 (4)	0.8810 (4)	0.2331 (4)	0.047 (1)
C(6)	0.4766 (4)	0.8202 (4)	0.3112 (5)	0.056 (2)
C(7)	0.3878 (4)	0.7337 (5)	0.5117 (5)	0.062 (2)

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

	(1)	(2)	(3)
O(1)—C(4)	1.356 (6)	1.347 (3)	1.351 (4)
O(2)—C(5)	1.256 (6)	1.235 (2)	1.241 (3)
O(3)—C(3)	1.370 (6)	1.355 (3)	1.363 (4)
O(3)—C(7)	1.346 (6)	1.334 (2)	1.356 (5)
C(1)—C(2)	1.512 (7)	1.511 (3)	1.489 (5)
C(2)—C(3)	1.497 (7)	1.471 (2)	1.495 (5)
C(3)—C(4)	1.349 (7)	1.344 (3)	1.352 (3)
C(4)—C(5)	1.441 (6)	1.434 (2)	1.444 (5)
C(5)—C(6)	1.421 (7)	1.428 (3)	1.425 (4)
C(6)—C(7)	1.337 (8)	1.318 (3)	1.320 (4)
O(1)···O(2^i)	2.724 (4)	2.676 (1)	2.711 (2)
C(3)—O(3)—C(7)	118.2 (4)	119.3 (2)	119.1 (2)
C(1)—C(2)—C(3)	111.9 (5)	112.4 (2)	111.8 (4)
O(3)—C(3)—C(2)	112.0 (4)	112.0 (2)	113.2 (2)
O(3)—C(3)—C(4)	121.1 (4)	121.1 (2)	120.3 (3)
C(2)—C(3)—C(4)	126.9 (5)	126.9 (2)	126.5 (3)
O(1)—C(4)—C(3)	118.0 (4)	118.5 (2)	118.8 (3)
O(1)—C(4)—C(5)	120.8 (4)	120.2 (2)	119.6 (2)
C(3)—C(4)—C(5)	121.3 (4)	121.3 (2)	121.6 (3)
O(2)—C(5)—C(4)	120.6 (4)	121.3 (2)	120.8 (3)
O(2)—C(5)—C(6)	124.1 (4)	124.7 (2)	124.4 (3)
C(4)—C(5)—C(6)	115.2 (4)	114.0 (2)	114.8 (2)
C(5)—C(6)—C(7)	119.7 (5)	121.3 (2)	120.5 (4)
O(3)—C(7)—C(6)	124.4 (5)	123.1 (2)	123.7 (3)

Symmetry codes: for polymorph (1), (i) $\frac{1}{2}-x, y-\frac{1}{2}, \frac{1}{2}-z$; for polymorph (2), (i) $\frac{1}{3}-y, -\frac{1}{3}-y+x, z-\frac{1}{3}$; for polymorph (3), (i) $2-x, 2-y, -z$.

The structures were solved by direct methods and refined by full-matrix least squares. H atoms bonded to C atoms were included in calculated positions (C—H 0.96 Å). With all non-H atoms refined with anisotropic displacement parameters the hydroxyl H atom H(1) was located as the highest residual electron-density peak and was included in the final cycles of least squares riding on atom O(1). All crystals of polymorph (1) gave broad, weak diffraction peaks, resulting in a small observed data set and consequent high value of *R*. Cell refinement and data collection: *XSCANS* (Fait, 1991). Data reduction, structure solution and refinement: *SHELXTL/PC* (Sheldrick, 1990). Molecular graphics: *SHELXTL/PC*.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: AS1151). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Hydrogen-Bonding Stabilization of *N*-Methyldopamine 4-*O*-Dihydrogenphosphate in HCl Acidic Solution: Synthesis of Z2055, a New Dopaminergic Prodrug

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Abstract

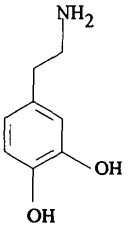
The crystal structure analysis of 4-[2-(methylamino)-ethyl]-1,2-benzenediol 1-(dihydrogenphospate) hydrochloride, $C_9H_{15}NO_5P^+.Cl^-$, shows that the Cl^- ion is an acceptor in a hydrogen-bonding system joining the ammonium cations in endless chains and involving one phosphate and the phenol hydroxyl groups together with the ammonium group, acting as proton donors. The stability of this system may justify the isomerization of the 4-hydroxy-3-*O*-phosphate to 3-hydroxy-4-*O*-phosphatephenethyl moiety, observed in strongly acidic HCl solution. This isomerization allows simplification of the synthesis of the Z2055 dopaminergic prodrug.

Comment

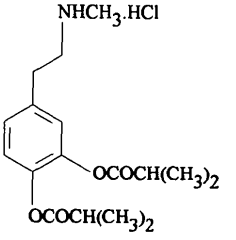
Dopamine [DA, (I)] has been studied extensively because of its important physiological endogenous role (Goldberg, 1972). A great deal of effort was devoted to the synthesis of DA analogues which overcame DA problems of oral low absorption and rapid metabolism (Ince, 1990). A second line of research focused on

the prodrug approach (Casagrande & Santangelo, 1990) yielding important results, *e.g.* L-dopa for the treatment of Parkinson's disease, which is decarboxylated in the central nervous system to give DA.

The simplest related DA agent is its *N*-methyl derivative which shows improved metabolic stability around the N atom, but still maintains the catechol moiety. Consequently, we have developed ibopamine (II), the 3,4-*O*-diisobutyl ester of *N*-methyldopamine, for the treatment of congestive heart failure and which is marketed in many European countries (Casagrande, Santangelo, Saini, Gerli & Cerri, 1986).

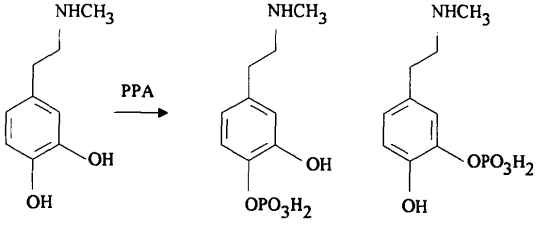


(I)

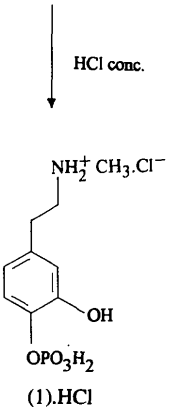


(II)

Continuing our efforts in this direction, we synthesized *N*-methyldopamine 4-*O*-dihydrogenphosphate (Z2055) which showed an interesting renal selectivity (Casagrande *et al.*, 1988). The first preparation of Z2055 required a multistep synthesis (Casagrande & Santangelo, 1987), starting from 3-*O*-benzyloxy-4-hydroxybenzaldehyde in order to overcome the intrinsic difficulty of distinguishing regiochemically between the 3- and 4-hydroxy groups of a catecholamine.



N-Methyldopamine (1) Z2055 (2)



(1).HCl

On the other hand, we succeeded in preparing the equiratio mixture of (1) and (2) by single step phosphorylation of *N*-methyldopamine, and, looking for a way to separate (1) from (2), we surprisingly discovered that in strong acidic conditions (concentrated aqueous HCl), the hydrochloride of (1) selectively crystallized. Even more surprising was the fact that no amount of (2) remained in the mother solution because pure (2) is not stable in these conditions: it quickly isomerizes to (1) which quantitatively separates from the solution as crystals of (1).HCl. In spite of repeated efforts, the hydrochloride of (2) could not be obtained.

To find a possible explanation of this behaviour, the X-ray crystal structure analysis of (1).HCl was carried out and the results are reported in the present paper.

Fig. 1 shows an *ORTEP* (Johnson, 1965) drawing of the organic cation and the chloride ion. From the geometrical parameters of Table 2, if compared with the expected values [C_{ar}—C_{ar} = 1.384 (13), C_{ar}—C_{sp^3} = 1.510 (9), C_{sp^3}—N_{sp^3} = 1.494 (16), C_{ar}—OH = 1.362 (15), P═O = 1.467 (7), P—OH = 1.560 (9), P—O(—C) = 1.587 (14) Å (Allen *et al.*, 1987)], it appears that the observed geometry is quite acceptable in spite of the poor values of the residual error indices (see *Experimental*). Also, the angular values are as expected and the asymmetry of the exocyclic angles at C3 and C4 caused by intramolecular hindrance is noteworthy.

The cation has an extended conformation particularly favourable for hydrogen-bonding interactions with the

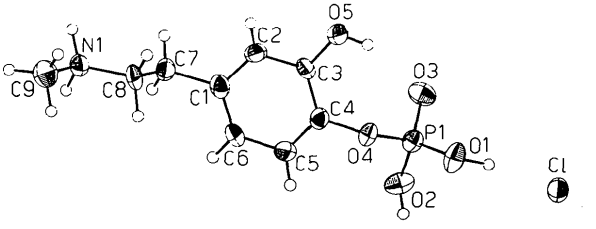


Fig. 1. *ORTEP* (Johnson, 1965) drawing of the two ions system. Displacement ellipsoids are at the 50% probability level.

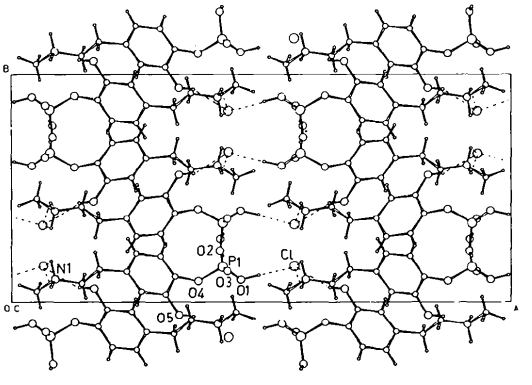


Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) drawing of packing showing the hydrogen-bonding system involving the Cl^- anions.

Cl^- anions, which join the cations in chains running along the *a* axis, as shown in Fig. 2.

The observed hydrogen-bonding system involving Cl^- is peculiar to the crystals of the (1).HCl isomer and must correspond to an energetically more stable state than any accessible for (2).HCl; the latter is not formed, but instead (2) isomerizes to (1), probably by a low-activation-energy process.

Experimental

Under a nitrogen atmosphere, 200 g of *N*-methyldopamine hydrochloride were added to 362 g of polyphosphonic acid (PPA) in portions at 353 K while stirring in 1.5 h. After 2.5 h the mixture was cooled to room temperature and 750 ml of concentrated HCl were added. The mixture was stirred for 18 h and the white precipitate was collected and washed with 100 ml of cooled HCl, then suspended in 1000 ml of acetone for 0.5 h. Finally, after filtration and drying under vacuum, 151.1 g (54% yield) of white crystals were recovered. M.p. 448–451 K (determined with a Büchi apparatus, not corrected); ^{1}H NMR (Varian Gemini 200 MHz, D_2O) δ(p.p.m.) 2.48 (*s*, 3H), 2.72 (*t*, 2H), 3.06 (*t*, 2H), 6.60 (*dd*, 1H), 6.69 (*d*, 1H), 7.02 (*d*, 1H).

Crystal data

$C_9H_{15}NO_5P^+.Cl^-$
M_r = 283.65
Orthorhombic
Pbca
a = 26.60 (1) Å
b = 12.219 (2) Å
c = 7.822 (2) Å
V = 2542 (1) Å^3
Z = 8
D_x = 1.482 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 30 reflections
θ = 14.06–37.67°
μ = 3.975 mm^{-1}
T = 293 (2) K
Very thin plate
0.35 × 0.28 × 0.12 mm
Colourless

Data collection

Siemens AED diffractometer
$\theta/2\theta$ scans
Absorption correction: none
4744 measured reflections
2412 independent reflections
1838 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.1094
θ_{max} = 70.09°
$h = -32 \rightarrow 31$
$k = -2 \rightarrow 14$
$l = -5 \rightarrow 9$
1 standard reflection monitored every 50 reflections
intensity decay: no significant variation

Refinement

Refinement on F^2
$R(F)$ = 0.1077
$wR(F^2)$ = 0.2085
S = 1.325
2412 reflections
215 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0756P)^2 + 3.3468P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.700 e Å^{-3}
$\Delta\rho_{min}$ = −0.667 e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.001 (0)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

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

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

	x	y	z	U_{eq}
P1	0.42232 (6)	0.1541 (2)	0.0551 (2)	0.0337 (5)
Cl	0.56593 (6)	0.1587 (2)	−0.1026 (2)	0.0435 (5)
O1	0.4591 (2)	0.0986 (5)	−0.0711 (6)	0.048 (2)
O2	0.4169 (2)	0.2756 (4)	0.0197 (7)	0.048 (2)
O3	0.4317 (2)	0.1351 (4)	0.2384 (6)	0.048 (2)
O4	0.3732 (1)	0.0923 (4)	−0.0071 (5)	0.033 (1)
O5	0.3343 (2)	−0.0587 (4)	0.2284 (6)	0.045 (2)
N1	0.0879 (2)	0.1002 (5)	0.2071 (7)	0.033 (2)
C1	0.2304 (2)	0.1333 (6)	0.2037 (8)	0.036 (2)
C2	0.2600 (2)	0.0446 (6)	0.2479 (8)	0.036 (2)
C3	0.3080 (2)	0.0329 (5)	0.1832 (8)	0.033 (2)
C4	0.3261 (2)	0.1110 (6)	0.0695 (8)	0.035 (2)
C5	0.2980 (3)	0.2007 (6)	0.0292 (9)	0.039 (2)
C6	0.2498 (3)	0.2127 (7)	0.0961 (9)	0.042 (2)
C7	0.1768 (2)	0.1431 (6)	0.2690 (9)	0.036 (2)
C8	0.1410 (2)	0.0820 (7)	0.1523 (10)	0.038 (2)
C9	0.0500 (3)	0.0463 (8)	0.0940 (11)	0.049 (3)

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

P1—O3	1.474 (5)	C1—C6	1.383 (10)
P1—O2	1.517 (5)	C1—C2	1.384 (9)
P1—O1	1.546 (5)	C1—C7	1.520 (8)
P1—O4	1.586 (4)	C2—C3	1.380 (9)
O4—C4	1.406 (7)	C3—C4	1.391 (9)
O5—C3	1.366 (7)	C4—C5	1.364 (9)
N1—C8	1.491 (8)	C5—C6	1.394 (9)
N1—C9	1.495 (9)	C7—C8	1.516 (9)
O3—P1—O2	110.3 (3)	C3—C2—C1	121.0 (6)
O3—P1—O1	116.4 (3)	O5—C3—C2	117.6 (6)
O2—P1—O1	111.9 (3)	O5—C3—C4	123.3 (6)
O3—P1—O4	111.3 (3)	C2—C3—C4	119.0 (6)
O2—P1—O4	109.3 (3)	C5—C4—C3	120.6 (6)
O1—P1—O4	96.7 (2)	C5—C4—O4	121.3 (6)
C4—O4—P1	121.7 (4)	C3—C4—O4	118.1 (6)
C8—N1—C9	113.7 (6)	C4—C5—C6	120.2 (6)
C6—C1—C2	119.3 (6)	C1—C6—C5	119.9 (7)
C6—C1—C7	120.0 (6)	C8—C7—C1	110.4 (5)
C2—C1—C7	120.7 (6)	N1—C8—C7	110.3 (5)

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

D—H···A	D···A
O1—H1O···Cl	2.945 (5)
O5—H5O···Cl^{i}	3.084 (5)
N1—H1N1···Cl^{ii}	3.113 (6)
N1—H1N2···Cl^{iii}	3.229 (6)
O2—H2O···O3^{iv}	2.487 (7)
N1—H1N2···O1^{v}	3.237 (8)
N1—H1N2···O4^{v}	3.406 (7)

Symmetry codes: (i) $1-x, -y, -z$; (ii) $x-\frac{1}{2}, \frac{1}{2}-y, -z$; (iii) $x-\frac{1}{2}, y, \frac{1}{2}-z$; (iv) $x, \frac{1}{2}-y, z-\frac{1}{2}$; (v) $\frac{1}{2}-x, -y, \frac{1}{2}+z$.

The integrated intensities were obtained by a modified version (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979) of the Lehmann & Larsen (1974) peak-profile analysis procedure. All reflections were corrected for Lorentz and polarization effects, but not for absorption, the sample being unsuitable for reliable experimental size or ψ-scan measurements.

The structure was solved by direct methods and refined by anisotropic full-matrix least squares. All the H atoms were found from a $\Delta\rho$ map and refined isotropically. The refinement converged smoothly for all the atoms including the H atoms, in spite of the poor quality of the intensity data

(R_{int} = 0.1094). This was due to the very poor quality of the crystal specimen which was a fragment cut from a very thin plate. This unfortunate experimental situation is reflected in the values of the *wR* and *R* indices which are rather higher than the standard values usually found for this kind of structure. Nevertheless, as sometimes happens, the molecular geometry (bond distances and angles) obtained in the present analysis is quite as expected and allows the interpretation given in the *Comment*.

The calculations were carried out on the ENCORE91 and GOULD-POWERNODE 6040 computers of the Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma), and on a COMPAQ-486c portable computer.

Data collection: local programs. Cell refinement: *LQPARM* (Nardelli & Mangia, 1984). Data reduction: local programs. Program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965) and *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *PARST* (Nardelli, 1983) and *PARSTCIF* (Nardelli, 1991).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: HA1141). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Conformation at the Amide N Atom of 1-Carboxamide Indole Derivatives

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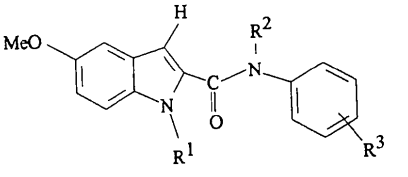
Abstract

Knowledge of the conformation at the amide N atom of *N*-3-methoxyphenyl-2-(5-methoxyindole)carboxamide, $C_{17}H_{16}N_2O_3$, and *N*-methyl-*N*-phenyl-2-(5-methoxyindole)carboxamide, $C_{17}H_{16}N_2O_2$, allows an interpretation of the ^{1}H NMR behaviour of the two compounds. The structures and conformations of the two molecules are compared.

Comment

During a study of 1-carboxamide indole derivatives, an intriguing observation was made concerning the ^{1}H NMR spectra (Caubère, Caubère, Renard, Bizot-Espiart, Jamart-Grégoire, 1994). From an examination of the aromatic part of these spectra it appears that simply changing the H atom of the amide N atom into a methyl group leads to a dramatic shielding of an aromatic or pseudo-aromatic proton. This observation is very general and effective when R^2 is different from H.



(1*a*) R^1 = H, R^2 = H, R^3 = OMe
(1*b*) R^1 = H, R^2 = Me, R^3 = H

A possible interpretation of this finding is that the presence of the methyl group forces the molecule into a conformation so that the H atom at C3 (C8 in Fig. 1) is in the shielding cone of