Conformation of 1-Benzyloxy-4-methoxypyridinium Perchlorate: X-Ray, AM1 and PM3 Studies

Zofia Dega-Szafran, Mariusz Jaskólski, Zofia Kosturkiewicz, Mirosław Szafran and Ewa Tykarska
Department of Chemistry, A. Mickiewicz University, 60780 Poznan, Poland

The crystal structure of 1-benzyloxy-4-methoxypyridinium perchlorate has been deduced from single-crystal X-ray diffraction data. The crystals are monoclinic, space group $P2_1/a$, with a = 9.254 0(7), b = 21.532(2), c = 7.335 2(8)Å, β = 102.69(1)° and Z = 4. The final R value is 0.084 for 1593 observed reflections. The molecule is extended with a *trans* conformation around the central C(1)–O(1) bond linking the phenyl and pyridine residues. The aromatic ring planes are almost perpendicular to the linking C(1)–O(1) bond and the rings are twisted 9.1(2)° to each other. The N–O distance [1.401(7) Å] is much longer than that found in pyridine *N*-oxides and is typical for an N–O single bond. Both the PM3 and AM1 methods predict that the *trans* conformer is less stable (by *ca.* 3 kcal mol^{-1}) than the *gauche* conformer in the gas phase. The problem of the conformation of the phenyl group (D) and pyridinium group (A) in compounds of the type DCH(R^1)CHR^{2}A (R^1 = R^2 = H or alkyl) is reviewed.

The conformation, in solution and in the solid state, of bridged compounds (D–CH$_2$–A, D–CH$_2$CH$_2$–A and D–O–A, where D is a substituted phenyl group and A is a heterocyclic ring) has been extensively studied.[1] Some of these compounds are used in clinical practice as nootropic drugs and activity–conformational relationships are of interest.[1e] Substituted *N*-aralkylpyridinium ions have been used as model compounds in studies on intramolecular charge-transfer (CT) interaction and on the NAD$^+$/NADH redox system.[2]

In the present work, the conformation of 1-benzyloxy-4-methoxypyridinium perchlorate, in the crystal and in the gas phase, is studied by X-ray diffraction and the AM1[3] and PM3[4] methods.

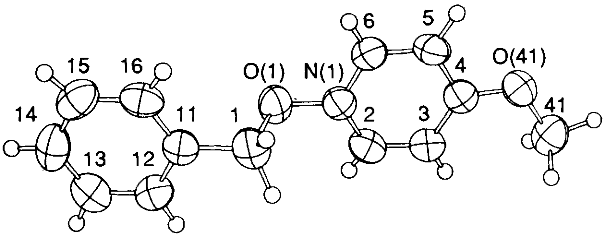

Fig. 1 ORTEP drawing of the 1-benzyloxy-4-methoxypyridinium cation in the solid state. Thermal ellipsoids are drawn at the 50% probability level.

Experimental

The synthesis of 1-benzyloxy-4-methoxypyridinium perchlorate has been described elsewhere.[5]

Single crystals were obtained from methanol–dimethyl ether. The space group was determined from oscillation and Weissenberg photographs. The intensity measurements were performed on a Syntex $P2_1$ diffractometer and the lattice parameters were determined from least-squares refinement of angular settings of 15 reflections. Reflections were measured in the 2θ range 0–115° for $0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 24$, $-9 \leqslant l \leqslant 9$ on a specimen 0.30 × 0.30 × 0.30 mm using graphite-monochromated Cu-Kα radiation (λ = 1.541 78 Å). Two standard reflections were monitored every 1.5 h, and the intensities were obtained from peak profiles according to the method of Lehmann and Larsen.[6] Of 1866 measured reflections, 1593 had $I \geqslant 2\sigma(I)$ and these were used in the calculations. The intensity data were corrected for Lorentz and polarization effects but not for absorption (μ = 26.5 cm^{-1}). The structure was solved by direct methods using SHELX76[7] and refined by minimizing $\Sigma w(|F_0| - |F_c|)^2$ in full-matrix least-squares calculations, initially with isotropic and finally with anisotropic temperature factors for all non-H atoms. Hydrogen atoms at generated positions were allowed to ride on their parent atoms (–CH$_3$ refined as a rigid group). The O atoms in the perchlorate group were refined with high temperature factors but no alternative orientation for the ClO$_4$ tetrahedron could be deduced from difference-Fourier maps. Reflection $\bar{1}32$ with high $\Delta F/\sigma$ was excluded from final refinements. The refinement converged with R = 0.084, wR = 0.080 and Δ/σ = 0.24 and the final ΔF map had residual density between −0.45 and 0.7 θ Å^{-3} (within the perchlorate group). Tables of thermal parameters and hydrogen atom coordinates have been deposited at the Cambridge Crystallographic Data Centre (CCDC).*

AM1 and PM3 semiempirical computations were performed with the MOPAC package.[8] The planarity of both phenyl and pyridine rings was assumed, but the conformation of the CH$_2$–O and OCH$_3$ fragments was optimized. All calculations were carried out with complete geometry optimization.

Results and Discussion

X-Ray Diffraction.—Final atomic parameters, bond lengths, bond angles and torsion angles are given in Tables 1–3, respectively. The labelling sequence and a view of the cation are presented in Fig. 1. The conformation around the central C(1)–O(1) bond is almost perfectly *trans* [177.7(5)°]. The phenyl and pyridine rings are planar (χ^2 10.8 and 1.51, respectively). The planes of the two rings are nearly parallel with an angle between them of 9.1(2)°. The methoxy substituent is located within the pyridine plane, and the C(5)–C(4)–O(41)–C(41) torsion angle is 176.8(6)°. The pyridine ring shows some asymmetry [bond lengths are not equal, N(1)–C(6) > N(1)–C(2); C(5)–C(6) > C(2)–C(3)].

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* For details, see 'Instructions for Authors' (1991), *J. Chem. Soc., Perkin Trans. 2*, in the January issue.

In the molecule investigated the N–O bond [1.401(7) Å] is much longer by comparison with the N–O bond (1.293 Å) in pyridine *N*-oxide[9] but is nearly identical to the single N–O bond in gaseous nitric acid [1.405(5) Å].[10] The present N–O distance is 0.2 Å beyond the upper limit in the list of N–O distances in free, H-bonded and metal-complexed pyridine *N*-oxides compiled by Eichhorn.[9] With a mean N–C distance of 1.336(9) Å, the present structure fits very well the C–N/N–O correlation in pyridine *N*-oxides.[10] By eliminating one lone pair at the O atom, the addition of the benzyl group to the *N*-oxide function reduces the resonance between the lone pairs of the O atom and the pyridine aromatic system. This increased localization of the oxygen p electrons leads to a decrease in the π-bond order of the N–O bond. Consequently, the N–O bond is lengthened and corresponds to that in aliphatic piperidine *N*-oxides [1.402(2) Å in 1,2-dipiperidinoethane mono-*N*-oxide].[11] The high temperature factors of the perchlorate O atoms (Table 1) indicate that this group is disordered, either statically or dynamically. This is consistent with the lack of any H-bond donors in this structure which would interact with the anion. The crystal packing is characterized by alternating cationic (at $z = 0,1\ldots$) and anionic (at $z = \frac{1}{2},\frac{3}{2}\ldots$) layers perpendicular to *c*. When viewed along *c* (Fig. 2), the anions superimpose over those parts of the cationic layers in which the N(1)–O(1)–C(1)–C(11) bridges are located.

Table 1 Final X-ray fractional atomic coordinates (with esds in parentheses)

Atom	*x*	*y*	*z*
Cl	0.327 6(2)	0.149 15(8)	0.587 9(2)
O(1P)	0.207 2(7)	0.188 7(3)	0.598(1)
O(2P)	0.452(1)	0.181 7(4)	0.576(2)
O(3P)	0.296(1)	0.105 5(6)	0.465(2)
O(4P)	0.367(1)	0.125 9(6)	0.759(1)
C(41)	−0.320 5(8)	0.040 0(4)	−0.297(1)
O(41)	−0.168 6(5)	0.041 2(2)	−0.193 7(6)
C(4)	−0.105 3(7)	0.095 9(3)	−0.139 3(9)
C(3)	−0.172 2(8)	0.153 4(4)	−0.182 7(9)
C(5)	0.038 7(8)	0.093 1(4)	−0.032(1)
C(6)	0.111 5(8)	0.146 7(4)	0.030(1)
N(1)	0.043 2(6)	0.201 4(3)	−0.018 1(7)
C(2)	−0.093 0(9)	0.205 0(4)	−0.123(1)
O(1)	0.124 1(5)	0.256 0(2)	0.034 6(6)
C(1)	0.083(1)	0.284 3(4)	0.198(1)
C(11)	0.171 4(7)	0.343 1(3)	0.235 4(8)
C(12)	0.108 5(8)	0.398 6(4)	0.169 8(9)
C(13)	0.189(1)	0.453 9(4)	0.204(1)
C(14)	0.333(1)	0.452 3(5)	0.305(1)
C(15)	0.397 2(9)	0.396 4(5)	0.370(1)
C(16)	0.316 6(8)	0.342 7(4)	0.337(1)

AM1 and PM3 Calculations.—In contrast with the X-ray data both the AM1 and PM3 methods predict that the *gauche* conformer [ΔH_f = 174.95 kcal mol^{-1} (AM1), and 171.08 kcal mol^{-1} (PM3)] is more stable than the *trans* conformer [ΔH_f = 178.25 kcal mol^{-1} (AM1) and 175.45 kcal mol^{-1} (PM3)] in the gas phase (Fig. 3).

The conformation differs in the crystalline state, the gas phase and solution. The *p*-anisoyl and 4-cyanopyridinium groups in *N*-[2-(*p*-anisoyl)ethyl]-4-cyanopyridinium iodide in solution occupied both *gauche* (0.7 mol fraction) and *trans* (0.3 mol fraction) positions, but only the *gauche* position in the crystalline state.[1b] On the other hand 1,2-diphenylethane[1f] and 6-(2-phenylethyl)purine[1c] were found to crystallize in a *trans* conformation. The conformation in solution and in the gas phase is controlled by the repulsion between the D and A rings[1a] and substituents in the rings can make a significant contribution. 4-Chlorophenoxymethyl-1,3-dioxolan-2-one crystallized in a twisted *trans* conformation.[12]

Optimized by the AM1 and PM3 methods, bond lengths and angles are given in Tables 2 and 3, respectively. Comparison of the PM3 geometries of the *trans* conformer with the experimental X-ray data shows that: (i) the pyridine bond lengths obtained by the PM3 method are, on average, longer by 0.031 Å (sample standard deviation σ_{n-1} = 0.011 Å) than the bond lengths determined by X-ray crystallography; (ii) the phenyl ring bond lengths predicted by the PM3 method are longer by 0.013 Å (σ_{n-1} = 0.012 Å) by comparison with the X-ray data; (iii) the N–O bond length calculated by the PM3 method is longer by 0.063 Å but that calculated by the AM1 method is shorter by 0.072 Å than that determined by X-ray crystallography; (iv) differences in the bond angles between the PM3 and X-ray data are within +1.5°; (v) two angles [O(1)–C(1)–C(11) and C(1)–O(1)–N(1)] and two bonds [N(1)–O(1) and O(1)–C(1)] are very sensitive to change of conformation; and (vii) the PM3 method predicts bond lengths and bond angles slightly better than does the AM1 method.

The data indicate that the replacement of one of the CH_2 groups by oxygen in D–CH_2–CH_2–A has essentially no effect on the conformation.

Biological activity of 1-benzyloxy-4-methoxypyridine perchlorate is unknown, but research in this field is planned.

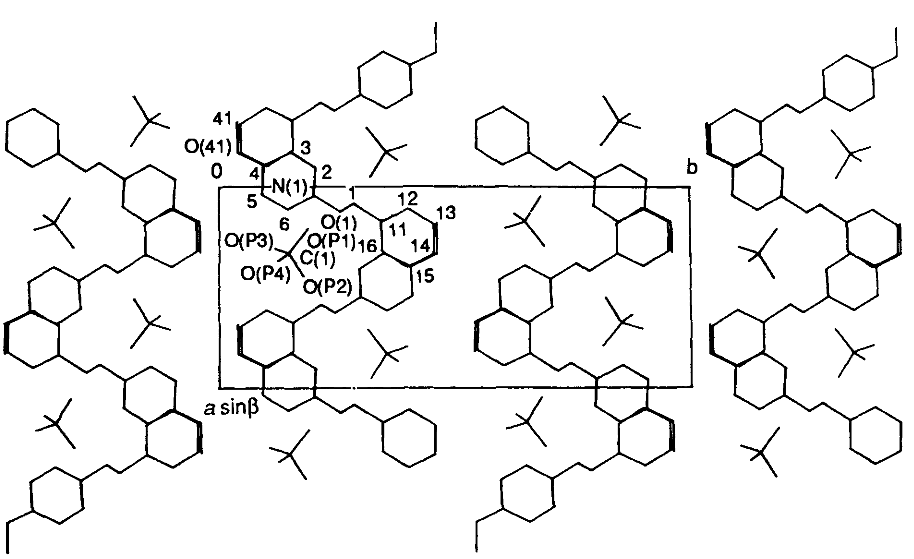

Fig. 2 Crystal packing in the 1-benzyloxy-4-methoxypyridinium perchlorate structure

Table 2 Bond lengths/Å in the solid state and isolated molecule

	X-Ray	PM3		AM1	
		trans	*gauche*	*trans*	*gauche*
N(1)-O(1)	1.401(7)	1.464	1.483	1.329	1.329
N(1)-C(2)	1.326(9)	1.373	1.371	1.378	1.378
N(1)-C(6)	1.346(9)	1.381	1.378	1.382	1.382
C(2)-C(3)	1.350(11)	1.384	1.385	1.391	1.390
C(3)-C(4)	1.389(10)	1.410	1.409	1.411	1.411
C(4)-C(5)	1.391(9)	1.421	1.421	1.422	1.423
C(5)-C(6)	1.363(10)	1.380	1.380	1.384	1.385
O(1)-C(1)	1.469(10)	1.441	1.417	1.483	1.467
C(1)-C(11)	1.498(10)	1.495	1.495	1.485	1.483
C(11)-C(12)	1.371(10)	1.396	1.396	1.400	1.401
C(12)-C(13)	1.398(11)	1.389	1.390	1.393	1.394
C(13)-C(14)	1.372(11)	1.393	1.393	1.396	1.396
C(14)-C(15)	1.383(13)	1.392	1.392	1.396	1.396
C(15)-C(16)	1.369(13)	1.390	1.390	1.393	1.394
C(16)-C(11)	1.386(9)	1.396	1.395	1.400	1.400
Cl-O(1P)	1.418(7)				
Cl-O(2P)	1.365(10)				
Cl-O(3P)	1.293(12)				
Cl-O(4P)	1.326(10)				

Table 3 Bond angles and selected torsion angles/° in the solid state and isolated molecule

	X-Ray	PM3		AM1	
		trans	*gauche*	*trans*	*gauche*
C(1)-O(1)-N(1)	110.9(5)	113.03	114.87	116.67	118.01
O(1)-N(1)-C(2)	119.5(6)	118.40	118.35	119.43	119.43
O(1)-N(1)-C(6)	118.1(5)	119.74	119.79	119.63	119.66
N(1)-C(2)-C(3)	121.3(7)	119.79	119.84	120.12	120.09
C(2)-C(3)-C(4)	118.4(7)	119.89	119.88	119.98	120.05
C(3)-C(4)-C(5)	119.4(6)	119.00	118.95	118.88	118.93
C(4)-C(5)-C(6)	119.6(7)	119.78	119.72	119.55	119.39
C(5)-C(6)-N(1)	119.0(7)	119.63	119.74	120.51	120.63
C(6)-N(1)-C(2)	122.3(6)	121.86	121.86	120.94	120.90
O(1)-C(1)-C(11)	105.7(6)	103.91	114.53	103.82	112.98
C(1)-C(11)-C(12)	120.0(6)	120.25	120.13	120.25	119.96
C(1)-C(11)-C(16)	121.3(7)	119.82	119.99	119.86	120.30
C(11)-C(12)-C(13)	120.8(7)	119.93	119.95	119.95	119.99
C(12)-C(13)-C(14)	119.3(8)	120.12	120.11	120.12	120.14
C(13)-C(14)-C(15)	120.2(8)	119.95	119.92	119.95	119.94
C(14)-C(15)-C(16)	119.8(8)	120.20	120.16	120.20	120.18
C(15)-C(16)-C(11)	121.1(7)	119.86	119.97	119.85	120.00
C(12)-C(11)-C(16)	118.7(7)	119.93	119.88	119.93	119.74
O(1P)-Cl-O(2P)	112.2(4)				
O(1P)-Cl-O(3P)	114.3(5)				
O(1P)-Cl-O(4P)	103.5(5)				
O(2P)-Cl-O(3P)	113.4(6)				
O(2P)-Cl-O(4P)	101.2(7)				
O(3P)-Cl-O(4P)	111.1(8)				
C(41)-O(41)-C(4)-C(3)	−3.6(10)	0.38	0.51	0.36	0.57
C(41)-O(41)-C(4)-C(5)	176.8(6)				
C(1)-O(1)-N(1)-C(2)	82.2(7)	99.96	103.41	92.07	90.60
C(1)-O(1)-N(1)-C(6)	−102.2(7)	−80.04	−76.59	−87.93	−119.40
O(1)-N(1)-C(2)-C(3)	177.3(6)	180	180	180	180
O(1)-N(1)-C(6)-C(5)	−175.1(6)	−180	−180	−180	−180
N(1)-O(1)-C(1)-C(11)	−177.7(5)	180	−64.73	180	−64.65
O(1)-C(1)-C(11)-C(12)	97.3(7)	105.43	114.24	109.0	114.43
O(1)-C(1)-C(11)-C(16)	−83.1(8)	−74.57	−65.76	−71.00	−67.57

Although X-ray crystal studies provide precise molecular geometry, structural determination of flexible molecules yields a solid-state conformation which may deviate considerably from that in solution. This problem is of crucial importance in biological compounds where activity is related to conformation.[13,14] The results presented can thus be helpful in any conformation-activity relationship study on this general type of compound.

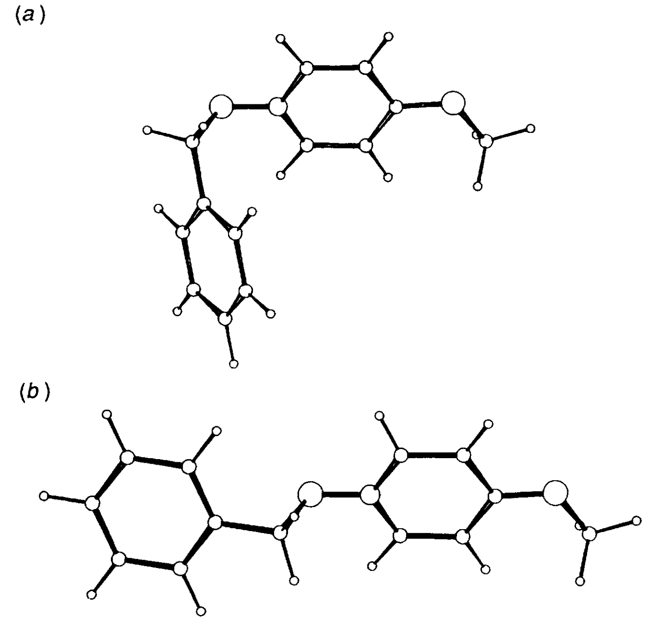

Fig. 3 Two conformations of the 1-benzyloxy-4-methoxypyridinium cation: (*a*) *gauche* and (*b*) *trans*, as calculated by the AM1 method

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