ring with the out-of-plane vibrational modes of its planar form. According to group theory there exist just $N-3$ modes and hence it is reasonable to project from $3N-6$ to $N-3$. On the other hand, no method exists which reduces from N bond (or dihedral) angles to $N-3$ conformational parameters in an exact, mathematically well defined manner (Essén & Cremer, 1984). Thus any formula based on N rather than $N-3$ parameters (bond and/or dihedral angles) cannot be used to describe a general (symmetrical or asymmetrical) puckered ring in $(N-3)$-dimensional conformation space.

PDG claim that 'there is no straightforward relation between the conformation of a ring and the corresponding CP parameters'. They elucidate their point by re-examining results given by Takagi & Jeffrey (1979) on the puckering of the perhydropyran ring of α-L-xylopyranose. The experimentally determined geometry suggests an almost perfect $^1C_4$ chair conformation with $Q=0{\cdot}575$ Å, $\theta=0{\cdot}8°$ and $\varphi=323{\cdot}2°$. Thus, it is reasonable to consider just the perhydropyran ring and to assume C_s symmetry for the chair form, which implies $\varphi=0$ or 180°. When experimental coordinates are averaged under this constraint, puckering parameters change to $Q=0{\cdot}575$, $\theta=0{\cdot}6$ and $\varphi=0°$ in perfect agreement with the values given by Takagi & Jeffrey (1979).

The averaging procedure carried out by PDG is erroneous since it tries to fix nine or ten parameters (three bond lengths, Q, φ, θ, and three or four internal angles) where only eight independent internal coordinates (*e.g.* three bond lengths, Q, φ, θ, and two internal angles) are group-theoretically allowed.

In summary, the calculational results in Tables 1, 2, 3 and Figs. 1, 2, 3 of PDG reflect the hazards of using 'standard' ring forms without defining what is meant by conformation and conformational phenomena like puckering and pseudorotation. By selecting $2N$ bond lengths and bond angles for their 'standard' ring forms, PDG violate the hierarchy of parameters inherent to the CP approach: (1) $N-3$ puckering parameters, (2) $2N-3$ bond lengths and angles. Therefore, the PDG results do not allow any judgement on the use of the CP parameters as quantitative descriptors of ring shape; in particular, they do not reveal any limitations of the CP parameters.

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The Conformations of Five Tetra- and Pentamethoxylated Phenyl Derivatives: Weberine Analogs and Polymethoprims

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(*Received* 13 *December* 1983; *accepted* 15 *May* 1984)

Abstract

Crystal and molecular structure analyses by X-ray diffraction have established the conformations of methoxy groups on phenyl rings when there are four or more adjacent methoxy groups. In three of the compounds studied, the methyl C atoms are placed alternately above and below the plane of the aryl group in a regular fashion, while in two very similar compounds there are unexpected irregularities in the rotations about the C_{Ph}–O bonds and consequent crowding of adjacent OCH_3 groups. Relative potential-energy profiles calculated by the *MM*2 program for the rotation about C_{Ph}–O bonds in the free molecules do not provide any clues for the irregularities. The unexpected methoxy conformations appear to result from packing interactions. The structures determined were those of 5,6,7,8-tetramethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (1-methylweberine.HCl) (compound 2) $[C_{15}H_{24}NO_4^+.Cl^-]$, $M_r=317{\cdot}81$, *Pbca*, $a=10{\cdot}262\,(4)$, $b=17{\cdot}865\,(4)$, $c=18{\cdot}127\,(4)$ Å, $V=3323{\cdot}23$ Å^3, $Z=8$, $D_x=1{\cdot}270$ g cm^{-3}, $F(000)=1360$,

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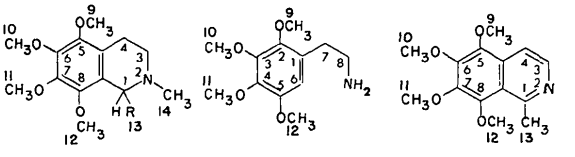
0108-7681/84/050500-07$01.50 © 1984 International Union of Crystallography

$R = 6{\cdot}8\%$ for 2009 reflections]; 2-(2,3,4,5-tetramethoxyphenyl)ethylamine hydrochloride (compound 3) [$C_{12}H_{20}NO_4^+.Cl^-$, $M_r = 277{\cdot}75$, $P2_1/a$, $a = 10{\cdot}646\ (8)$, $b = 7{\cdot}623\ (6)$, $c = 18{\cdot}862\ (10)$ Å, $\beta = 104{\cdot}47\ (6)°$, $V = 1482{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}244$ g cm^{-3}, $F(000) = 592$, $R = 7{\cdot}7\%$ for 1105 reflections]; 5,6,7,8-tetramethoxy-1-methylisoquinoline hydrochloride (compound 4) [$C_{14}H_{18}NO_4^+.Cl^-$, $M_r = 311{\cdot}76$, $P\bar{1}$, $a = 9{\cdot}298\ (4)$, $b = 9{\cdot}679\ (4)$, $c = 9{\cdot}664\ (4)$ Å, $\alpha = 80{\cdot}77\ (3)$, $\beta = 63{\cdot}44\ (3)$, $\gamma = 70{\cdot}36\ (3)°$, $V = 732{\cdot}7$ Å^3, $Z = 2$, $D_x = 1{\cdot}359$ g cm^{-3}, $F(000) = 316$, $R = 4{\cdot}9\%$ for 1787 reflections]; 2,4-diamino-5-(2,3,4,5-tetramethoxybenzyl)pyrimidine (tetramethoprim) (compound 6) [$C_{15}H_{20}N_4O_4$, $M_r = 320{\cdot}35$, $P2_1/n$, $a = 12{\cdot}335\ (10)$, $b = 11{\cdot}828\ (10)$, $c = 12{\cdot}511\ (10)$ Å, $\beta = 119{\cdot}00\ (6)°$, $V = 1596{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}333$ g cm^{-3}, $F(000) = 680$, $R = 10{\cdot}3\%$ for 1075 reflections]; 2,4-diamino-5-(2,3,4,5,6-pentamethoxybenzyl)pyrimidine (pentamethoprim) (compound 7) [$C_{16}H_{22}N_4O_5$, $P\bar{1}$, $a = 6{\cdot}016\ (4)$, $b = 8{\cdot}319\ (5)$, $c = 18{\cdot}613\ (10)$ Å, $\alpha = 82{\cdot}73\ (5)$, $\beta = 83{\cdot}58\ (5)$, $\gamma = 89{\cdot}29\ (5)°$, $V = 918{\cdot}3$ Å^3, $Z = 2$, $D_x = 1{\cdot}267$ g cm^{-3}, $F(000) = 372$, $R = 8{\cdot}6\%$ for 1531 reflections]. Rotations about the two bonds linking the aryl groups are similar in pentamethoprim and trimethoprim but quite different from tetramethoprim. Relative potential energies for both conformations are similar. Only trimethoprim exhibits potent antifolate activity.

Introduction

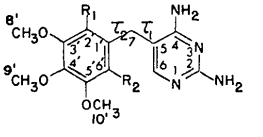
Crystal structure analyses of numerous compounds containing a monomethoxyphenyl moiety show that the overwhelmingly preferred conformation for the OCH_3 group has the C atom of the methyl group coplanar with the phenyl ring, *i.e.* the torsional angle is within 7° of zero. One H atom of the methyl group is *trans* with respect to the C_{Ph}–O bond and the remaining two H atoms straddle an H atom on an adjacent C in the phenyl ring, Fig. 1(*a*). *o*-Dimethoxyphenyl moieties, with very few exceptions, also have the O, C and H (*trans* to the C_{Ph}–O) atoms in both OCH_3 groups coplanar with the plane of the phenyl ring, Fig. 1(*b*), if there is an H atom on the adjacent C in the phenyl group. A substituent larger than H will hinder coplanarity, except perhaps F where the $C_{Me}\cdots F$ distance may be very nearly the same as the $C_{Me}\cdots H$ distance of 2·48 Å. However, the van der Waals radius of F is larger than that of H by ~0·15 Å. A survey of monomethoxy- and *o*-dimethoxyphenyl structures has been published by Anderson, Kollman, Domelsmith & Houk (1979). Spatial considerations for three adjacent methoxy groups predict from simple arguments that the methyl C of the central methoxy be directed nearly perpendicularly out of the plane of the phenyl as has been found in the structures of reserpine (Karle & Karle, 1968) or trimethoprim (Koetzle & Wiliams, 1976), for example. In these molecules the two outer OCH_3 groups are adjacent to H atoms on the phenyl group and, consequently, are coplanar with the phenyl group, Fig. 1(*c*).

Recently, the aromatic, tetramethoxy tetrahydroisoquinoline alkaloid, called weberine (1), has been isolated from the Mexican cactus *Pachycereus weberi* (Mata & McLaughlin, 1980). The rare occurrence of four adjacent OCH_3 groups on an aryl moiety prompted the present study. Crystal structure analyses of 1-methylweberine.HCl (2), two tetramethoxy weberine analogs (3) and (4), and the tetramethoxy (6) and pentamethoxy (7) analogs of trimethoprim (5) are reported. These compounds were synthesized by Takahashi & Brossi (1982) and brought to our attention. The numbering scheme is shown below (O atoms and amino N atoms have the same numbers as the ring C atoms to which they are bonded).

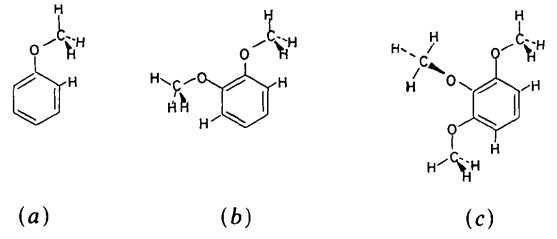


(1) R = H
(2) R = CH_3

(3) (4)



(5) $R_1 = R_2 = H$
(6) $R_2 = H$, $R_1 = OCH_3$
(7) $R_1 = R_2 = OCH_3$



(*a*) (*b*) (*c*)

Fig. 1. Preferred conformations of methoxy groups on phenyl rings. (*a*) Monomethoxy. (*b*) *o*-Dimethoxy. (*c*) *o*-Trimethoxy.

In addition to analyzing and comparing the crystalline conformations of the sterically hindered methoxy groups, some theoretical calculations for minimum potential energy that concern hindered rotation and preferred conformations about C_{Ph}–O bonds in the weberine analogs and in the polymethoprims are presented. The different conformations in tetramethoprim and pentamethoprim about the bonds joining the two aryl rings are compared to trimethoprim (Koetzle & Williams, 1976), a potent antifolate drug.

Table 1. *Experimental data*

	(2)	(3)	(4)	(6)	(7)
Crystal size (mm)	0·20×0·10×0·05	0·25×0·05×0·03	0·20×0·08×0·05	0·20×0·10×0·03	0·70×0·06×0·02
Max. 2θ (°)	112	110	112	40	42
Max. h, k, l	10, 19, 17	9, 8, ±20	10, ±10, ±10	±11, 11, 10	±6, ±8, 18
No. independent reflections	2116	1517	1787	1498	1960
No. reflections used in least squares	$2009>3\sigma$	$1105>3\sigma$	1787	$1075>2\sigma$	$1531>2\sigma$
Radiation	Cu	Cu	Cu	Mo	Mo
R (%)	6·8	7·7	4·9	10·3	8·6
R_w (%)	8·8	9·3	4·2	6·5	6·2
S	3·5	2·9	0·6	1·5	1·6
$(\Delta/\sigma)_{max}$	0·20	0·67	0·56	0·11	0·40

Table 2. *Fractional coordinates and B_{eq} values* (Å^2) *for molecule* (2)

The e.s.d.'s are near 0·0004 for x, and 0·0002 for y and z.

	x	y	z	B_{eq}
C(1)	0·7887	0·0985	0·4505	3·45
N(2)	0·8418	0·1229	0·5243	3·45
C(3)	0·8153	0·2047	0·5384	3·71
C(4)	0·8930	0·2513	0·4845	3·71
C(4a)	0·8845	0·2224	0·4070	3·17
C(5)	0·9288	0·2672	0·3490	3·20
C(6)	0·9229	0·2431	0·2767	3·33
C(7)	0·8763	0·1713	0·2609	3·59
C(8)	0·8379	0·1253	0·3189	3·32
C(8a)	0·8384	0·1504	0·3912	3·00
C(9)	0·9061	0·3995	0·3485	4·89
C(10)	1·0869	0·2829	0·1956	5·60
C(11)	0·7477	0·1357	0·1583	6·53
C(12)	0·8951	0·0024	0·2839	6·43
C(13)	0·6402	0·0917	0·4497	4·77
C(14)	0·7946	0·0760	0·5874	4·77
O(5)	0·9862	0·3356	0·3655	3·98
O(6)	0·9563	0·2903	0·2195	3·91
O(7)	0·8753	0·1478	0·1890	4·77
O(8)	0·7943	0·0532	0·3047	4·02
Cl^-	0·1285	0·0998	0·5228	4·02

Table 3. *Fractional coordinates and B_{eq} values* (Å^2) *for molecule* (3)

The e.s.d.'s are near 0·0009 for x, 0·0010 for y and 0·0005 for z.

	x	y	z	B_{eq}
N(1)	0·3730	1·3222	0·0369	4·84
C(1)	0·5828	1·1487	0·2165	4·40
C(2)	0·5479	1·1934	0·2798	4·23
C(3)	0·5815	1·0841	0·3409	4·58
C(4)	0·6552	0·9344	0·3401	4·37
C(5)	0·6921	0·8916	0·2758	4·57
C(6)	0·6541	0·9992	0·2143	4·71
C(7)	0·5430	1·2603	0·1491	5·22
C(8)	0·4061	1·2223	0·1081	4·60
C(9)	0·5410	1·4768	0·3272	6·67
C(10)	0·4137	1·0978	0·4036	7·71
C(11)	0·7979	0·8756	0·4521	6·87
C(12)	0·7968	0·6874	0·2137	7·58
O(2)	0·4716	1·3416	0·2807	5·05
O(3)	0·5480	1·1244	0·4053	5·12
O(4)	0·6873	0·8262	0·3998	5·44
O(5)	0·7666	0·7416	0·2796	5·36
Cl^-	0·4120	0·7357	0·0501	4·90

Experimental procedure

Crystal data for compounds (2), (3), (4), (6) and (7) are listed in the *Abstract*. Intensity data measured on the Nicolet $R3m$ four-circle automatic diffractometer, graphite monochromator, scan width 2°, variable scan speed, θ–2θ mode. Reference reflections checked every 60 measurements and found to remain constant for all five crystals. 12 to 21 centered reflections used to determine the cell parameters. Some of the crystals were extremely tiny and scattered very weakly. Absorption corrections not applied.

All of the structures were solved by direct phase determination using in-house programs and refined by full-matrix anisotropic least squares (Busing, Martin, Levy, Ellison, Hamilton, Johnson & Thiessen, 1975). $\sum w\|F_o|-|F_c\|^2$ minimized, where w is based on counting statistics and includes a term for random error set equal to 0·02 (Gilardi, 1973). Atomic scattering factors from *International Tables for X-ray Crystallography* (1974). H atoms placed in idealized positions. Coordinates for H atoms were refined in structures (2), (3) and (4) and kept constant in structures (6) and (7). Additional experimental details are given in Table 1. Coordinates and B_{eq} values ($B_{eq}=\frac{1}{3}\sum_i\sum_j B_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$) are listed in Tables 2–6.† Torsional angles for molecules (2), (3) and (4) are listed in Table 7 and those for molecules (5), (6) and (7) are listed in Table 8.

Results

Two separate conformational problems resulted from the study of the structures of (2), (3), (4), (6) and (7). The first concerned the original intention of determining the conformations of hindered OCH_3 groups, and the second resulted from rotations about the two bonds between the rings in the polymethoprims. They will be discussed separately.

Methoxy conformations

Figs. 2 and 3 show the structures of (2), (3) and (4), and (5), (6) and (7), respectively. Immediately apparent is the coplanarity with the aromatic group

† Lists of structure factors, anisotropic thermal parameters, bond lengths and bond angles, and coordinates for H atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39464 (56 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 4. *Fractional coordinates and B_{eq} values* (Å^2) *for molecule* (4)

The e.s.d.'s are near 0·0003 for all coordinates.

	x	y	z	B_{eq}
C(1)	0·3216	0·4335	1·1883	2·3
N(2)	0·3927	0·4559	1·2729	2·7
C(3)	0·5544	0·3830	1·2529	2·8
C(4)	0·6514	0·2803	1·1440	2·7
C(4a)	0·5867	0·2479	1·0489	2·2
C(5)	0·6847	0·1368	0·9382	2·5
C(6)	0·6197	0·1011	0·8499	2·7
C(7)	0·4568	0·1852	0·8631	2·5
C(8)	0·3587	0·2948	0·9706	2·2
C(8a)	0·4191	0·3280	1·0695	2·1
C(9)	0·9809	0·0539	0·7779	4·1
C(10)	0·7201	−0·0398	0·6186	5·1
C(11)	0·3645	0·2554	0·6617	4·2
C(12)	0·0760	0·2992	1·0482	3·3
C(13)	0·1411	0·5216	1·2369	3·2
O(5)	0·8429	0·0621	0·9285	3·3
O(6)	0·7149	−0·0213	0·7642	3·7
O(7)	0·3941	0·1476	0·7753	3·2
O(8)	0·2019	0·3756	0·9811	2·6
Cl^-	0·7991	0·3259	0·4692	3·6

Table 5. *Fractional coordinates and B_{eq} values* (Å^2) *for molecule* (6)

The e.s.d.'s are near 0·0008 for all coordinates.

	x	y	z	B_{eq}
N(1)	0·1382	0·4222	0·1201	3·6
C(2)	0·0647	0·3938	0·1663	3·5
N(2)	−0·0502	0·4406	0·1126	4·3
N(3)	0·0921	0·3230	0·2571	3·3
C(4)	0·2037	0·2728	0·3092	3·4
N(4)	0·2289	0·1987	0·3997	4·2
C(5)	0·2912	0·2981	0·2705	3·1
C(6)	0·2523	0·3728	0·1743	3·9
C(7)	0·4186	0·2426	0·3307	3·8
C(1′)	0·5024	0·2921	0·2841	3·0
C(2′)	0·5693	0·3905	0·3326	3·4
C(3′)	0·6394	0·4381	0·2848	3·2
C(4′)	0·6424	0·3879	0·1882	3·2
C(5′)	0·5706	0·2917	0·1359	3·3
C(6′)	0·5038	0·2413	0·1846	3·8
O(2′)	0·5618	0·4397	0·4285	4·9
O(3′)	0·7064	0·5344	0·3343	4·6
O(4′)	0·7132	0·4322	0·1391	4·3
O(5′)	0·5752	0·2535	0·0338	4·4
C(7′)	0·6709	0·4315	0·5455	6·9
C(8′)	0·6339	0·6339	0·3250	7·3
C(9′)	0·6800	0·5382	0·0810	6·6
C(10′)	0·5064	0·1513	−0·0202	6·4

Table 6. *Fractional coordinates and B_{eq} values* (Å^2) *for molecule* (7)

The e.s.d.'s are near 0·0010 for x, 0·0007 for y and 0·0003 for z.

	x	y	z	B_{eq}
N(1)	1·0098	0·7914	0·5454	4·2
C(2)	0·8120	0·7753	0·5204	4·2
N(2)	0·7344	0·9063	0·4788	5·5
N(3)	0·6847	0·6423	0·5322	4·0
C(4)	0·7558	0·5140	0·5749	3·8
N(4)	0·6248	0·3814	0·5849	4·4
C(5)	0·9571	0·5187	0·6062	3·5
C(6)	1·0760	0·6589	0·5881	4·3
C(7)	1·0452	0·3751	0·6533	4·1
C(1′)	0·9218	0·3420	0·7291	3·8
C(2′)	0·7802	0·2092	0·7493	3·9
C(3′)	0·6753	0·1738	0·8203	3·8
C(4′)	0·7156	0·2719	0·8723	4·6
C(5′)	0·8592	0·4042	0·8540	4·6
C(6′)	0·9571	0·4401	0·7830	4·1
O(2′)	0·7344	0·1126	0·6973	4·9
O(3′)	0·5373	0·0403	0·8395	4·9
O(4′)	0·6054	0·2397	0·9417	6·2
O(5′)	0·9051	0·4988	0·9062	6·5
O(6′)	1·0909	0·5755	0·7626	5·1
C(7′)	0·8343	−0·0422	0·7037	7·1
C(8′)	0·3160	0·0657	0·8211	8·0
C(9′)	0·7312	0·1513	0·9926	9·2
C(10′)	0·7545	0·6208	0·9205	9·1
C(11′)	1·3084	0·5648	0·7875	7·9

Table 7. *Torsional angles* (°) *in* (2), (3) *and* (4)

E.s.d.'s are ~1°.

Angle in (2) and (4)	(4)	(2)	(3)	Angle in (3)
			−174	N(1)–8–7–1
3–4–4a–5	−177	167	100	8–7–1–6
4a–5–O(5)–9	−127	−107	−113	1–2–O(2)–9
5–6–O(6)–10	−148	95	73	2–3–O(3)–10
6–7–O(7)–11	−116	−114	−87	3–4–O(4)–11
7–8–O(8)–12	72	73	175	4–5–O(5)–12

Table 8. *Torsional angles* (°) *in trimethoprim* (5), *tetramethoprim* (6) *and pentamethoprim* (7)

E.s.d.'s are ~1° in (6) and (7).

	(5)*	(6)	(7)
τ_1 = 4–5–7–1′	−89	−174	−74
τ_2 = 5–7–1′–2′	153	84	108
1′–2′–O(2′)–7′		109	108
2′–3′–O(3′)–8′	−5	−64	−82
3′–4′–O(4′)–9′	−101	−66	98
4′–5′–O(5′)–10′	−172	178	−84
5′–6′–O(6′)–11′			74

* Koetzle & Williams (1976).

of methoxy groups adjacent to H atoms in (3) and (6), and of course in (5) as previously mentioned in accordance with the observations of planar conformations in mono- and *o*-dimethoxy aromatic compounds. All the other OCH_3 moieties in these compounds are crowded by neighboring OCH_3 groups or other substituents and consequently the methyl C atoms are rotated above or below the plane of the aromatic moiety.

A pleasing and orderly arrangement of methoxy groups in which the methyl groups are alternately rotated above and below the plane of the phenyl is exhibited by pentamethoprim (7), Fig. 3. The torsional angles about the C_{Ph}–O bonds, listed in Table 8, are within 18° of ±90°. A similar regular alternation of the direction of methyl groups occurs in (2) and in (3), Fig. 2 and Table 7, except for the methoxy adjacent to an H atom which is coplanar with the phenyl. Furthermore, in molecules (2), (3) and (7), the CH_3 group on C(1), the alkylamine chain and the pyrimidine substituent, respectively, offer first- and second-neighbor atoms to the phenyl groups with a geometry that simulates an OCH_3 substituent. Importantly, the adjacent OCH_3 groups are oriented in opposite directions to the second exocyclic nonhydrogen atom. A generalization for the disposition of methoxy groups cannot be made, however, because their arrangment is at variance with the above scheme in compounds (4) and (6), Figs. 2 and 3. In (6) the methyl groups would have been expected to be down, up, down, planar, but instead, they are directed down,

up, up, planar. In (4) the disposition of three OCH_3 groups is the same as in (2). The OCH_3 group on C(6), however, has a torsion angle of −148° in (4) as compared to +95° in (2). In (4) the methyl groups on the methoxy moieties are directed up, somewhat up, up and down with respect to the planar aromatic group.

These apparent anomalies in very similar molecules suggested a closer inspection of geometric parameters. The C–C–O bond angles in all six molecules fall into two groups: 120° (±1°) for the 19 methoxy groups not coplanar with the phenyl ring and 125° for the two coplanar methoxy groups. These values are in agreement with those found in the survey of mono-, *o*-di- and *o*-trimethoxy compounds (Anderson *et al.*, 1979). The neighboring $O\cdots CH_3$ distances are a factor that limits the rotation about the C_{Ph}–O bond. These distances cluster between 3·0–3·6 Å except for two very short approaches in (4) where $O(6)\cdots C(9) = 2{\cdot}86$ and $O(7)\cdots C(10) = 2{\cdot}80$ Å. The closest intramolecular $CH_3\cdots CH_3$ distance [$C(10)\cdots C(11) = 3{\cdot}47$ Å] also occurs in (4). However, there appears to be no clue here for the anomalous conformations of the OCH_3 groups.

An examination of space-filling models shows that with some difficulty it is possible to rotate adjacent OCH_3 groups past each other. In fact, the model shows the possibility of having all methyl groups directed to the same side of the phenyl ring. As a consequence, a limited number of calculations were performed with the molecular-mechanics program *MM2* of Allinger & Yuh (1980) (see also Allinger, 1976), in order to compare relative potential-energy values upon rotation about some of the C_{Ph}–O bonds. The starting parameters for each molecule were those established in the crystal structure analyses. Relative energy values were calculated for rotations at 45° intervals about the C(6)–O(6) bonds in (2) and (4) and about the C(4′)–O(4′) bonds in (6) and (7).

The results of the calculations for the free molecules are shown by the potential-energy curves in Figs. 4 and 5 where the heavy bars indicate the conformation found in the crystalline state. In each case the calculated minimum energy occurs near +90°, the value

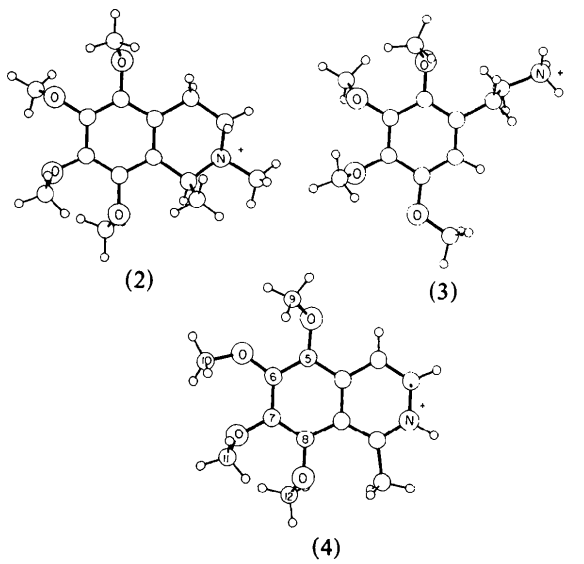


Fig. 2. Conformations of (2), (3) and (4). The figures were drawn by computer (*ORTEP*, Johnson, 1965) using the experimentally determined coordinates.

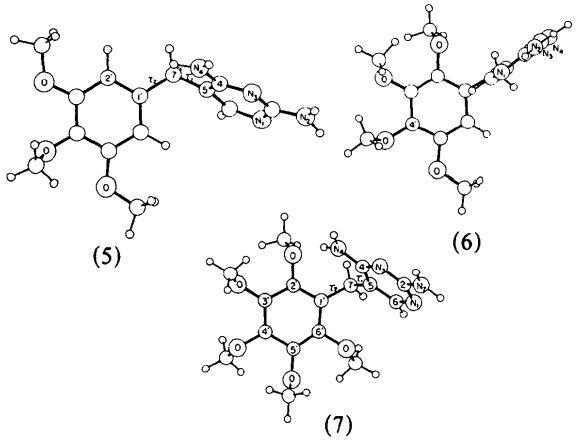


Fig. 3. Conformations of trimethoprim (5), tetramethoprim (6), and pentamethoprim (7) in the crystalline state.

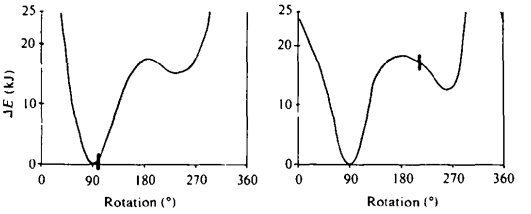


Fig. 4. Calculated potential-energy profiles for the rotation about the C(6)–O(6) bonds in (2) (left) and (4) (right) in the free molecules. The experimentally determined torsion angles in the crystals of (2) and (4) are shown by the heavy bars.

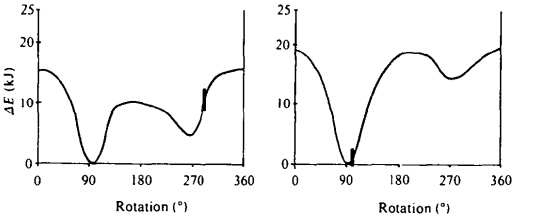


Fig. 5. Calculated potential-energy profiles for the rotation about the C(4′)–O(4′) bonds in (6) (left) and (7) (right) in the free molecules. The experimentally determined torsion angles in the crystals of (6) and (7) are shown by the heavy bars.

expected for adjacent OCH_3 groups alternating up and down as in (2) and (7). For molecule (4), the crystalline orientation of the OCH_3 on C(6) occurs near a secondary maximum that is 20 kJ above the minimum energy. For molecule (6), the orientation of the OCH_3 on C(4′) occurs in the crystal near a secondary minimum at a rotation angle that is 11 kJ above the minimum energy. Thus, the unexpected orientations of the OCH_3 groups found in the crystalline state are not explained by the molecular-mechanics calculations for free molecules as reported here. It appears that in polymethoxyphenyl compounds, adjacent OCH_3 can both be rotated to the same side of the phenyl group and that conformational predictions cannot be made easily even in very similar molecules.

An examination of the crystal packing shows that the packing is dominating the selection of conformation for the OCH_3 groups, particularly the unusual conformations of the OCH_3 on C(6) in (4) and the OCH_3 on C(4′) in (6). In each case, rotation about the C_{Ph}–O bond brings the CH_3 group much too close to atoms in neighboring molecules. In (6), for example, the more 'normal' position for C(9′) of the OCH_3 group on C(4′) brings that atom within 2·6 Å of N(2) at $1+x, y, z$.

A point of interest is that the crystal density for (4) and (6) with the aberrant conformations for OCH_3 groups is significantly higher, 1·36 and 1·33 g cm^{-3} respectively, than the density for the similar substances (2), (3) and (7) with the expected conformations for OCH_3 groups, 1·24 to 1·27 g cm^{-3} (see *Abstract*). The higher density values imply that intermolecular separations are smaller and, consequently, that thermal parameters, especially for peripheral atoms, are smaller. Both effects are observed in these compounds. In comparing (6) and (7), in (6) there are five intermolecular approaches between the C atoms of CH_3 groups and atoms in neighboring molecules, specifically C(7′)···O(2′), C(8′)···N(3), C(8′)···O(5′), C(9′)···N(2) and C(10′)···N(3), that range between 3·32 and 3·44 Å while in (7) none of the CH_3 groups are involved in intermolecular approaches closer than 3·47 Å. Associated with the tighter packing are smaller B_{eq} values. For atoms C(7′) to C(10′) in (6), the B_{eq} values range from 6·4–7·3 Å^2, whereas in (7) the comparable atoms have B_{eq} values of 7·1–9·2 Å^2. Similarly in (4), aside from the hydrogen bond between N^+H–Cl^- (3·00 Å), there are the following short approaches between molecules: C(3)···Cl^- (3·59 Å); C(6)···C(6) (3·54 Å); C(6)···C(7) (3·60 Å); C(9)···C(10) (3·58 Å); while in (2) and (3), aside from N^+H–Cl^- hydrogen bonds, all intermolecular distances are larger, consistent with the lower density for (2) and (3). In addition, the B_{eq} values for atoms C(9) to C(12) in (4) are only 3·3–5·1 Å^2 whereas they are 4·9–6·4 Å^2 in (2) and 6·7–7·7 Å^2 in (3).

Thus, molecules (4) and (6) occur in a higher-energy state than (2), (3) and (7), but pack more efficiently in the crystal lattice. There may be a compensation between the two effects.

Polymethoprim conformations

Aside from the OCH_3 groups, the tri-, tetra- and pentamethoprims have only two degrees of conformational freedom which can be described by rotations about the C(5)–C(7) and C(1′)–C(7) bonds labeled τ_1 and τ_2. Koetzle & Williams (1976) calculated a potential-energy map for trimethoprim as a function of rotations about τ_1 and τ_2. Their plot indicated that the free molecule can assume a large variety of conformations with all values of τ_2 allowable and with some restrictions on τ_1. The crystalline conformation of trimethoprim had $\tau_1 = -89°$ and $\tau_2 = +153°$. In pentamethoprim, $\tau_1 = -74°$ and $\tau_2 = +108°$, relatively close to the conformation of trimethoprim. Tetramethoprim, on the other hand, has assumed a quite different conformation with $\tau_1 = -174°$ and $\tau_2 = +84°$, Fig. 3. These latter values for tetramethoprim do fall in a low-energy region on the trimethoprim energy plot. Again, with space-filling models it is possible to twist from one of the above conformations to the other, even for the pentamethoprim with the additional OCH_3 groups that do hinder some of the rotational possibilities.

Calculations with the *MM*2 program of the conformational potential energy for tetramethoprim (6) with τ_1 and τ_2 as found in the crystal and also with τ_1 and τ_2 values as found for trimethoprim (5) showed a $\Delta E = 11$ kJ. A similar calculation for pentamethoprim (7) with the experimentally found τ_1 and τ_2 and also the τ_1 and τ_2 values from trimethoprim resulted in $\Delta E = 3$ kJ.

The association of pentamethoprim molecules in the crystal is very similar to that in the trimethoprim crystal. An infinite ribbon of pyrimidine moieties is formed in which each 2,4-diaminopyridine ring makes pairs of hydrogen bonds with two others around two different centers of symmetry. The pairs of hydrogen bonds formed are N(2)H···N(1), N(4)H···N(3) and their symmetry equivalents. The N(2)···N(1) and N(4)···N(3) distances are 2·92 and 3·04 Å, respectively.

The tetramethoprim not only has a different conformation, but also packs differently in the crystal. Only N(1) and N(2)H participate in a pair of hydrogen bonds around the origin where N(1)···N(2) = 3·04 Å, while N(3) and N(4) do not participate in any hydrogen bonding.

Despite structural and conformational similarities, only trimethoprim has a broad spectrum of antibacterial properties. Tetramethoprim and pentamethoprim did not exhibit any noteworthy antibacterial properties *in vitro* (Brossi, Sharma, Takahashi,

Chiang, Karle & Seibert, 1983). Diaveridine, a molecule like trimethoprim with a similar conformation and similar packing but lacking one of the OCH_3 groups (Koetzle & Williams, 1978), has some antibacterial activity, but much less than trimethoprim. This remarkable difference in antibacterial properties appears to be associated with the number of methoxy groups and their disposition, not with the orientation of the two aryl groups with respect to each other. Increasing the number of methoxy groups, particularly since they protrude above and below the plane of the phenyl ring, obviously increases the thicknesss of this part of the molecule. Another factor that may be associated with the biological activity is the accessibility of the O atoms and the attractive forces they represent. In the tetra- and pentasubstituted molecules, the CH_3 groups tend to shield the O atoms from the exterior, while in trimethoprim the three O atoms present a concerted charge density to the exterior. Diaveridine, which exhibits partial activity, has only two O atoms to present to the exterior.

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The Structure and Thermal Motion of Phosphorylethanolamine at 122 K from Neutron Diffraction

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(*Received* 15 *December* 1983; *accepted* 5 *March* 1984)

Abstract

At 122 K, the crystal structure of phosphorylethanolamine ($C_2H_8NO_4P$) is monoclinic, space group $P2_1/c$, $Z=4$, with $a=9{\cdot}015\ (1)$, $b=7{\cdot}745\ (1)$, $c=8{\cdot}788\ (2)$ Å, $\beta=102{\cdot}51\ (1)°$, $\lambda=1{\cdot}0470\ (1)$ Å, $\mu=0{\cdot}233\ mm^{-1}$. Full-matrix least-squares refinement based on 2473 neutron reflections with $\sin\theta/\lambda \leq 0{\cdot}79\ Å^{-1}$ gave convergence with $R_w(F^2)=0{\cdot}041$. Nuclear anisotropic thermal parameters have been analyzed to describe the molecular thermal motion including non-rigid vibrations. Librational corrections for the bond lengths [*maximum* 0·008 (1) Å] are highly significant in terms of the e.s.d.'s in uncorrected values [0·001 Å or less]. The C–H distances with both harmonic librational and anharmonic stretching-motion corrections range from 1·095 (4) to 1·099 (4) Å. These are estimated r_e bond lengths in satisfactory agreement with values determined for C–H theoretically and by other experimental methods. The conformation at the P–O bonds in the monoester H–O–P–O–C group is (+)-*ac*, (−)-*sc*. The terminal O–H and NH_3 groups are twisted 40° and 20° respectively from ideally staggered

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0108-7681/84/050506-06$01.50

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