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On the Conformation of Methoxy Groups in the Crystal Structures of *o*-Dimethoxybenzene Derivatives

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Abstract

Among 32 crystal structures of compounds bearing *o*-methoxy substituents, the planar conformation is preferred in 30 cases; only two structures contain a non-planar methoxy group. The present work tries to explain these differences in conformational properties.

I. Introduction

It is remarkable that, in spite of the absence of steric hindrance, *o*-dimethoxybenzene derivatives exist with a non-planar conformation in the gas phase. Partition coefficients, dipole moments and dielectric relaxation times also indicate the presence of a non-planar conformation. *Ab initio* STO3G calculations for non-planar *o*-dimethoxybenzene derivatives are in much better agreement with the photoelectron spectra of the compounds studied than are the calculations for the planar compounds (Anderson, Kollman, Domelsmith & Houk, 1979).

On the other hand, crystal structures of numerous methoxy-substituted aromatics have been examined but, of 32 crystals studied, only two exhibit non-planar *o*-dimethoxy structures. It was interesting to study

these two and some of the other 30 structures for comparison, with the aim of explaining why one conformation is preferred over another for a given crystal structure.

The only non-planar compounds are trimethylated catechinic acid (McCandlish, Hanson & Stout, 1976) and mesembranol (Luhan & McPhail, 1973). Among the planar conformations, we have chosen four structures: (1) *N*-demethyl-*N*-formylmesembrenone (Karle, 1977); (2) polycarpine (Damak & Riche, 1977); (3) tetra-*O*-methyldehydrocaffeic acid dilactone (Nakamura, Iitaka, Kumada, Takeuchi & Umezawa, 1977); (4) 2-amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole (Ekstrand & van der Helm, 1977).

The use of only four of the planar compounds was motivated by computation-time considerations: the large sizes of the molecules demanded a significant amount of time for each case. No systematic consideration was involved in the choice of the molecules themselves, however.

II. Method

The method of computing the crystal lattice energy has been described extensively in preceding papers (Caillaet

& Claverie, 1974, 1975, 1980; Caillet, Claverie & Pullman, 1976, 1977, 1978*a,b*).

The main features of the method follow: The interaction energy is considered as the sum of the long-range contributions (electrostatic, polarization and dispersion) and a short-range contribution (repulsion). To reduce the computation time, the point-dipole approximation is used when the intermolecular distance is large enough. All these energies are expressed as a sum of atom-atom contributions, except for the polarization energy which is not pair-wise additive; this term is expressed as the sum of polarization energies of all molecules, each of these energies being obtained by using the electric field created by all the other molecules. The charge distributions of the molecules were obtained with the CNDO method; it must be emphasized that, besides the atomic net charges, the atomic (hybridization) dipoles were taken into account. However, these dipoles were not used directly, but replaced by effective atomic charges (obtained from the decomposition of the atomic dipoles along the bonds), and these charges, when added to the atomic charges proper, give rise to effective total charges (Claverie, 1978). Very recently, a thorough comparative study (Langlet, Claverie, Caron & Boeue, 1981) has shown that this simplified molecular charge distribution gives values of the electrostatic term that are too weak when compared with the values given by much more elaborate charge distributions provided by *ab initio* calculations (charges, dipoles and quadrupoles located at the atoms, and at the middles of segments joining the atoms, among which essentially the chemically bonded ones). Fortunately, this systematic bias causes no serious problem for the present study, because the dispersion and short-range repulsion play an essential role here, as will appear from the results displayed below.

III. Results and discussion

Crystal data for all the crystals studied are summarized below.

(a) Non-planar conformations

(1) Trimethylated catechic acid (A) (McCandlish *et al.*, 1976). Crystal data: orthorhombic, $P2_12_12_1$, $a = 16.703$, $b = 13.286$, $c = 7.32$ Å, $Z = 4$.

(2) Mesembranol (B) (Luhan & McPhail, 1973). Crystal data: monoclinic, $P2_1$, $a = 13.45$, $b = 7.84$, $c = 7.68$ Å, $\beta = 104.6^\circ$, $Z = 2$.

The two formulae are given in Fig. 1(A,B). For trimethylated catechic acid, the perpendicular methoxy group is identified as $O_{24}(CH_3)_{17}$ and in mesembranol the group studied is $O_{19}(CH_3)_{20}$.

In each case, two minimizations of the crystal energy were performed, starting from the experimental crystal

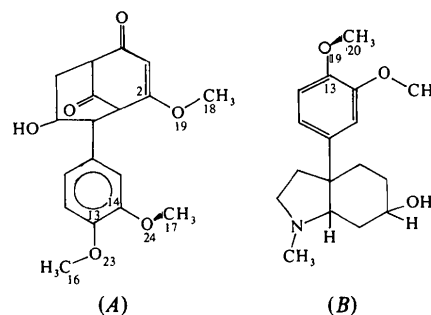


Fig. 1. Structural formulae of the non-planar compounds. (A) Trimethylated catechic acid. (B) Mesembranol.

on the one hand, and from a hypothetical one, obtained by rotating the perpendicular methyl group to make the molecule studied planar, on the other. The results for these molecules are collected in Table 1. In this table are given the different contributions to the energy: electrostatic (E_{el}), polarization (E_{pol}), dispersion (E_{disp}) and short-range repulsion (E_{rep}). For each minimization, the different energy components before and after minimization are given, under headings (a) and (b) respectively.

The last two columns give the sums $E_{disp} + E_{rep}$ and the sum of all the contributions $E_{el} + E_{pol} + E_{disp} + E_{rep}$. In the case of the 'planar' trimethylated catechic acid, the minimization leads to a crystal cell with an enlarged b value ($13.29 \rightarrow 14.89$ Å) indicating that steric hindrance is important with $O_{24}(CH_3)$ in the plane of the phenyl ring.

Together with the cell parameters, the Euler angles and the translations obtained in this minimization, the energy for 'non-planar' catechic acid has also been calculated (-120.71 kJ mol $^{-1}$): the stabilization is slightly smaller than that of the crystal obtained with the 'planar' molecule.

For the 'planar' mesembranol, only a slight rotation of the molecule allows one to obtain a good crystal energy but the crystal thus obtained is less stable than the experimental one. It is seen, in fact, that the experimental crystals correspond to a stronger stabilization in these two cases.

(b) Planar conformations

Of the 30 planar conformations, the following were chosen:

(I) Tetra-*O*-methyldehydrodicaffeic acid dilactone (Nakamura *et al.*, 1977). Crystal data: orthorhombic, $P2_12_12_1$, $a = 10.343$, $b = 34.014$, $c = 5.597$ Å, $Z = 4$.

(II) Polycarpine (Damak & Riche, 1977). Crystal data: triclinic, $P\bar{1}$, $a = 8.480$, $b = 8.867$, $c = 14.077$ Å, $\alpha = 100.36$, $\beta = 87.46$, $\gamma = 109.55^\circ$, $Z = 2$.

(III) *N*-Demethyl-*N*-formylmesembranolone (Karle, 1977). Crystal data: monoclinic, $P2_1/a$, $a = 14.698$, $b = 9.176$, $c = 12.161$ Å, $Z = 4$.

Table 1. *Lattice energies of the non-planar compounds*

(A) Trimethylated catechic acid. (B) Mesembranol. (a) Before minimization. (b) After minimization. In Tables 1–3, the different components of the energy are expressed in kJ mol⁻¹ ($E_{\text{total}} = E_{\text{el}} + E_{\text{pol}} + E_{\text{disp}} + E_{\text{rep}}$).

| | Electrostatic | Polarization | Dispersion | Repulsion | $E_{\text{disp}} + E_{\text{rep}}$ | E_{total} |
|----------------------------------|---------------|--------------|------------|-----------|------------------------------------|--------------------|
| (A) Experimental | | | | | | |
| (a) | -11.64 | -6.07 | -189.59 | +67.7 | -121.89 | -139.60 |
| (b) | -11.97 | -6.95 | -223.00 | +92.91 | -130.09 | -149.01 |
| Rotation of $\pi/2$ around 14–24 | | | | | | |
| (a) | -15.32 | -7.62 | -699.90 | +2998.06 | +2298.16 | +2275.22 |
| (b) | -15.87 | -4.77 | -181.76 | +78.09 | -103.67 | -124.31 |
| (B) Experimental | | | | | | |
| (a) | -6.24 | -4.14 | -186.66 | +83.91 | -102.75 | -113.13 |
| (b) | -5.28 | -3.81 | -181.97 | +66.28 | -115.69 | -124.77 |
| Rotation of $\pi/2$ around 13–19 | | | | | | |
| (a) | -8.00 | -4.69 | -197.63 | +118.87 | -78.76 | -91.45 |
| (b) | -7.12 | -4.35 | -187.74 | +86.42 | -101.33 | -112.79 |

Table 2. *Lattice energies of the planar compounds*

(I) Tetra-*O*-methyldehydrodicaffeic acid dilactone. (II) Polycarpine. (III) *N*-Demethyl-*N*-formylmesembrenone. (IV) 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole. (a) Before minimization. (b) After minimization.

| | Electrostatic | Polarization | Dispersion | Repulsion | $E_{\text{disp}} + E_{\text{rep}}$ | E_{total} |
|----------------------------------|---------------|--------------|------------|-----------|------------------------------------|--------------------|
| (I) Experimental | | | | | | |
| (a) | -29.60 | -10.72 | -250.51 | +82.27 | -168.23 | -208.55 |
| (b) | -29.60 | -10.72 | -250.51 | +82.27 | -168.23 | -208.55 |
| Rotation of $\pi/2$ around 23–27 | | | | | | |
| (a) | -32.83 | -12.52 | -428.50 | +1139.45 | +710.95 | +665.61 |
| (b) | -33.41 | -12.81 | -323.28 | +403.84 | +80.56 | +34.33 |
| Rotation of $\pi/2$ around 13–17 | | | | | | |
| (a) | -31.36 | -10.34 | -582.75 | +2067.71 | +1484.96 | +1443.26 |
| (b) | -32.87 | -13.73 | -341.53 | +358.45 | +16.92 | -29.69 |
| (II) Experimental | | | | | | |
| (a) | -7.49 | -7.75 | -205.46 | +62.72 | +142.73 | -157.98 |
| (b) | -7.49 | -7.75 | -205.46 | +62.72 | +142.73 | -157.98 |
| Rotation of $\pi/2$ around 7–22 | | | | | | |
| (a) | -9.80 | -10.17 | -968.58 | +4715.82 | +3747.24 | +3727.27 |
| (b) | -12.56 | -8.58 | -410.12 | +1148.28 | +738.17 | +717.02 |
| Rotation of $\pi/2$ around 6–20 | | | | | | |
| (a) | -6.57 | -8.12 | -335.34 | +809.31 | +473.97 | +459.27 |
| (b) | +1.09 | -7.54 | -272.45 | +326.33 | +53.89 | +47.44 |
| (III) Experimental | | | | | | |
| (a) | -24.49 | -9.38 | -180.54 | +52.80 | -127.74 | -161.62 |
| (b) | -24.49 | -9.38 | -180.54 | +52.80 | -127.74 | -161.62 |
| Rotation of $\pi/2$ around 14–17 | | | | | | |
| (a) | -17.96 | -8.83 | -242.80 | +279.40 | +36.59 | +9.80 |
| (b) | -22.27 | -9.96 | -199.97 | +80.60 | -119.37 | -151.61 |
| Rotation of $\pi/2$ around 13–19 | | | | | | |
| (a) | -16.20 | -10.59 | -255.87 | +392.53 | -136.66 | +109.87 |
| (b) | -18.34 | -11.81 | -189.96 | +104.13 | -85.83 | -115.98 |
| (IV) Experimental | | | | | | |
| (a) | -12.02 | -4.77 | -162.41 | +50.20 | -112.21 | -129.00 |
| (b) | -11.39 | -4.73 | -170.24 | +51.88 | -118.37 | -134.48 |
| Rotation of $\pi/2$ around 7–15 | | | | | | |
| (a) | -11.01 | -4.14 | -167.35 | +62.43 | -104.93 | -120.08 |
| (b) | -10.17 | -3.68 | -209.22 | +87.42 | -121.80 | -135.66 |
| Rotation of $\pi/2$ around 8–16 | | | | | | |
| (a) | -11.43 | -4.10 | -286.14 | +745.33 | -459.19 | +443.65 |
| (b) | -10.01 | -3.94 | -201.01 | +174.89 | -26.13 | -40.07 |

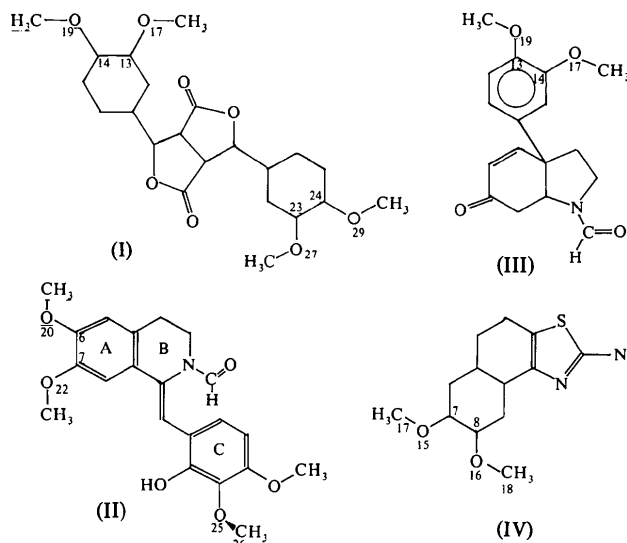


Fig. 2. Structural formulae of the planar compounds. (I) Tetra-*O*-methyldehydrocaffeic acid dilactone. (II) Polycarpine. (III) *N*-Demethyl-*N*-formylmesembrenone. (IV) 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole.

(IV) 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole (Ekstrand & van der Helm, 1977). Crystal data: orthorhombic, *Pbca*, $a = 6.778$, $b = 21.041$, $c = 17.410$ Å, $Z = 8$.

The chemical formulae are shown in Fig. 2. For these compounds, the minimum energy was also calculated for the crystal structure observed with planar methoxy groups. To build non-planar conformations for the purpose of comparison, it is possible to turn one or other of the two *o*-methoxy groups. Two possibilities exist for the molecules (II), (III) and (IV), and the energy minimization has been performed for all the corresponding crystal structures. For molecule (I) there are four possibilities of rotating the methyl groups so as to obtain a non-planar molecule; only two possibilities were studied: rotation around the $C_{23}O_{27}$ and $C_{13}O_{17}$ bonds. The results of these calculations are collected in Table 2. It can be seen that the experimental crystals corresponding to planar conformations are more stable than the other (hypothetical) ones.

However, in the case of the substituted thiazole (IV), the results displayed in Table 2 indicate, for one of the hypothetical structures (corresponding to a non-planar conformation generated by a $\pi/2$ rotation of the methoxy group around the bond 7–15), a minimum energy (-135.43 kJ mol $^{-1}$) slightly stronger than that calculated for the experimental structure (-134.26 kJ mol $^{-1}$). The parameters defining these two structures are somewhat different: (i) minimum corresponding to the experimental structure: cell parameters: $a = 6.70$, $b = 21.01$, $c = 17.4$ Å; displacement of molecule 1 in

the central cell: rotation whose angle is $\omega = 4.04^\circ$ around an axis passing through the 'centre' of the molecule and defined by its direction cosines $c_1 = 0$, $c_2 = -0.481$, $c_3 = -0.877$ (the centre of the molecule used here is defined as the 'centre of mass' obtained by putting on each atom a weight equal to its atomic number); translation: $t_1 = 0.031$, $t_2 = 0.019$, $t_3 = -0.0294$ Å; (ii) minimum corresponding to the non-planar conformation: cell parameters: $a = 6.87$, $b = 21.07$, $c = 15.64$ Å; displacement of molecule 1: $\omega = 8.34^\circ$, $c_1 = 0.040$, $c_2 = 0.635$, $c_3 = 0.771$; translation: $t_1 = 0.772$, $t_2 = 0.948$, $t_3 = -0.294$ Å.

The difference concerns essentially the cell parameter c , and to a lesser extent the translation (t_1, t_2, t_3). As concerns the energy difference, it is too small to be considered very significant, in comparison with the necessarily limited accuracy of the present theoretical method. The reason why one of these structures is chosen by the experimental crystal may be connected with the crystallization process: if one of these configurations (here corresponding to the planar conformation) is more favourable at the stage of small clusters, then the growing crystal may simply remain trapped in the corresponding local minimum, since there is no marked advantage in switching to the other (energetically almost equivalent) minimum. It may be noted here that in a previous work (concerning adrenaline: Caillet *et al.*, 1976) the still stranger case was encountered of a local minimum significantly deeper than the one corresponding to the experimental structure (conformations A_1 and A_2 in Caillet *et al.*, 1976). Once more, one must warn here that the problem posed by the existence of several local minima and of the choice between these minima is certainly a highly non-trivial problem plaguing the study of crystals (except perhaps when only very simple molecules are involved).

It is interesting to note that, in Table 2, the various terms of the interaction energy are of the same order of magnitude as those of Table 1, at least as far as the experimental crystal structures are concerned (for the hypothetical structures, steric hindrances result in values of the repulsion and dispersion terms that are too high). Thus one can say that, in the case of these crystallized methoxy compounds, the crystal environment is an important factor in the determination of the molecular conformation.

For these cases enlarged cells were used with factors varying from 1.1 to 1.3. The most significant results are given in Table 3. The different enlargement factors are given; of several values for these factors, a value was chosen giving a non-repulsive energy already before minimization. For all the crystals considered, it can be seen that the minimum energy of the hypothetical conformations corresponds to a stabilization weaker than in the case of the experimental conformation.

Table 3. *Lattice energies with initially enlarged crystal cells*

(I) Tetra-*O*-methyldehydrocaffeic acid dilactone. (II) Polycarpine. (III) *N*-Demethyl-*N*-formylmesembrenone. (IV) 2-Amino-4,5-dihydro-7,8-dimethoxynaphtho[1,2-*d*]thiazole. (a) Before minimization. (b) After minimization.

| | Electrostatic | Polarization | Dispersion | Repulsion | $E_{\text{disp}} + E_{\text{rep}}$ | E_{total} |
|--|---------------|--------------|------------|-----------|------------------------------------|--------------------|
| (I) Rotation of $\pi/2$ around 23–27 (cell $\times 1.2$ before minimization) | | | | | | |
| (a) | -6.78 | -3.10 | -85.75 | +42.58 | -43.17 | -53.05 |
| (b) | -11.39 | -3.73 | -81.65 | +21.31 | -60.33 | -75.45 |
| Rotation of $\pi/2$ around 13–17 (cell $\times 1.2$ before minimization) | | | | | | |
| (a) | -9.42 | -2.01 | -88.18 | +95.84 | +7.66 | -3.77 |
| (b) | -25.41 | -7.58 | -246.66 | +104.26 | -142.40 | -175.39 |
| (II) Rotation of $\pi/2$ around 7–22 (cell $\times 1.1$ before minimization) | | | | | | |
| (a) | -3.56 | -2.93 | -114.26 | +57.91 | -56.36 | -62.85 |
| (b) | -0.54 | -3.73 | -124.06 | +39.94 | -84.12 | -88.39 |
| Rotation of $\pi/2$ around 6–20 (cell $\times 1.2$ before minimization) | | | | | | |
| (a) | -0.67 | -1.93 | -84.33 | +69.29 | -15.03 | -17.63 |
| (b) | -6.41 | -3.47 | -99.78 | +42.41 | -57.36 | -67.24 |
| (III) Rotation of $\pi/2$ around 13–19 (cell $\times 1.1$ before minimization) | | | | | | |
| (a) | -16.83 | -7.62 | -118.37 | +94.58 | -23.78 | -48.23 |
| (b) | -16.75 | -7.03 | -112.88 | +63.68 | -49.20 | -72.98 |
| (IV) Rotation of $\pi/2$ around 8–16 (cell $\times 1.3$ before minimization) | | | | | | |
| (a) | -1.17 | -0.54 | -24.58 | +1.47 | -23.11 | -24.83 |
| (b) | -6.45 | -2.34 | -72.52 | +23.91 | -48.61 | -57.40 |

In Table 3, for the hypothetical crystal of *N*-demethyl-*N*-formylmesembrenone (III), the minimum energy ($-72.98 \text{ kJ mol}^{-1}$) obtained by starting with an enlarged cell is weaker than the energy ($-115.79 \text{ kJ mol}^{-1}$) obtained when starting with the experimental cell; thus another minimization was made by starting with the cell parameters, Euler angles and translations corresponding to this first (apparent?) minimum lying at ($-72.98 \text{ kJ mol}^{-1}$). This second minimization actually led to a new minimum ($-137.61 \text{ kJ mol}^{-1}$), now deeper than the one obtained when starting from the non-enlarged cell. Moreover, the geometrical parameters corresponding to these minima appear significantly different: (i) for the value $-115.79 \text{ kJ mol}^{-1}$, $a = 14.7$, $b = 9.2$, $c = 12.2 \text{ \AA}$, $\beta = 107.7^\circ$; parameters for the displacement of molecule 1 of the central cell: rotation angle $\omega = 10.35^\circ$; direction cosines of the rotation axis $c_1 = 0$, $c_2 = 0.387$, $c_3 = -0.922$; components of the translation: $t_1 = 0.0015$, $t_2 = -0.0138$, $t_3 = -0.0455 \text{ \AA}$ (the orthonormal coordinate system *Oxyz* is defined by taking *Ox* along **a** and *Oy* along **b**); (ii) for the value $-137.61 \text{ kJ mol}^{-1}$, the corresponding values are $a = 14.4$, $b = 10.8$, $c = 11.8 \text{ \AA}$, $\beta = 120.10^\circ$; $\omega = 7.43^\circ$, $c_1 = -0.03$, $c_2 = -0.5$, $c_3 = 0.86$; $t_1 = 0.959$, $t_2 = 1.48$, $t_3 = -0.328 \text{ \AA}$.

We must conclude that several local minima may exist on the energy hypersurface, as already suggested in previous works [see, for example, the discussion concerning nitrobenzene in Caillet & Claverie (1975)]. As concerns the purpose of the present work, namely the study of the conformation of methoxy groups, the

essential conclusion is that both hypothetical minima (-115.79 and $-137.61 \text{ kJ mol}^{-1}$) corresponding to the non-planar compound under consideration ($\pi/2$ rotation around the 13–19 bond) are actually less stable than the minimum corresponding to the experimental crystal (with planar conformation), namely $-161.35 \text{ kJ mol}^{-1}$.

It must be emphasized that, in all the cases investigated, the relative orders are the same for the partial sums (dispersion + repulsion) as for the corresponding total lattice energies (and this holds whether the crystal structure considered is an experimental or a hypothetical one). Therefore, as mentioned above, it is immaterial for the present investigation whether this evaluation of the electrostatic energy is somewhat biased, since the (dispersion + repulsion) part of the interaction energy is the truly determinative factor.

In the study of Anderson *et al.* (1979) it can be seen that the difference between conformational energies is small enough (about 4 kJ mol^{-1} for methoxy- and hydroxybenzenes). Supposing that the non-planar conformation is also preferred for the dimethoxy compounds already studied, and that the energy difference between the conformations is of the same order, one may note that the relative order of the different energies is preserved when these intrinsic conformational energy differences are added to the differences between the calculated lattice-energy values, since the latter are significantly larger than the former.

IV. Conclusion

From the results of the different calculations, it can be seen that the preferred conformation of the *o*-dimethoxy compounds in the crystal phase is the planar one. Consideration of the partial sum ($E_{\text{disp}} + E_{\text{rep}}$) allows one to conclude that steric hindrance is predominant for this choice of conformation of the compound. If it is accepted that a systematic preference for non-planar conformations exists for these compounds *in vacuo*, planar conformations appear in the crystal owing to the steric hindrances that are generally expected to arise when non-planar molecules are stacked, except for a few cases where 'holes' persist in the crystal structures which allow for the accommodation of methoxy groups outside the main molecular plane, and therefore for the maintenance of a non-planar conformation in the crystal.

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