intermediate **16**[18] (63% yield), the structure of which was confirmed by a complete three-dimensional single-crystal X-ray analysis. A major problem that we had to deal with was a partial racemization during this cyclization step. Eventually we found that traces of acids in the reaction medium were catalyzing the loss of optical activity, which could be completely prevented by addition of small amounts of barium or calcium oxide.[19]

Cleavage of the isoxazolidine ring (Zn dust, AcOH/H_2O, 70 °C) and acylation of the free amine ($ClCO_2Me$, THF/2*n*Na_2CO_3, 0 °C) gave the bicyclic intermediate **17** (65% yield from **16**), which on treatment with barium hydroxide in refluxing aqueous dioxane underwent hydrolysis of the lactam moiety and concomitant cyclization to the imidazolidinone **18** (87% yield). Left to be solved at this point was the elimination of the superfluous hydroxy group in the side chain without affecting the vicinal chiral center. This was effected as follows. Thionyl chloride treatment in ether and subsequent quenching with methanol gave the chloro ester **19** (68% yield). X-ray single-crystal analysis of this product revealed that the hydroxy group was replaced with retention of configuration. Dechlorination to **20** was effected with excess of sodium borohydride in dimethylformamide (80 °C, 76% yield). Finally, treatment of **20** with aqueous hydrobromic acid[19] gave *d*-biotin (**1**; 85% yield), which was isolated and characterized as the corresponding methyl ester:[20] mp 165-166 °C; $[\alpha]^{25}_D$ +80.5° (*c* 0.3, MeOH). Its spectroscopic data were identical with those of *d*-biotin methyl ester prepared from the natural product.

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(18) **16**: mp 129-130 °C; $[\alpha]^{25}_D$ = +78.3° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 4.00 (1 H, d, *J* = 8.2 Hz), 4.28 (1 H, d, *J* = 8.2 Hz), 4.50 (1 H, br s), 6.10 (1 H, br s), 7.33 (5 h, br m).

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Methoxy Group Conformations of Phenyl Methyl Ethers in Solution

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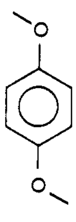
In a previous investigation, Anderson and co-workers[1] have reported the conformations of a group of methoxy-substituted benzenes in the gas phase through use of photoelectron spectroscopy and ab initio STO-3G calculations. The preferred conformations of methoxybenzene and *p*- and *m*-dimethoxybenzene (**1**, **2**) were reported to be planar. In contrast, *o*-dimethoxybenzene (**3**) in the gas phase was found to have one methoxy group predominantly in the nonplanar conformation with the O-CH_3 bond perpendicular to the plane of the aromatic ring. Principally on the basis of partition coefficient measurements, the authors concluded that also in solution *o*-dimethoxybenzenes had one of their methoxy groups in the nonplanar conformation. In a following publication, these results were used to explain some crucial aspects of the pharmacological activity of methoxy-substituted hallucinogenic amphetamines.[2]



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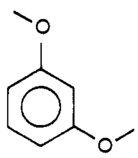

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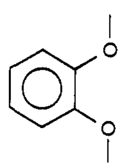

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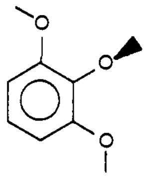

4

In the present communication, we report on the conformational analysis of methoxy groups in the same methoxy-substituted benzenes in solution by using a ^{13}C NMR method previously developed in this laboratory.[3] Our results show significant disagreement with the previously published conclusions.[1,2] The present study was carried out on the three dimethoxybenzenes (**1**-**3**). 1,2,3-trimethoxybenzene (**4**), a compound that was expected to have its 2-OCH_3 group in the out-of-plane conformation, was also included as a reference. The method we used relies on the observation that out-of-plane methoxy groups have abnormally high ^{13}C chemical shifts and unusually long T_1 values.

In planar arylmethoxy groups, the π orbitals of the aromatic ring tend to overlap with the lone-pair electron orbitals of the methoxy oxygen, leading to a delocalization of the nonbonding oxygen electrons and a strengthening of the Ar-O bond. This also results in increased electron density at the ring carbons ortho and para to the methoxy group. In the out-of-plane conformation the conjugation of the nonbonding oxygen electrons with the π bond of the ring is interrupted. Earlier studies[4,5] have shown that arylmethoxy groups that are believed to exist in the planar conformation have ^{13}C chemical shifts very similar to that of unsubstituted anisole (δ 55.1[6]). On the other hand, methoxy groups that are expected to exist predominantly in the out-of-plane conformation have chemical shifts 5-7 ppm downfield from that of anisole and not very different from those of aliphatic methoxy groups. Although the origin of the deshielding effect in the out-of-plane methoxy groups is not immediately evident, this observation is very consistent.[6]

Except for the 2-OCH_3 group in **4** all methoxy carbons had nearly equivalent and "normal" chemical shifts ($\delta_{^{13}C} \simeq 55$) characteristic of planar arylmethoxy groups. On the other hand, the ^{13}C resonance for the out-of-plane 2-OCH_3 (**4**) was shifted to lower fields ($\delta_{^{13}C}$ 60.8, Table I). The evidence for a predominantly all-planar *o*-dimethoxybenzene obtained from the OCH_3 ^{13}C value (55.8 ppm) is congruent with the observed chemical shift for the C_4 aromatic carbon ($\delta_{^{13}C}$ 120.9) in this molecule. If the methoxy groups in **3** are in the planar conformation, the para aromatic carbons should experience the full mesomeric shielding effect produced by the unshared oxygen electrons of the methoxy group similar to that experienced by C_4 in unsubstituted anisole. Since the effect of a *m*-methoxy group on an aromatic carbon is negligible, these two molecules would be expected to have similar

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Table I. ^{13}C Chemical Shifts (δ)[a] for Protonated Carbons

compd	OCH_3 subst	OCH_3	OCH_3	OCH_3	phenyl
1	1,4	55.7	55.7		114.7 (C_2, C_3, C_5, C_6)
2	1,3	55.2	55.2		100.5 (C_2), 106.2 (C_4, C_6); 129.9 (C_5)
3	1,2	55.8	55.8		111.5 (C_3, C_6), 120.9 (C_4, C_5)
4	1,2,3	56.0	60.7	56.0	105.3 (C_4, C_6), 123.6 (C_5)

[a] Downfield from internal Me_4Si.

Table II. ^{13}C Spin-Lattice Relaxation Times (T_1, s)[a] for Protonated Carbons

compd	OCH_3 subst	OCH_3	OCH_3	OCH_3	phenyl
1	1,4	4.5	4.5		5.5 (C_2, C_3, C_5, C_6)
2	1,3	3.7	3.7		5.4 (C_2), 4.5 (C_4, C_6), 5.3 (C_5)
3	1,2	3.6	3.6		4.4 (C_3, C_6), 4.8 (C_4, C_5)
4	1,2,3	3.6	6.1	3.6	2.9 (C_4, C_6), 3.1 (C_5)

[a] Measurements were carried out at 15.1 MHz, with degassed solutions, 1 M in $CDCl_3$ at 30 °C. T_1 values were determined by using the inversion recovery method[9] and estimated from peak intensities by using the Bruker T_1 Program/II. They are the average of four determinations (±5%).

C_4 chemical shifts. Indeed their chemical shifts are $\delta_{^{13}C}$ 120.9 and 120.1, respectively. On the other hand, in **4** the carbon para to the *out-of-plane* 2-OCH_3 (C_5), which is expected to experience less shielding, resonates about 3 ppm downfield ($\delta_{^{13}C}$ 123.6).

We used T_1 values as indices of molecular motion for individual methoxy carbons in each molecule. In previous work we described the dramatic variation in T_1 values between planar and out-of-plane methoxy groups. This was explained[3] by invoking hindered rotation for the in-plane methoxy by the ortho protons of the ring. In contrast, methoxy groups that are perpendicular to the plane of the aromatic ring are unhindered by their ortho substituents and experience considerably faster rotation, as reflected by their longer T_1 values. The present data (Table II) support the conclusion that OCH_3 groups in the three dimethoxybenzenes (**1-3**) exist predominantly in the planar conformation while **4** has its 2-OCH_3 group in the out-of-plane conformation and the other two methoxy groups planar.

During the interpretation of the ^{13}C T_1 values for OCH_3 carbons two uncertainties were considered: (a) the possibility that spin-rotation relaxation may have a significant contribution in the overall relaxation rate; (b) the possibility that anisotropic tumbling of the entire molecule may be affecting differently the relaxation rates of the various OCH_3 carbons in the dimethoxybenzenes and may therefore not allow legitimate comparisons between their T_1 values. The first uncertainty was resolved through the measurement of $^{13}C-^{1}H$ NOE values for all protonated carbons. These uniformly showed maximum NOE values ($\eta \approx 2.0$),[7] indicating that $^{13}C-^{1}H$ dipolar relaxation is the only significant ^{13}C relaxation mechanism with no substantial contribution from spin-rotation. The second uncertainty was more difficult to deal with in a quantitative fashion. Examination of the T_1 values showed some variation among the protonated phenyl carbons in those molecules in which not all the CH aromatic carbons are equivalent, indicating some anisotropic character in the motion for the phenyl ring. However, careful consideration of the data indicated that this relatively modest anisotropic behavior does not alter the interpretation of our results.

Each arylmethoxy group is subject to two possible rotational processes, one around the Ar-O bond and the second around the $O-CH_3$ bond. Of these, rotation around the Ar-O bond is expected to be the slowest because of a considerably higher rotational barrier, a result of the partial double-bond character of this bond. Theoretical calculations have shown this to be the case.[8] Although both rotational processes should influence the spin-lattice relaxation of each methoxy carbon, the measured T_1 values are expected to be more sensitive to changes in the faster $O-CH_3$ rotations. The considerably longer T_1 value (6.1 s) of the 2-OCH_3 group in **4** is, thus, a reflection of freer rotation of an $O-CH_3$ bond perpendicular to the plane of the aromatic ring. On the other hand, the slightly higher OCH_3 T_1 value in *p*-dimethoxybenzene is more likely to be a reflection of a higher degree of anisotropy in the overall reorientation of this molecule.

The data provided in this communication give two independent types of evidence indicating that at least in solution, *o*-dimethoxybenzene has its two methoxy groups predominantly in a conformation in which the $O-CH_3$ bonds are coplanar with the phenyl ring. These results are in agreement with the majority of the X-ray crystallographic data[8] on molecules with aromatic *o*-dimethoxy substitution. Our results differ from the previously reported conformational analysis of *o*-dimethoxybenzene in the gas phase and in solution.[1] It is possible to explain the differences between the results described here and those obtained from gas-phase[1] measurements on the basis of a solvent effect. Indeed, large differences were found in the rotational barrier of OCH_3 in anisole when this was measured in the gas phase and in the liquid phase.[10] However, the discrepancy between our data and the conclusions drawn in the previous investigation for the preferred conformations in solution should point out the dangers involved in the use of partition coefficient measurements for conformational analysis.

Registry No. *p*-Dimethoxybenzene, 150-78-7; *m*-dimethoxybenzene, 151-10-0; *o*-dimethoxybenzene, 91-16-7; 1,2,3-trimethoxybenzene, 634-36-6.

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Pseudopterolide, an Irregular Diterpenoid with Unusual Cytotoxic Properties from the Caribbean Sea Whip *Pseudopterogorgia acerosa* (Pallas) (Gorgonacea)

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Chemical investigations of marine soft corals of the order Gorgonacea (Cnidaria, Alcyonaria), the sea whips and fans, have yielded several metabolites possessing potent biological activities.[1] Our investigations of these beautiful marine invertebrates have been guided by the in situ evaluation of cytotoxicity using appropriate cell lines such as the fertilized sea urchin egg.[2] During

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