Methoxy Group Nonplanarity in *o*-Dimethoxybenzenes. Simple Predictive Models for Conformations and Rotational Barriers in Alkoxyaromatics

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Abstract: Photoelectron spectroscopy and ab initio STO-3G calculations provide evidence that *o*-dimethoxybenzene and derivatives exist in predominantly nonplanar conformations in the gas phase. By contrast, the preferred conformations of methoxybenzene and *m*- and *p*-dimethoxybenzene are planar, and the nonplanar structures are significantly less stable. For both hydroxy- and methoxybenzenes, the STO-3G calculated barriers to rotation about the Ar–OR bond decrease in the order *m*-di- > mono- > *p*-di- > *o*-di-. Partition coefficient, dipole moment, and dielectric relaxation measurements on *o*-dimethoxybenzene are consistent with the presence of nonplanar conformations in solution. On the other hand, the crystal structures of compounds bearing *o*-dimethoxy substituents indicate a preference for planar conformations: of 32 examples found in the literature, only two structures contain a nonplanar methoxy group. The relevant differences between the gas-phase, solution, and crystal conformations of *o*-dimethoxy substituted aromatics are discussed and rationalized. The origin of the rotational barriers in methoxy- and hydroxybenzenes is analyzed in terms of both resonance and frontier molecular orbital arguments which indicate that the preferred conformations are those maximizing two-electron stabilizing interactions and minimizing four-electron destabilizing interactions. A simple method of predicting rotational conformational preferences, based on π charge densities, is proposed and used to explain the influence of substitution on the hallucinogenic properties of several polyalkoxyamphetamines.

Introduction

In the absence of steric hindrance, substituents with lone pairs attached to aromatic rings prefer planar conformations over gauche or perpendicular conformations.[2a] Maximization of conjugation between the substituent p-type lone-pair orbital and the aromatic system is commonly invoked to account for this preference.[2b] Only in sterically hindered cases, such as occurs when the 2 and 6 positions are substituted, has evidence been presented for nonplanarity of donors such as methoxy groups.[3,4] We wish to report that, in spite of no obvious steric hindrance, this preference is altered in *o*-dimethoxybenzene (catechol dimethyl ether) in the gas phase. Measurements of partition coefficients, dipole moments, and dielectric relaxation times of *o*-dimethoxy substituted aromatics also indicate the presence of nonplanar conformations in solution. In crystals, however, the planar arrangement of methoxy groups is usually found.[5]

Initial evidence implicating nonplanar conformations in *o*-dimethoxybenzenes came from our investigations of structure-activity relationships in a series of substituted amphetamines. Two anomalies in the physical properties emerged: (1) the octanol-water partition coefficients of amphetamines containing the *o*-dimethoxy substitution pattern were about five times less than expected on the basis of group contributions (π values).[6] In simple dimethoxybenzenes (DMBs), the same is true: *o*-dimethoxybenzene (*o*-DMB) is partitioned into water from 1-octanol almost five times more readily than either *m*- or *p*-DMB (resorcinol and hydroquinone dimethyl ethers).[7] (2) The photoelectron spectra of a variety of *o*-DMBs revealed unusually high first ionization potentials as compared to the corresponding meta or para derivatives, or as compared to expectation from ab initio STO-3G calculations performed on the planar conformation.[8] Calculations for the molecule with one perpendicular methoxy are in much better agreement with the photoelectron spectrum.[8]

We report here ab initio calculations and detailed analyses of the photoelectron spectra of methoxybenzenes which prove the existence of nonplanar conformations in *o*-DMB and show that both the barriers to rotation and substituent stabilization energies decrease in the series *m*-di- > mono- > *p*-di- > *o*-di- for both hydroxy- and methoxybenzenes. Furthermore, an explanation for these effects is offered based on both simple resonance arguments and on a frontier orbital interaction model using substituent and aromatic fragment orbitals. Such a model allows conformational predictions for other donor-substituted aromatic and heterocyclic systems.

Results and Discussion

Molecular Orbital Calculations on Methoxy- and Hydroxybenzenes. Ab initio calculations on the methoxybenzenes (MBs) and hydroxybenzenes (HBs) illustrated in Figure 1 were performed. The STO-3G minimal basis set[9] and both standard[10] and partially optimized geometries were used, and the conformational energies are summarized in Tables I and II. Also included are the stabilization energies for the isodesmic reactions, ArH + MeOMe → ArOMe + MeH.

The calculations using standard geometries indicate a barrier to rotation in anisole (**1**) of about 1 kcal/mol compared to deductions from far-infrared spectra which indicate that the barrier in the gas phase is 3.6 kcal/mol.[11] The planar conformation was predicted to be the global minimum; similar results have been reported by Hofer[12a] using the MINDO/3 method, and also by Tylli[12b] and us[12c] from CNDO/2 calculations.

Substitution of a methoxy group at the meta position of anisole (resulting in *m*-DMB (**2**)) provides more stabilization than substitution of a methoxy group on benzene, as judged by the isodesmic comparison, and the barrier to rotation of the methoxy group in *m*-DMB is correspondingly higher. By contrast, the barrier in *p*-DMB (**3**) is almost zero, while *o*-DMB (**4**) has lower rotational barriers and a preferred nonplanar conformation. These trends are consistent with the smaller stabilizing effect of the second methoxy group than the first in *p*-DMB and the even smaller effect in *o*-DMB. The parallel between the relatively high barriers to rotation and large stabilization energy was noted earlier by Pople and coworkers[2b,13] in their study of the rotational barriers in para-

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Table I. STO-3G Energies (kcal/mol) for Methoxybenzenes in Standard Geometries[a],[10]

anisole (**1**)		*m*-dimethoxybenzene (**2**)			*p*-dimethoxybenzene (**3**)			*o*-dimethoxybenzene (**4**)		
E(stab)[b]	10.0 (5.5)[2b]		11.0			8.5			6.7	
ϕ, deg	E_{rel}	ϕ_1, deg	ϕ_2, deg	E_{rel}[c]	ϕ_1, deg	ϕ_2, deg	E_{rel}[c]	ϕ_1, deg	ϕ_2, deg	E_{rel}
0	0[d]	0	0	0[e]	0	0	0[f]	0	0	1.07[g]
22.5	0.87	90	0	2.25	90	0	0.16	30	0	1.90
45	1.05							60	0	0.98
60	0.86							90	0	0.34
67.5	0.85							180	0	10.14
90	0.94							60	60	0.96
								90	90	0
								90	270	5.64

[a] Drawings show geometries for $\phi = 0$. [b] Defined as the energy of the isodesmic reaction: ArH + MeOMe → ArOMe + MeH. Methane and dimethyl ether energies are from ref 13. [c] We expect that for *m*- and *p*-dimethoxy isomers the energy of $\phi_1 = 0°$, $\phi_2 = 0°$ will be approximately identical with that of $\phi_1 = 0°$, $\phi_2 = 180°$; i.e., the methyls are too far apart to interact significantly. [d] Total energy is −340.3042 au. [e] Total energy is −452.7192 au. [f] Total energy is −452.7164 au. [g] Total energy is −452.7124 au.

Table II. STO-3G Energies (kcal/mol) for Hydroxybenzenes in Standard Geometries[a]

phenol (**5**)		*m*-dihydroxybenzene (**6**)			*p*-dihydroxybenzene (**7**)			*o*-dihydroxybenzene (**8**)		
E(stab)	8.8 (12.4)[2b]		9.3			7.4			4.6	
ϕ, deg	E_{rel}	ϕ_1, deg	ϕ_2, deg	E_{rel}	ϕ_1, deg	ϕ_2, deg	E_{rel}	ϕ_1, deg	ϕ_2, deg	E_{rel}
0	0[b]	0	0	0[c]	0	0	0[d]	0	0	0[e]
90	4.71 (5.16)[2b]	90	0	4.94	90	0	3.81 (4.21)[2b]	90	0	2.60

[a] See footnotes *a* and *b*, Table I. [b] Total energy is −301.7237 au. [c] Total energy is −375.5573 au. [d] Total energy is −375.5543 au. [e] Total energy is −375.5499 au.

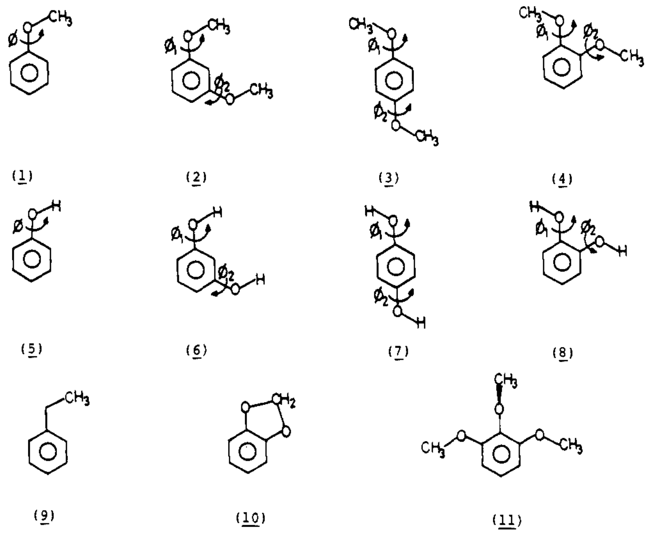


Figure 1. Molecules for which calculations were performed.

substituted phenols. Our calculations indicate a strong preference for rotation of one or both methoxys out of planarity as long as the methyl groups in *o*-DMB are rotated away from each other.

The calculations for the HBs **5–8** show entirely analogous trends. That is, the barrier to rotation is highest for *m*-DHB (resorcinol), and decreases along the series phenol, *p*-DHB (hydroquinone), *o*-DHB (pyrocatechol). As noted previously by Pople, the calculated barrier for phenol (5.16[2b] or 4.7 kcal/mol calculated here) is higher than the experimental values (3.3[14] to 3.6[15] kcal/mol), but the change in rotational barrier upon para substitution is predicted quite accurately (±0.08 kcal/mol) except for *p*-hydroxybenzaldehyde, where the increase in the C–O rotational barrier is underestimated by 0.4 kcal/mol. If the changes in the barriers calculated here are accurate, the 0°, 90° conformation of *o*-DHB is only 1.2–1.5 kcal/mol higher in energy than the planar conformation.

Table III. STO-3G Energies (kcal/mol) and Dipole Moments (D) for Anisole and *o*-DMB Using Partially Optimized Geometries[a]

anisole (**1**)			*o*-dimethoxybenzene (**4**)			
ϕ, deg	E_{rel}	μ	ϕ_1, deg	ϕ_2, deg	E_{rel}	μ
0	0[b]	1.16	0	0	0.03[c]	0.96
30	0.70	1.21	0	30	0.46	1.29
60	1.55	1.28	0	60	0.88	1.72
90	1.34	1.35	0	90	0	2.06
			90	90	0.22	0.43

[a] The values of $r_{O\text{-}C(aromatic)}$, C–C–O, and C–O–CH$_3$ angles were optimized for anisole at $\phi = 0$ and 90°. For $\phi = 0°$, these values were 1.401 Å, 125.5°, and 117.28°, respectively; at $\phi = 90°$, these values were 1.403 Å, 120°, and 110.23°. These values were used for **4** as well. For the $\phi = 30$ and 60° geometries of anisole and *o*-DMB, the bond lengths and angles were linearly interpolated from the 0 and 90° geometries and the C–O–C–H dihedral angles were optimized to minimize CH$_3$-*o*-H repulsions. These angles were found to be $\phi' = 43$, 163, and 283° for $\phi = 30°$ and $\phi' = 58$, 178, and 298° for $\phi = 60°$. [b] Total energy is −340.3089 au. [c] Total energy is −452.7224 au.

Calculations were also carried out on anisole, optimizing $r_{O\text{-}C}$ (aromatic), the C–C–O angle, and the C–O–CH$_3$ angle, and these results are summarized in Table III and graphed in Figure 2. As can be seen, the rotational barrier in the optimized geometry is greater than the corresponding barrier in the standard geometry, However, both show four local minima and in both the planar conformations (0 and 180°) are preferred over the perpendicular (90 and 270°) orientations. Hehre et al.[13] have shown that optimization of only the C–O–CH$_3$ angle caused the planar conformation of anisole to remain 0.06 kcal/mol more stable than the perpendicular. In our studies, the largest stabilization due to geometry optimization occurred in the C–C–O bond angle (optimum = 125.5°, standard = 120°) of planar anisole; the optimum angle for the perpendicular conformation was 120°. Comparison of the conformational preferences of phenol (**5**), ethylbenzene (**9**), and anisole yields insight into the origins of the rotational barrier in MBs. In phenol, the planar conformation is preferred owing to favorable conjugation between the p-type lone-pair electrons and the aromatic ring. Theoretical and experimental data in-

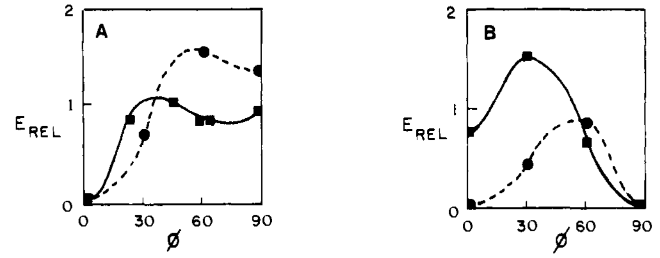


Figure 2. STO-3G calculated rotational barriers in anisole (A) and *o*-DMB (B) using standard geometries (boxes and solid line) and optimized geometries (circles and dashed line).

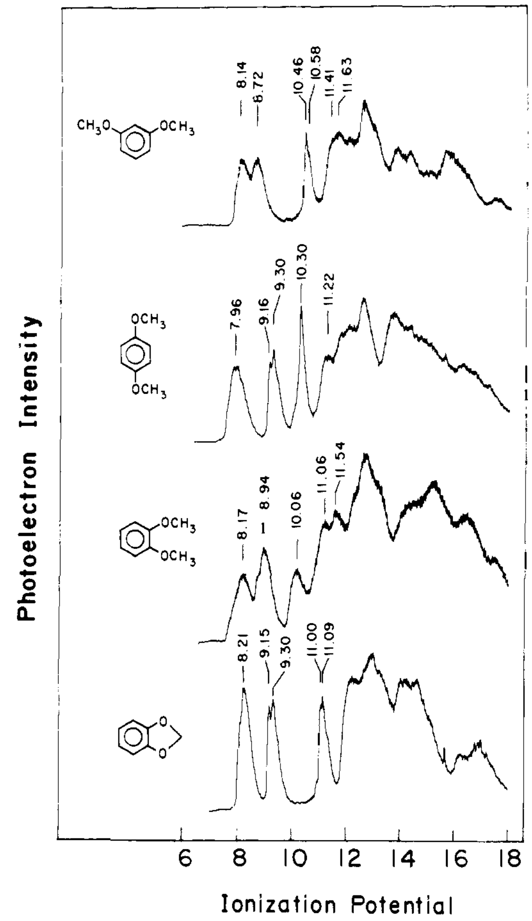


Figure 3. Photoelectron spectra of (top to bottom) *m*-dimethoxybenzene, *p*-dimethoxybenzene, *o*-dimethoxybenzene, and benzo-1,3-dioxole.

dicate that the perpendicular conformation of ethylbenzene is preferred over the planar by 2.2[13] and 1.3[15] kcal/mol, respectively. Undoubtedly, the perpendicular preference in ethylbenzene results from unfavorable steric interactions between the methyl group and the ortho H's in the planar arrangement. The conformation of anisole is a compromise between attractive (conjugative) and repulsive (steric) influences, but, since both theoretical and experimental evidence show that the planar conformation is preferred, clearly the conjugative interactions dominate (even though the C-O bond length in anisole is shorter than the corresponding C-C bond in ethylbenzene, and consequently repulsions in MBs would be expected to be larger than in ethylbenzene for the planar conformations). A simple calculation employing empirical nonbonded potential functions[16] indicates that steric repulsion in the planar orientation of anisole arises almost exclusively from CH_3, ortho-H interactions which are 2.2 kcal/mol higher in the planar conformation than the perpendicular. Consistent with this calculation is the observation that the energetic preferences for planarity in the MBs are 2.7-3.8 kcal/mol less than in the analogous HBs. Furthermore, scrutiny of the optimum geometries illustrates how anisole relieves steric repulsions in the planar conformation; the internal C-C-O angle increases from 120° (optimum in the perpendicular conformation) to 125.5°. This distortion increases the distance between the methyl hydrogens and ortho hydrogens, thereby decreasing the repulsion. Similar angle distortions are found in the X-ray structures of the planar and nonplanar MBs (see below).

When *o*-DMB calculations were carried out using the optimum anisole geometries for the methoxy group, the planar conformation is stabilized so that the nonplanar conformation (0°, 90°), is only 0.03 kcal/mol more stable than the planar conformation. Nevertheless, as compared to anisole, the rotational barrier in *o*-DMB is anomalously low. For example, in the standard geometry, the 90° conformation of anisole is 0.94 kcal/mol above the planar. If the rotational barriers were the same in *o*-DMB, the 90°, 90° conformation should be 1.9 kcal/mol above the 0°, 0°, whereas the calculations suggest that the 90°, 90° conformation is actually 1.1 kcal/mol more stable than the planar. Using optimized geometries and assuming no interaction between the methoxy groups, the anisole barrier implies that the 90°, 90° conformation should be 2.7 kcal/mol less stable than the 0°, 0 ° orientation; the calculated difference is only 0.2 kcal/mol. Hence, using either geometry, the 90°, 90° conformation of *o*-DMB is 2.5-3.0 kcal/mol more stable relative to the planar conformation than expected from additivity of the barriers in anisole.

While the calculated difference in the energies of the nonplanar and planar conformations in *o*-DMB in the partially optimized geometry is small, the predominant conformation in the gas phase is almost certainly nonplanar for the following reasons: (1) Conformational degeneracy predicts that the nonplanar forms would be favored four to one over the unique planar conformation, assuming that the energy of both were equal. (2) The experimental gas-phase barrier to rotation in phenol is 3.3-3.6 kcal/mol, whereas the calculated value is 4.7 kcal/mol. This suggests that at this level of theory (STO-3G) the stabilities of the planar conformations are only slightly overestimated with respect to the nonplanar structures. (3) There is a strong experimental evidence, detailed below, which indicates that in both gas phase and in solution the conformation of *o*-DMB is predominantly nonplanar.

Photoelectron Spectra of Dimethoxybenzenes and Methylenedioxybenzene. Experimental verification of the trends noted in the calculations (indeed one of the principal reasons for undertaking these calculations) is found in the photoelectron spectra of DMBs, along with that of benzo-1,3-dioxole (**10**), shown in Figure 3.[17] In MBs, the lowest two bands which fall in the 7.9-9.3-eV region are assigned to ionizations from orbitals related to the degenerate e_{1g} orbitals of benzene at 9.25 eV. The ionization potentials of *p*- and *m*-DMB and of benzo-1,3-dioxole relative to benzene and anisole models are reproduced quite accurately by STO-3G calculations, using Koopmans' theorem, which equates negatives of orbital energies to ionization potentials. The experimental vertical ionization potentials (IPs) are plotted in Figure 4, along with the STO-3G orbital energies corrected by the following equation: $IP_{calcd} = -0.70\epsilon_{STO\text{-}3G} + 3.75$ eV.[18] Particularly notable are the good agreement between the experimental data and IP_{calcd} for planar anisole and the poor agreement with the calculation for perpendicular anisole. For anisole, not only is there good agreement with the first two aromatic IPs, but the oxygen lone pair IPs are predicted to be in the region of the strong band at 11 eV in the spectrum only for the planar conformation. In the perpendicular conformation, the overlap between the p-type orbitals on oxygen (labeled π_O) is elimi-

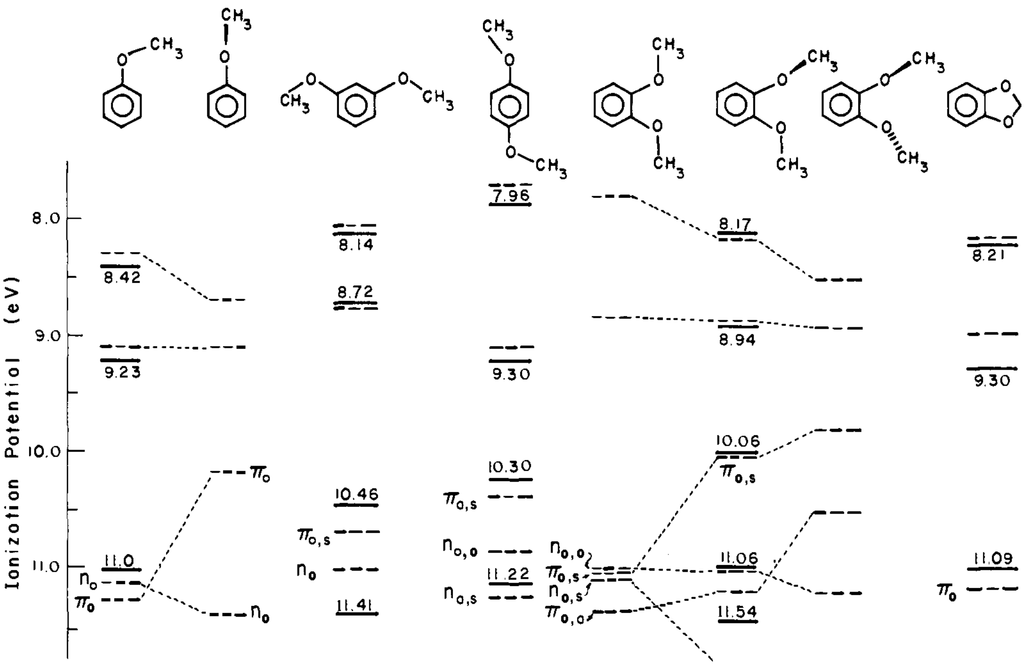


Figure 4. Experimental vertical ionization potentials (solid lines) and STO-3G calculated ionization potentials (dashed lines) from equation $IP_{calcd} = -0.70\epsilon + 3.75$ eV.

nated, so that π_O is substantially destabilized, and the highest occupied molecular orbital (HOMO) is stabilized.

Whereas a reasonable correlation is found for the spectra and calculations on planar conformations of *p*- and *m*-DMBs, the STO-3G predictions made for planar *o*-DMB do not agree with the observed ionization potentials: the calculated HOMO energy of planar *o*-DMB is slightly below that of *p*-DMB and is much above that of *m*-DMB; experimentally, the first IP of *o*-DMB is higher than those of either *p*- or *m*-DMB.

Calculations on the perpendicular conformation of *o*-DMB are in much better agreement with the spectrum. The appearance of the *o*-DMB spectrum is also considerably different from that of the other molecules. In addition to the broadness of the bands, which we attribute to the presence of several conformations in the gas phase (at approximately 60 °C, the temperature of our measurements), shoulders on the first two ionization bands indicate that a minor conformer is also present with significantly lower IPs than the dominant conformer. We attribute these bands to the planar conformation of *o*-DMB.

A third π band falls in the 10-11-eV region for planar anisole and DMBs. For *m*- and *p*-DMB and benzo-1,3-dioxole, this band is relatively sharp and is assigned to ionization from an orbital composed primarily of the symmetric combination of oxygen p lone pairs (π_O) mixed with the aromatic π orbital of the appropriate symmetry. However, for *o*-DMB, the third band is quite broad and appears at 10.06 eV. Such a low and broad third IP is only compatible with the predominance of a nonplanar conformation for *o*-DMB.

Further evidence for the assignment of the third band in the PE spectrum of *o*-DMB to the perpendicular methoxy p-type lone pair comes from comparisons with similar values of IPs of 1,2,3-trimethoxybenzene (the p lone pair of the central methoxy group which is geometrically constrained to a perpendicular is at 9.86 eV)[8] and 2,6-dimethylanisole (the p lone pair of the perpendicular central methoxy group is at 9.85 eV).[4a] In anisole and 2-methylanisole, the p-type lone pairs, which are conjugated in the preferred planar conformations of these species, appear at 11.02 and 10.90 eV, respectively.[4a]

The photoelectron spectra of other alkoxybenzenes[4] and alkoxyethylenes[9] show that the planar conformation is favored except when steric hindrance forces the alkoxy group out of plane. In planar systems, the π ionization potentials are lower than in molecules with analogous nonplanar conformations, and in some cases ionization potentials due to both conformations can be detected.

Unfortunately, attempts to observe changes in the PES upon raising the temperature (60-200 °C) led only to some broadening of bands, but no clear-cut changes which could be attributed to an alteration of equilibrium composition.

Comparison to Solution Data. Analysis of the vibrational spectra of liquid anisole suggests planarity of the methoxy group and a barrier to rotation about the aryl C-O bond of 6 kcal/mol.[20] Kerr constant[21] measurements performed on dilute solutions of anisole indicate a nonplanar minimum energy conformation in which $\phi = 20°$. The rotational barrier in the neat liquid is significantly higher than the gas-phase value, but the Kerr constant measurements are in accord with our calculations if they are interpreted to result from a mixture of planar and perpendicular conformations of anisole with the latter 0.9 kcal/mol higher in energy.

In solution, evidence for the presence of nonplanar methoxy groups in *o*-DMB is found in the measurement of the partition coefficient, dipole moment, and dielectric relaxation time.

The partition coefficient (log *P*), a distribution constant defined by the partitioning of a compound between octanol and water, is usually well represented as the sum of group contributions (π values)[6] of the substituent parts of a molecule. However, dramatic deviations from this additivity rule occur when strong interactions between neighboring groups cause conformational or electronic perturbations which alter the solvation of the substituents. For example, Leo et al.[6] have noted that the measured log *P* of 1,2,3-trimethoxybenzene (TMB) (1.53) is anomalously low in comparison with the expected additive value of 2.07. Furthermore, the π group value for the central nonplanar methoxy, derived by subtracting the partition coefficients of *m*-DMB from TMB ($1.53 - 2.09 = -0.56$), resembles the π value of an aliphatic methoxy (-0.47) more than an aromatic methoxy substituent (-0.02), as does the hybridization of the oxygen lone pairs. We have observed a similar effect in *o*-DMB and in 3,4-dimethoxyamphetamine;

Table IV. Summary of Physical Data Derived from the X-ray Structures of Monomethoxy-, *o*-Dimethoxy-, and *o*-Trimethoxy-Substituted Aromatics

aromatic substitution pattern	no. of groups examined	bond lengths (std dev), Å		bond angles[a] (std dev), deg		dihedral angles[a] (std dev), deg
		C-O	O-CH$_3$	C-C-O	C-O-CH$_3$	C-C-O-CH$_3$
monomethoxy[2]	30	1.37 (±0.02)	1.43 (±0.02)	124 (±1.1)	117.7 (±0.9)	6 (±6)
planar *o*-dimethoxy[5b]	58	1.37 (±0.02)	1.43 (±0.03)	125 (±2)	117 (±2)	7 (±6)
nonplanar *o*-dimethoxy[5a]	2	1.377 (±0.003)	1.41 (±0.03)	119.5 (±0.7)	115 (±1)	110 (±14)
o-trimethoxy[3]						
outer methoxy[b]	6	1.37 (±0.01)	1.42 (±0.02)	124.8 (±0.7)	118 (±1)	5 (±4)
inner methoxy	6	1.37 (±0.01)	1.43 (±0.01)	122 (±2)	115.2 (±0.7)	98.1 (±6.5)
outer methoxy[c]	6	1.371 (±0.006)	1.42 (±0.01)	117 (±4)	117.7 (±1)	5.2 (±1.9)

[a] Angles defined along the side of the aromatic ring bearing the methoxymethyl group. [b] Methoxy substituent furthest removed from the methyl group of the central methoxy. [c] Methoxy substituent nearest to the methyl group of the central methoxy.

the π values of the second methoxy in these compounds are −0.85 and −0.77, respectively.[7] A similar trend was found in several other ortho-disubstituted aromatics such as methoxyethoxy and methoxythiomethoxy, where, in the absence of steric hindrance, the derived π value of the methoxy group is consistently lower than expected, implicating the existence of nonplanar conformations of the methoxy substituents in these compounds. In contrast, the unusually high π value of the 1,3-dioxo group (−0.02 as compared with the expected additivity value of −0.50)[7] supports the conclusion that in solution the predominant conformation of *o*-DMB and derivatives is nonplanar.

Naggy and Hencsei[22] have reported that the experimentally measured dipole moments[23] of anisole (1.25 D), *p*-DMB (1.70 D), and *m*-DMB (1.59 D) can be accurately calculated by assuming free rotation about the Ar-O-CH$_3$ bond and averaging the conformational moments. In *o*-DMB, however, the experimental dipole moment (1.31 D) is dramatically different from the calculated moment of 2.09 D. These results have been interpreted to imply that free rotation (0 to 180°) does not occur in *o*-DMB and that the conformational moments must be weighted by the energies of the respective conformers.[22,24] Consistent with these considerations is the finding by DiBello and others[25] that the dipole moment of *o*-DMB, unlike anisole, *m*-DMB, or *p*-DMB, is temperature dependent in a number of solvents. If the three lowest energy conformations of *o*-DMB (with the optimum geometry) are weighted by their energies and degeneracies, our calculations predict a dipole moment of 1.54 D at 0 °C. Attempts, using our calculated energies and dipole moments, to reproduce the temperature dependence reported by DiBello were unsuccessful, probably owing to an incomplete knowledge of the conformational surface. Still, the increase in dipole moment with increasing temperature may result from population of high-energy conformations such as 90°, 270° which have large dipole moments (2.60 D).

Dielectric relaxation of MBs, as measured in solution by microwave dispersion, is dependent upon both internal rotations and molecular motions. Application of these methods to a series of methyl- and methoxy-substituted aromatics has been made by Roberti and Smyth and others[26a-c] with the consistent finding that the relaxation times of the methoxy compounds are slightly shorter than those of the corresponding methyl analogues; however, in *o*-DMB, the much lower relaxation time indicates that the internal methoxy rotations contribute significantly to the overall molecular relaxation processes. These observations are consistent with the predictions of a low rotational barrier in *o*-DMB reported from microwave studies conducted by Klages and Zentek[27] as compared to other MBs.

NMR measurements have also shown anomalous results for *o*-DMB. Martin and Dailey have shown that the chemical shifts of protons ortho to the methoxy substituents in *o*-DMB are not well expressed as a sum of the group shielding constants.[28a] Further, a study of MBs showed that in *o*-DMB the long-range spin-spin coupling between the OCH$_3$ and ortho protons is much smaller than usual for ortho-substituted anisoles.[28b] Similarly, Dhami and Stothers[28c] have studied the ^{13}C chemical shifts of a series of ortho-substituted anisoles and concluded that for *o*-DMB the magnitude of the chemical shift was poorly expressed as the sum of substituent contributions. These data are consistent with the presence of nonplanar methoxy substituents and low rotational barriers in *o*-DMB.

Additionally, Zweig[29] has found that the transition energies for charge-transfer complexes of many *o*-DMBs are at higher energy than expected on the basis of Hückel calculations and charge-transfer transition energies of other MBs. Naggy and Hencsei[22] have also found that PPP calculations of the UV transition energies for planar arrangements of anisole, *m*-DMB, and *p*-DMB were in good agreement with experimental values, but the high singlet energy of *o*-DMB was poorly predicted by calculations performed on the planar structure.

Comparisons to Crystal Structures. The X-ray crystal structures of numerous methoxy-substituted aromatics were examined in order to determine the preferred conformations of unhindered monomethoxy, *o*-dimethoxy, and *o*-trimethoxy substituents in the solid state. These data are summarized in Table IV. Scrutiny of 30 examples of unhindered monomethoxy derivatives shows the methoxy groups to be nearly planar. The C-C-O angle distortion observed in the optimized anisole geometry calculations was also present in the X-ray structures (anisole optimum = 125.5°, compared to 124.5° found in crystals). A planar orientation of methoxy groups was found in 30 of the 32 unhindered *o*-dimethoxy derivatives. However, for no obvious reason, the crystal structures of two unhindered *o*-dimethoxy compounds contained both a planar and a perpendicular methoxy group. In these derivatives, the nonplanar methoxy groups reside in a void in the crystal, have unusually large thermal parameters, and have significantly lower C-C-O angles (119.5 ± 0.7°) than the planar value of 125°. In the *o*-trimethoxy substituted compounds, the outer methoxys are nearly planar whereas the central methoxy is almost perpendicular. Both calculations and X-ray structures indicate that nonplanar methoxys have a significantly smaller COC angle (110°, calculated; 115°, X-ray) than planar me-

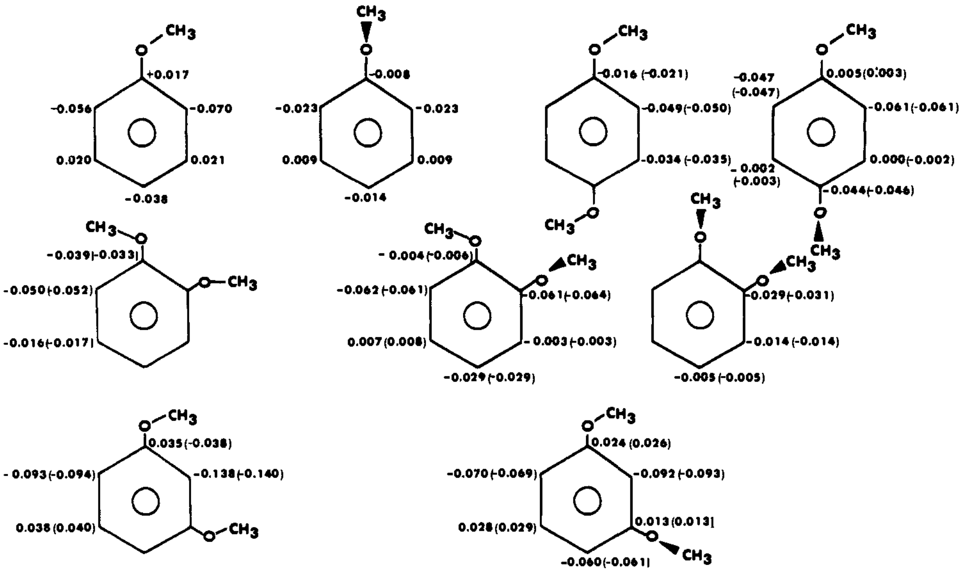


Figure 5. Carbon π charges in anisole (**1**) and the dimethoxybenzenes (**2–4**) in both planar and perpendicular conformations. For the dimethoxybenzenes, the charges in parentheses are those predicted by adding the appropriate anisole charges.

thoxys (117–118° calculated and X-ray). A common feature found in this substitution pattern is the expansion of the C-C-O angle of one of the outer methoxys and the contraction of the other.

In contrast to the gaseous and liquid phases, the preferred orientation of *o*-DMBs is clearly planar in the crystalline state. While many forces are known to affect conformations in crystals, planarity here probably results from stacking forces, which clearly favor the planar forms. Indeed, the 2.4 kcal/mol higher rotational barrier found for anisole in the neat liquid as compared with the gas-phase value is probably a manifestation of these stacking forces, even in solution.[11] Analysis of the immediate environment of the methoxy group in a manner similar to that proposed by Kitaigorodsky[30a] reveals that the space surrounding the two nonplanar *o*-DMBs is 37% freer than that in the corresponding planar structures; hence the favored planarity in the crystal structure is apparently associated with favorable crystal packing.[30b]

Origin of Variable Barriers to Rotation of Aromatic Hydroxy and Methoxy Groups

The trends in barriers to rotation observed for both HBs and MBs can be explained by resonance arguments such as those used by Radom et al.[2b] or by more detailed frontier orbital interaction arguments. Both of these approaches will be discussed here.

Correlations between π Charge Densities and Rotational Barriers. The ring carbon π charge densities from STO-3G calculations on phenol, anisole, and *o*-, *m*-, and *p*-DMBs are shown in Figure 5. For anisole, the net π charges (relative to benzene) are negative at the ortho and para positions and positive at the meta position. Methoxy or hydroxy are strong donors and polarizers when planar, and the planar conformation is most strongly favored when a second methoxy group is attached at the meta position. However, when attached para to a second methoxy, the planar conformation is destabilized somewhat, since rotation from planarity relieves electron donation to an already electron-rich carbon. Attachment at the ortho position is even less favorable owing to the larger negative charge at carbons ortho to a methoxy group.

This argument is of practical value, since the π charges of *o*-, *m*-, and *p*-DMBs can be easily calculated from the π charges of anisole (Figure 5). For example, the π charge on the carbon between the methoxys in *m*-DMB would be predicted to be −0.070 + −0.070 = −0.140, and the STO-3G calculated π charge is −0.138. The π charges of the other dimethoxybenzenes can be estimated simply by adding appropriate charges from the anisole calculation. The agreement with the STO-3G calculated π charges is very good (average error = 0.002, largest error = 0.006) not only for all planar conformations, but for conformations involving planar and perpendicular methoxy groups in the same molecule (using anisole, $\phi = 90°$, to derive the charges for DMBs with perpendicular methoxys). The reason this additivity works so well is that the perturbations of the benzene π electron distribution induced by the OMe groups are relatively small, as noted by Hehre et al.[13] The net π charge transferred to the benzene ring in anisole is only −0.1 e and the polarization of the π charges in the ring is at least as important as charge transfer in determining charge distributions.[31]

The predicted π charges on the carbon to which the methoxy is bonded correlate well with the rotational barrier; π charges of 0.035, 0.017, −0.016, and −0.039 for *m*-DMB, anisole, *p*-DMB, and *o*-DMB correspond to STO-3G calculated rotational barriers of 2.2, 0.9, 0.2, and −0.7 kcal/mol.[32] Focusing on the change in the π charge of the carbon to which the OH is attached for the para-substituted phenols analyzed by Radom et al.[2b] gives an excellent correlation with the calculated rotational barriers of para-substituted phenols. For X = OH, F, CH_3, H, CHO, CN, and NO_2, the π charges are −0.039, −0.021, −0.012, 0, 0.018, 0.028, and 0.043; the changes in the rotational barriers (relative to phenol) are −0.95, −0.53, −0.28, 0, 0.47, 0.66, and 1.02 kcal/mol, respectively.[33]

The good correlations between the calculated barriers and the π charges allows one to qualitatively predict rotational barriers in any polysubstituted benzene, for substituents for which the π charges in the monosubstituted species are available. Hehre et al.[13] have reported STO-3G calculations for 32 monosubstituted benzenes, so that rotational barriers may be easily predicted for most ordinary substituted aromatics.

Because of our interest in the properties of psychotomimetic phenylisopropylamines, we will discuss one example, that of 2,4,5-trimethoxyphenylisopropylamine, a particularly potent hallucinogen.[34] Photoelectron spectra reported earlier indicate that the influence of the aminopropyl side chain upon the electronic structure of the aromatic ring is essentially identical with that of a methyl group.[35] For that reason, 2,4,5-trimethoxytoluene is a reasonable model for this psychoto-

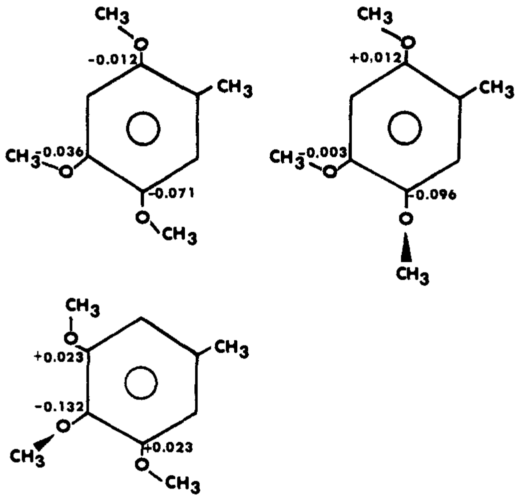


Figure 6. Predicted π charges at the methoxy positions for 2,4,5- and 3,4,5-trimethoxytoluene.

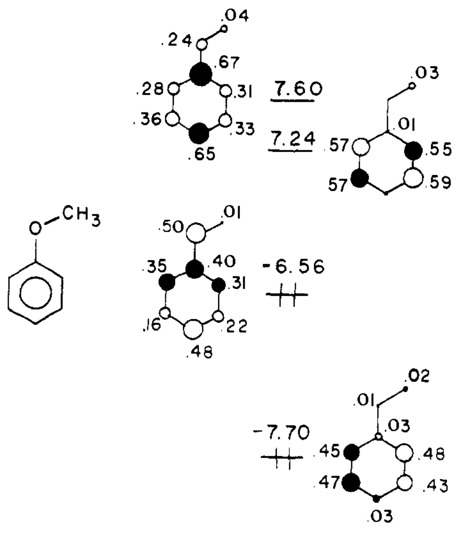
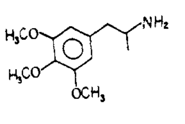
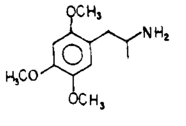


Figure 7. π molecular orbitals of anisole (STO-3G).

mimetic. The additively predicted π charges for the molecule given in Figure 6 suggest that the 5-methoxy group will be in a perpendicular conformation. Adjusting the charges accordingly, one predicts that the 2 and 4 methoxy groups may prefer planarity, but not by as much as the methoxy group in anisole. Put another way, the methoxy group ortho to one and para to another methoxy has a greater preference for nonplanarity than a methoxy ortho to one and meta to another.

This prediction allows the rationalization of the fact that substitution of the 4-methoxy by 4-ethoxy in 3,4,5-trimethoxyphenylisopropylamine (**12**) increases psychotomimetic potency by ~10, whereas the same substitution in the 2,4,5 compound (**13**) has no effect on the potency.[34] In the 3,4,5-trimethoxy compound, the 4-methoxy group is forced out of the ring plane by the steric and electronic effects of the neighboring 3- and 5-methoxys, while the 3- and 5-methoxys remain planar; in **13**, the 5-methoxy has the largest tendency for nonplanarity and the 4-methoxy prefers planarity. Thus, one expects the ethoxy group in 4-ethoxy-3,5-dimethoxyphenylisopropylamine to interact significantly with the receptor surface,[34] since the 4-ethoxy group extends out of the plane of the aromatic ring. However, the 4-ethoxy, like the 4-methoxy, of **13** is planar, and neither methyl nor ethyl groups can interact with the same hydrophobic part of the receptor surface.





The application of π charges to rationalize and predict rotational barriers is a simple and useful method which should be applicable to systems other than substituted benzenes such as alkoxyheteroaromatics and vinyl ethers. Steric effects can also play a role, but these are not necessarily large, even when groups are in close proximity; for example, *o*-methylphenol and *o*-methylanisole are planar.[4a]

A Frontier Orbital Model for Rotational Barriers. A more detailed rationalization of the variable rotational barriers can be constructed with the aid of the high-lying filled and low-lying vacant MOs of anisole, shown in Figure 7. As described in detail elsewhere, the degeneracies of the HOMOs and LUMOs of benzene are not only split by donor substitution, but significant polarization of these orbitals occurs as well, so that the highest occupied MO (HOMO) has coefficients $p > o > m$ and the second lowest unoccupied MO (SLUMO) has coefficients $p > m > o$.[8,31]

It has been shown in many previous investigations that the preferred conformations of molecules are those which maximize overlap between the high-lying filled orbitals of one fragment and the low-lying vacant orbitals of the other fragment (which leads to stabilizing two-electron interactions) and minimize overlap of the high-lying filled orbitals of the two fragments (which leads to destabilizing four-electron interactions).[36] Such arguments, along with the anisole MOs (which are very similar to those of phenol), can be used to rationalize the trends found here.

In benzene, the HOMO and SHOMO are degenerate, as are the LUMO and SLUMO. Attachment of a planar methoxy at any carbon results in four-electron closed-shell repulsion due to overlap of the filled methoxy π_O orbital with one of the filled aromatic HOMOs, and a stabilizing two-electron interaction of the filled π_O orbital with one of the aromatic LUMOs. In anisole, the six carbons are no longer equivalent owing both to the split in degeneracy and to the coefficient polarization. The HOMO is polarized away from the meta position, so that attachment of methoxy here results in less closed-shell repulsion than upon attachment of a methoxy to benzene.[31] At the same time, the SLUMO is polarized toward the meta carbon, and a larger π_O-SLUMO stabilizing interaction will result than when a methoxy is attached to benzene. Both of these effects increase the stabilizing effect of the second methoxy group and favor the planar conformation of *m*-DMB more than in anisole.

However, the HOMO has increased coefficients at the ortho and para positions relative to benzene. Similarly, the SLUMO is polarized away from the ortho and para positions. Less stabilization occurs upon attachment of a methoxy at these carbons, and barriers to rotation decrease.

The SHOMO and LUMO are essentially unaffected by the methoxy substituent, so that the influence of these orbitals on barriers to rotation of the second methoxy group is identical with the influence of these orbitals on the anisole barrier.

The parallelism of closed-shell repulsion between π_O and HOMO and stabilizing π_O-SLUMO interaction is no accident. In fact, much of the polarization of the anisole HOMO and SLUMO arises from admixture of the corresponding benzene orbitals in a negative fashion at the site of methoxy substitution in the HOMO and in a positive fashion in the LUMO.[31] The orbital polarizations which result also force electron density onto the ortho and para positions at the expense of the meta positions.

Further insight can be obtained by comparing the rotational barriers in MBs to the corresponding barriers in $H_2N\text{-}CH_2^+$ and $HO\text{-}CH_2^+$. In contrast to anisole or phenol, the rotational barriers in these carbonium ions increase as the charge residing in the carbon p-π orbital increases.[37] The dissimilar rotational barriers result from differences in the nature of the substituent perturbations; in the carbonium ions, only a bonding interaction occurs between the substituent orbital (filled) and the empty carbonium p orbital, whereas in MB both stabilizing and destabilizing interactions result from substituent perturbations. As discussed previously, the preferred planarity of MB or HB implies that the destabilizing influences are outweighed by the stabilizing influences. However, the relationship between the changes in the rotational barriers for methoxy-substituted benzenes and the carbon p-π population ipso to the methoxy group suggests that these barrier differences are dominated by the antibonding interactions illustrated by the HOMO shapes in Figure 7. Thus a decrease in the π charge on the ipso carbon is indicative of a reduction in the magnitude of the antibonding interactions.

Both of these qualitative explanations are quite general. For π systems with significant polarization, such as nonalternant hydrocarbons and heterocycles, hydroxy or methoxy groups attached to sites of plus charge or sites with small HOMO coefficients and large LUMO coefficients will have high rotational barriers. Conversely, attachment of a hydroxy or methoxy at a site of negative charge, or a site with large HOMO coefficient and small LUMO coefficient, will result in low rotational barriers or even nonplanarity. Interestingly, this is not a steric effect at all, but instead a pure electronic effect.

Conclusions

The results reported here show that *o*-dimethoxybenzene and derivatives exist in predominantly nonplanar conformations in the gas phase. Anomalies found in the measurements of the partition coefficients, dipole moments, and dielectric relaxation times of this compound are manifestations of similar conformations in solution. The X-ray crystal structures of most of these derivatives reveal planar arrangements of the methoxy groups; in two cases, a nonplanar orientation was found. Comparisons of the unit cell environments of the planar and nonplanar structures indicate fewer intermolecular contacts in the nonplanar analogues, suggesting that crystal packing favors the planar forms in the solid state. Analyses of the ab initio calculations indicate that the low rotational barrier and the nonplanar conformational preference of *o*-dimethoxy groups results from unfavorable electronic rather than steric repulsions occurring in the planar forms.

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Chiral Trialkylborane Reducing Agents. Preparation of 1-Deuterio Primary Alcohols of High Enantiomeric Purity

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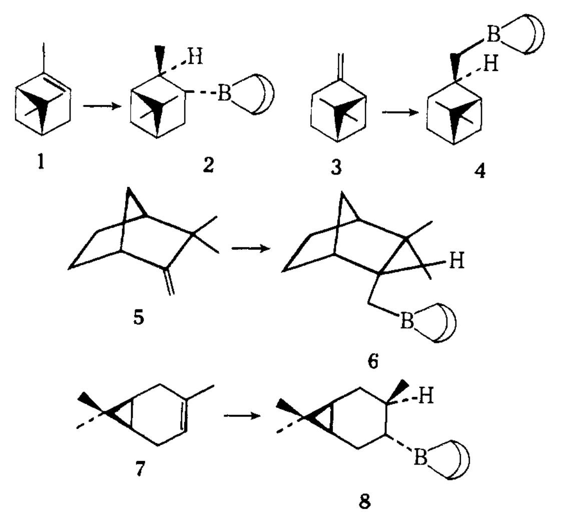
Abstract: *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane (3-pinanyl-9-BBN, prepared from (+)-α-pinene and 9-BBN) is an effective chemical reagent for the asymmetric reduction of 1-deuterio aldehydes to chiral 1-deuterio primary alcohols. For example, benzaldehyde-*1*-*d* is reduced to pure (*S*)-(+)-benzyl-*1*-*d* alcohol. A deuterated reagent prepared from α-pinene and 9-BBN-9-*d* was found to reduce a variety of aromatic, aliphatic, and α,β-unsaturated aldehydes to the corresponding chiral primary 1-deuterio alcohols. In each case a large excess of the *R* enantiomer is formed. Steric factors seem to have little effect on the extent of asymmetric induction, but electron-donating para substituents on benzaldehyde slightly decrease the enantioselectivity of the reduction. A number of other chiral-9-BBN derivatives were investigated. A model is proposed to account for the high asymmetric inductions.

We have previously shown that certain *B*-alkyl-9-borabicyclo[3.3.1]nonane (9-BBN) compounds reduce aldehydes under exceptionally mild conditions.[3] Thus the sluggish reaction originally reported by Mikhailov[4] can be made into a useful technique for the selective reduction of aldehydes.[5] Using the chiral reagent derived from α-pinene and 9-BBN, we have shown that benzaldehyde-*1*-*d* may be reduced to chiral benzyl-*1*-*d* alcohol of exceptionally high enantiomeric purity.[6] Such optically active primary 1-deuterio alcohols have been used extensively for mechanistic studies of chemical and biochemical processes.[7] However, previous techniques for their preparation are tedious or inefficient.[8] Herein we establish the organoborane route as an effective general method for the preparation of diverse 1-deuterio primary alcohols of high enantiomeric purity.

Results and Discussion

In the initial experiments the readily prepared[9] benzaldehyde-*1*-*d* was reduced by the *B*-alkyl-9-BBN reagents derived from (+)-α-pinene (**1**), (−)-β-pinene (**3**), (−)-camphene (**5**), and (+)-3-carene (**7**) (Scheme I). The optical purity of the resulting benzyl alcohol was determined using the chiral NMR shift reagent tris[(3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III),[8d] $Eu(hfc)_3$. The results are given in Table I. Since both enantiomers of α-pinene are readily available in high optical purity[10] and since the corresponding borane, **2**, gave the best results, it was chosen for further studies.

Scheme I



In refluxing tetrahydrofuran (THF), the 3-pinanyl-9-BBN

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