MOLECULAR ORBITAL CALCULATIONS AND ^{13}C NMR STUDIES TO EXPLAIN THE SELECTIVE DEMETHYLATION OF 3-ALKYL-1,2-DIMETHOXYBENZENES

By

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CHAPTER I

INTRODUCTION

The specific cleavage of methyl ethers of 3-alkyl catechols (ortho dihydroxy benzenes) has been reported.[1,2,9a,b] A methoxy group flanked by substituents (one of which is another methoxy group) on both sides is preferentially cleaved as compared to one having a single neighbor when a Lewis acid such as boron tribromide or iodotrimethylsilane is used. The central methoxy group also shows a downfield ^{13}C shift of about 4 ppm in the NMR spectrum as compared to that of an isolated methoxy group.[1] Thus, the ^{13}C shift and selective cleavage seem to be related.

The purpose of this study is to present an explanation of these phenomena. Model compounds were synthesized and purified for NMR studies, including spin-lattice relaxation time (T_{1s}) measurements. Molecular orbital calculations were also carried out using a PRDDO[3-5] (partial retention of diatomic differential overlap) computer program to obtain the least energy configuration of each molecule and the electron densities of the atoms.

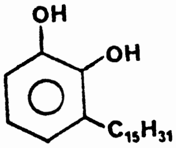
This study could be of utility in natural product work and in medicinal chemistry, since many natural products have a catechol nucleus or the corresponding mono- or dimethyl ethers.

CHAPTER II

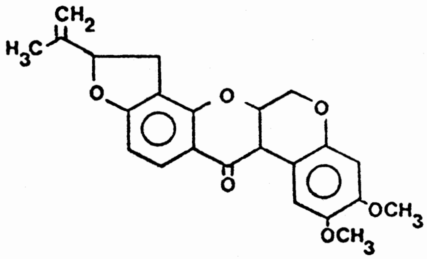
HISTORICAL

Selective Demethylation

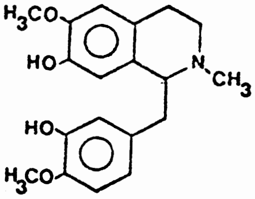
The acid cleavage of ethers is an important reaction in synthetic organic chemistry. Ethers are prevalent in natural products and numerous drugs, and they are frequently used as protecting groups for phenols. Selective methylation and demethylation is important in many compounds with a catechol nucleus. Examples of compounds whose synthesis depends upon selective cleavage are derivatives of 3-n-pentadecylcatechol (3-PDC), a component of poison ivy.[6] Rotenone, an insecticide and fish poison,[1] and reticulene, an intermediate in morphine biosynthesis, are other examples.



3-PDC



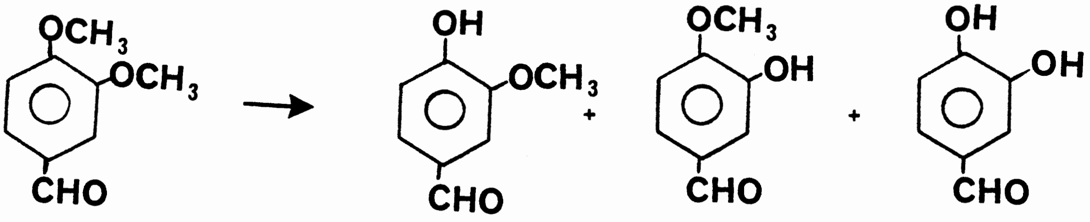
Rotenone



Reticulene

Several acidic reagents have been used to demethylate phenol ethers. These reagents include aluminum chloride, boron tribromide, hydrogen bromide, hydrogen iodide, pyridine hydrochloride, and iodotrimethylsilane. Some of the more common Lewis acids have been compared in the demethylation of veratraldehyde (1a) (for structures see Appendix B). Veratraldehyde (1a) was selectively cleaved to either vanillin (1b), isovanillin (1c), or 3,4-dihydroxybenzaldehyde (1d) by varying the acid concentration as shown in Table I. The reaction is presented in Scheme I. Other examples of selective demethylations are shown in Table II.

Scheme I



1a 1b 1c 1d

Methoxy groups positioned ortho to a carbonyl group are selectively cleaved. The selective dealkylation in these cases is thought to depend upon coordination of the boron atom with two oxygen atoms to form the six-membered ring intermediate shown in Scheme II.[8] The final complex is easily disrupted by water resulting in the formation of the corresponding phenol.

Scheme II

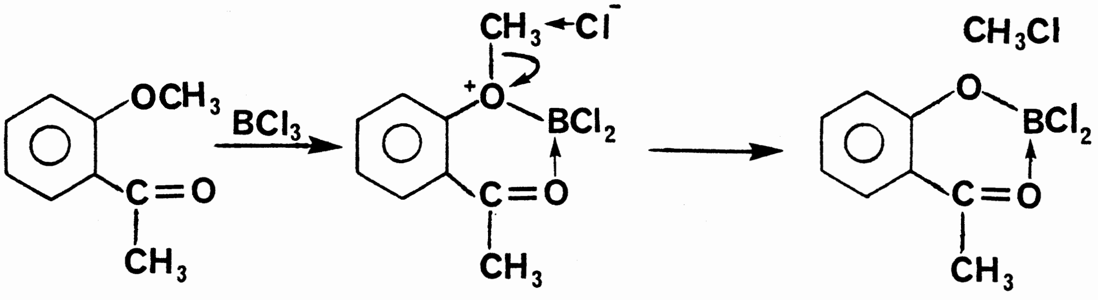


TABLE I

DEMETHYLATION OF VERATRALDEHYDE (<u>1a</u>) WITH LEWIS ACIDS

Reagent		Relative Percent[a]		
		<u>1b</u>	<u>1c</u>	<u>1d</u>
$AlCl_3$[b]	0.5 moles[c]	--	100	--
$AlCl_3$	0.7 moles	5	95	--
$AlCl_3$	1.0 moles	35	55	10
$AlCl_3$	1.5 moles	78	3	19
$AlCl_3$	2.0 moles	65	2	33
BCl_3[d]	0.5 moles	--	100	--
BCl_3	1.5 moles	84	7	9
BBr_3[e]	0.5 moles	5	95	--
BBr_3	1.5 moles	50	--	50
Pyridine HCl[f]	0.25 moles	46	54	--
Pyridine HCl	0.5 moles	42	39	19
Pyridine HCl	1.0 moles	--	--	100

[a] Determined by GLC on a 6 ft SE-100 column at 180°.

[b] In benzene, 40 min at 90°.

[c] Relative to veratraldehyde (<u>1a</u>).

[d] In light petroleum, 3 h at 10°.

[e] In benzene, 3 h at 80°.

[f] Five min at 180°.

TABLE II

SELECTIVE DEMETHYLATIONS OF CATECHOL ETHERS

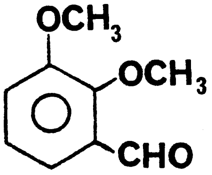
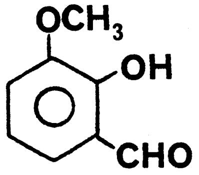
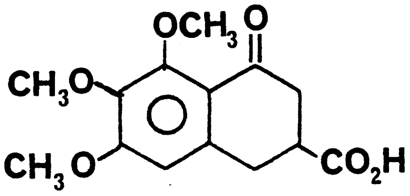
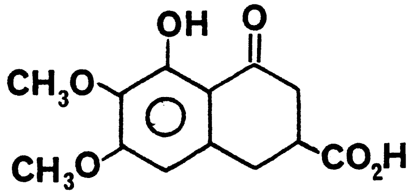
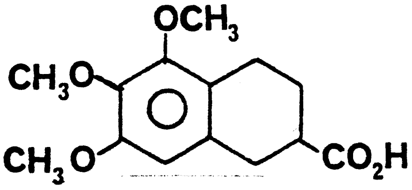
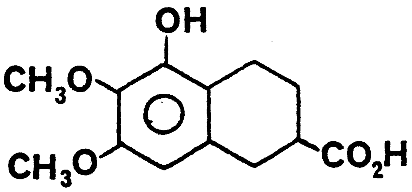
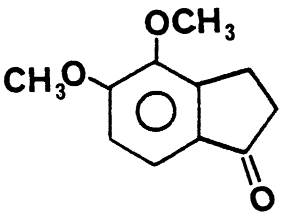
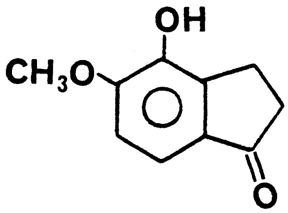
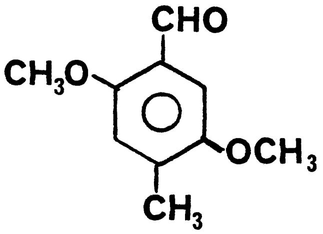
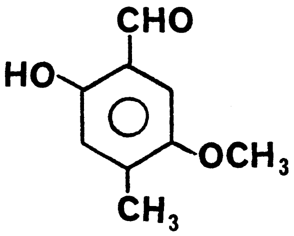
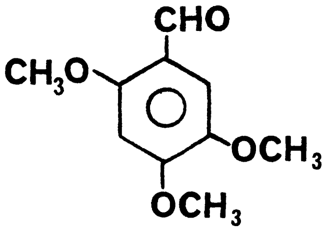
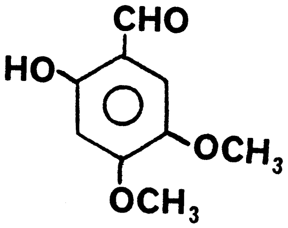
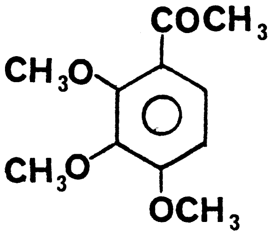
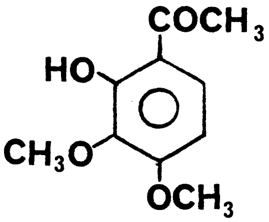
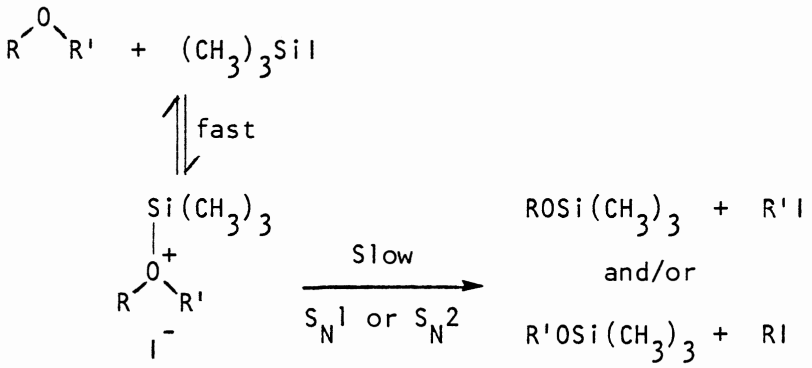
Reactant	Acid	Product	Yield %
	BCl_3		93^{8}
	BCl_3		86^{9a}
	Ditute HCl		95^{9a}
	Methionine, methane sulfonic acid		70^{9b}

TABLE II (Continued)

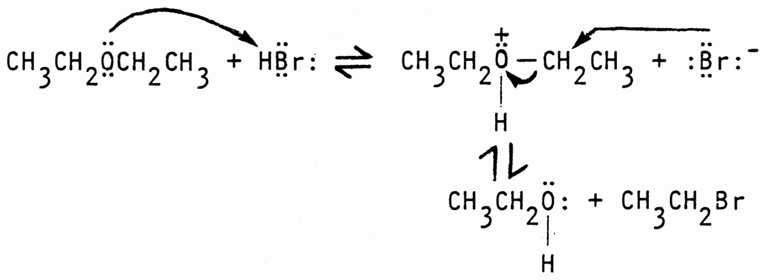
Reactant	Acid	Product	Yield %
	BCl_3		65[10]
	BCl_3		86[11]
	BCl_3		88[12]

The mechanism proposed for the general cleavage of ethers using iodotrimethylsilane is shown in scheme IIIa[13] and this rationalization may be applied to the dealkylation by other Lewis acids of catechol ethers. The mechanism for the cleavage of ethers (ethyl ether, for example) using proton acids is shown in scheme IIIb.[14] Primary alkyl groups tend to undergo S_N2 displacement by halide or other nucleophiles, whereas tertiary alkyl groups are cleaved through an S_N1 process.

Scheme IIIa



Scheme IIIb



As mentioned earlier, a methoxy group flanked by another methoxy group on one side and an alkyl group on the other side is cleaved preferentially as compared to one having a single neighbor.[1,2,9a,b] Prior to this study, there was no satisfactory explanation for this phenomenon.

During cyclization of 4,5-dimethoxy-2-methylcrotonophenone (2), there is specific cleavage of the methoxy groups to yield 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (3a) as shown in scheme IV.[1,15] The structure of 3a was distinguished from 3,7-dimethyl-5-hydroxy-4-methoxy-1-indanone (3b), 3,7-dimethyl-4,5-dimethoxy-1-indanone (3c), and 3,7-dimethyl-4,5-dihydroxy-1-indanone (3d) by infrared (IR) dilution studies, ^{13}C chemical shifts, and by studying the effect of Sievers' reagent on the ^{1}H NMR spectrum.[1] The cleavage reaction also was studied by using a variety of acids. The results are shown in Table III.[1] All the acids caused formation of 3a except p-toluene sulfonic acid (pTSA) which failed to cause a reaction, and Amberlyst XN-1010[16] which caused cyclization but no ether cleavage to form 3c.

TABLE III

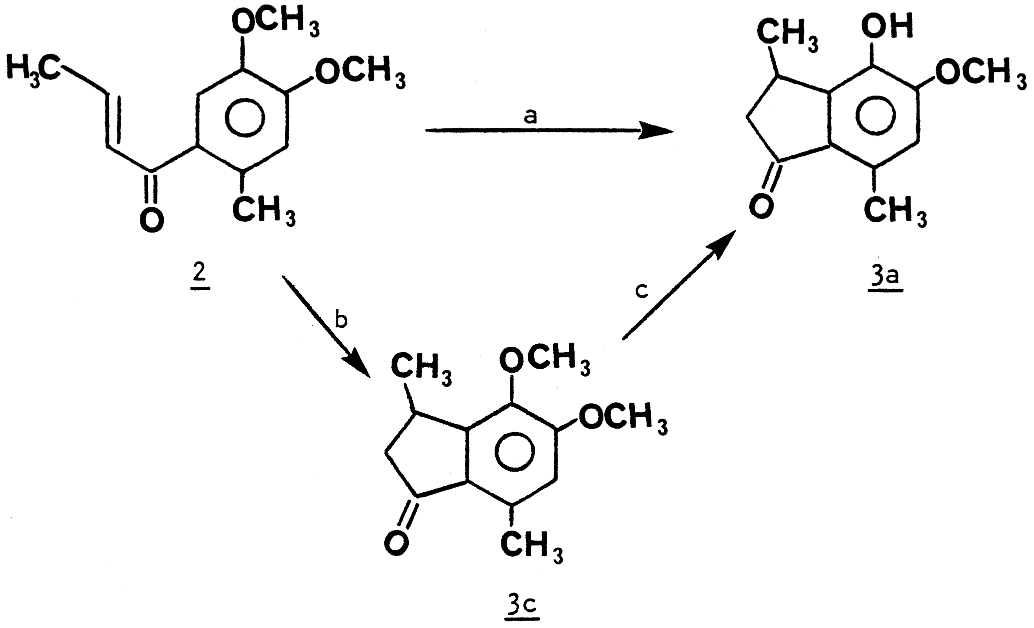
REACTION CONDITIONS FOR THE CYCLIZATION OF 4,5-DIMETHOXY-2-METHYL-2-CROTONOPHENONE (2)

Acid	Conc. of Acid	Hours	°C	Yield
A-15[a] + water[b]	10g/L	42	138	40% of 3a
A-15 (anh.)[b]	10g/L	42	138	40% of 3a
A-15[c]	10g/L	42	132	40% of 3a
CH_3SO_3H[c]	Neat	2	130	30% of 3a
CH_3SO_3H[c]	50% by Vol.	4	132	40% of 3a
CH_3SO_3H[c]	4.4g/L	24	132	38% of 3a
PTSA[c]	8g/L	24	132	NR
XN-1010[c,d]	10g/L	42	132	40% of 3c

[a] Amberlyst-15. [b] Xylene. [c] Chlorobenzene. [d] Amberlyst XN-1010.

To determine if the demethylation occurred before or after cyclization, 3c was treated with Amberlyst 15 in refluxing xylene. This treatment also produced the ketophenol 3a. This shows that the methoxy group cleavage may have occurred after the cyclization.[1] Scheme IV summarizes the aforementioned reactions. Treatment of 3c with iodotrimethylsilane and boron tribromide gave only 3a. The catechol 3d was not obtained, even though 2.2 equivalents of iodotrimethylsilane were used. Addition of 4.2 equivalents of boron tribromide to 3a failed to provide the catechol, even though the latter reagent is known to convert keto diethers to keto catechols.[7]

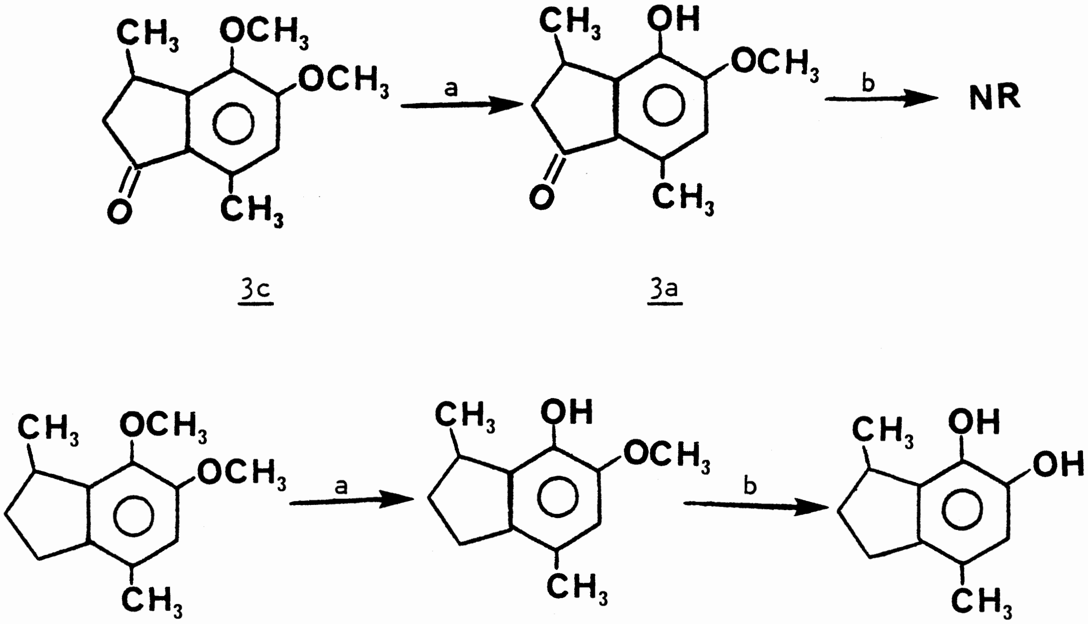
Scheme IV



[a] Various acids. [b] Amberlyst XN-1010. [c] Amberlyst 15.

A different result was obtained when 4b was reacted with 2.2 equivalents of iodotrimethylsilane followed by 8.1 equivalents of boron tribromide. The reaction of iodotrimethylsilane yielded the monophenol 4a and the reaction of boron tribromide yielded the catechol 4d. A summary of these demethylations is reported in scheme V.[1]

Scheme V



3c 3a

4b 4a 4d

[a]Excess iodotrimethylsilane. [b]Excess boron tribromide.

Similar demethylations were carried out on some model compounds to determine whether the demethylations were general in nature. The results are given in Table IV.[1] 1,2-Dimethoxybenzene (5a) yielded an approximately statistical ratio of 5a, 2-methoxyphenol (5b), and catechol (5d) when reacted with 1.1 equivalents of iodotrimethylsilane or boron tribromide. Treatment of 5a with 2.2 equivalents of either reagent provided a quantitative yield of catechol (5d).

TABLE IV

DEMETHYLATION OF 5a, 5b, 6b, 7b, AND 8b

Starting Material	Equiv. TMSI[a]	Equiv. BBr_3	Products (%)			
			5a	5b		5d
5a	1.1		21	64		15
5a		1.1	18	60		22
5a	3.3		0	0		100
5a		3.3	0	0		100
			5b	5d		
5b	1.1		33	67		
5b		1.1	0	100		
			6a	6b		6c
6b	1.1		0	6		94
6b		1.1	18	40		42
6b	3.3		70	0		30
6b		3.3	100	0		0
			7a	7b		7c
7b	1.1		4	0		96
7b		1.1	46	30		24
7b	3.3		53	0		47
7b		3.3	100	0		0
			8a	8b	8c	8d
8b	1.1		13	28	33	26
8b		1.1	22	31	26	21
8b	3.3		100	0	0	0
8b		3.3	100	0	0	0

[a] Iodotrimethylsilane.

The reaction of either 1,2-dimethoxy-3-methylbenzene (6b) (2,3-dimethoxytoluene) or 1,2-dimethoxy-3-(1-methylethyl)benzene (7b) with 1.1 equivalents of iodotrimethylsilane yielded only the monophenol corresponding to cleavage of the middle methoxy group, 6c or 7c.

When 3.3 equivalents of iodotrimethylsilane were used, a mixture of the monophenol 6c or 7c and the catechol 6a or 7a was obtained. The use of 3.3 equivalents of boron tribromide gave only the catechol 6a or 7a.

The selective demethylations could result from steric factors due to the crowding caused by the ortho substituents or as a result of electronic factors since both ortho substituents are electron releasing. If the selectivity was caused by electronic factors, the same effect should be observed when catechol ethers with a para alkyl group are reacted instead of catechol ethers with an ortho alkyl group. 4-Methylveratrole (8b) was subjected to the same conditions as used for the ortho substituted catechol ethers. As shown in Table IV,[1] there is no significant regioselectivity. Therefore, the regioselectivity observed in demethylating 3c, 4b, 6b, and 7b must be caused by steric factors and not electronic factors.

^{13}C NMR Studies

In every compound that exhibits regiospecific methoxy group cleavage reported by Vickery, the methoxy group most vulnerable to cleavage (the middle one) shows a downfield ^{13}C NMR shift of about 4 ppm.[1] He has postulated that the specific cleavage and ^{13}C NMR shift have related origins.

There are several literature precedents showing hindered methoxy groups having a downfield shift.[17-22] In diortho-substituted anisoles the signal is shifted progressively to lower fields as the bulk of the substituted groups increases from methyl to *t*-butyl.[17] The methoxy absorption peak for 2,6-di-*t*-butylanisole is about 7 ppm downfield from that of 2,6-dimethylanisole and about 10 ppm downfield from that of anisole. It has been suggested that the steric crowding of the ortho groups causes the electron release of the methoxy group to be significantly reduced.[17] The NMR shifts of the ring carbons support this hypothesis.

^{13}C NMR Relaxation

A relatively new tool for examining the environments of carbon atoms is the study of relaxation times.[22-27] Relaxation time is the time required for nuclei population to return to a Boltzman distribution.

In a magnetic field, nuclei (with I = 1/2) can have two orientations with respect to the field. It may be aligned with the field (the low energy state) or against the field (the high energy state). The amount of energy required to flip nuclei to a higher energy state depends upon the environment of the particular type of nuclei and the strength of the magnetic field. When the proper radio frequency is passed through the sample at a given magnetic field strength, absorption occurs. Upon relaxation, the nuclei emit energy which is detected as an NMR signal.[23]

According to the Boltzman distribution law, the ratio of the number of nuclei in the lower energy level to the number of nuclei in the upper energy level is:

$$e^{\Delta E/RT} = e^{2\mu H_o/KT}$$

where ΔE is the change in energy, R and K are the gas constants, T is the absolute temperature, μ is the nuclear magnetic moment, and H_o is the magnetic field. At room temperature and a magnetic field of 1.4 Tesla, the lower state population exceeds that of the higher state by only 0.0001 percent.[26] If no relaxation mechanisms were present, saturation would occur and the NMR signal would degenerate to zero.

There are two types of nuclear relaxation. Spin-spin relaxation (measured as T_2-values) occurs when a nucleus transfers its energy to a neighboring nucleus. In spin-lattice relaxations (T_1), the energy of the nuclear spin is converted into thermal energy of the molecular system (solvent plus solute--the lattice). Relaxation times, T_2 and T_1, are measures of the efficiency of these relaxations. T_1 studies have been the most useful in studying the environments of carbon nuclei.

There are several spin-lattice relaxation mechanisms.[23-27] Dipole-dipole relaxation is usually the most important. This efficient relaxation mechanism occurs when the nucleus undergoing relaxation is directly bonded to a second nucleus possessing a magnetic spin. The lack of this mechanism gives quaternary carbons their characteristic long relaxation times.

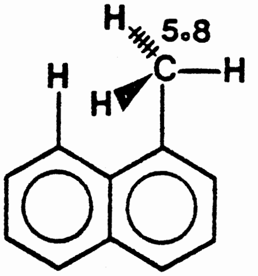
Spin-rotation relaxation is an important relaxation mechanism in small highly symmetrical groups such as aliphatic side chains or methyl groups. This arises from fluctuating magnetic fields generated by the movement of atoms within the molecule. An increase in spin-rotation relaxation leads to a decrease in the more efficient dipole-dipole relaxation and thus to a longer relaxation time.

Paramagnetic relaxation occurs when dissolved oxygen or other paramagnetic impurities are present in the sample. Paramagnetic substances such as chromium acetylacetonate are often added to samples to enhance the signal, but they must be excluded if consistent T_1 measurements are to be obtained.

Scalar relaxation and chemical shift anisotropy are less important types of relaxation mechanisms. The former occurs when ^{13}C nuclei are spin-spin (scalar) coupled to a nucleus that is undergoing rapid spin-lattice relaxation because of the fluctuating scalar interaction between the two nuclei. The only cases where this mechanism has proven important is in cases where bromine is directly bonded to carbon. The latter occurs because of anisotropy in the shielding tensor of the nucleus when the molecule tumbles in solution.[23]

Since T_1 values are dependent on molecular reorientation, they can be used as sources of information for molecular motions. The information can be used to make spectral assignments and in studies of hindered rotation, axes of rotation, segmental motion, association, and complexation.

An interesting example of the effect of hindered rotation on methyl ^{13}C T_1 values is found for 1-methylnaphthalene (13) and 9-methylanthracene (14) which yield values of 5.8 sec and 14.5 sec, respectively.[23] In 13 the interaction with the *peri* proton causes a preferred orientation, thereby hindering its rotation and leading to a smaller T_1 value. In 14 there is no longer a preferred conformation of the methyl group because of the additional *peri* hydrogen, thus enhancing rather than retarding rotation and increasing the T_1 value.



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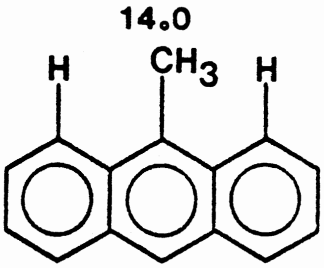
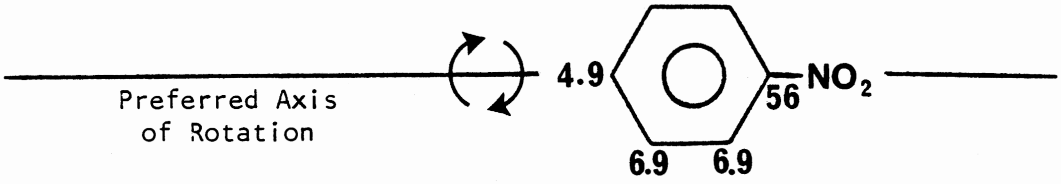


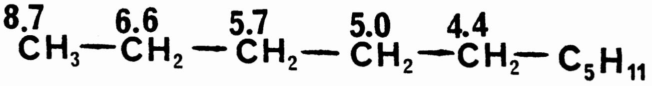
14

An example of a preferred axis of rotation affecting ^{13}C T_1 values is nitrobenzene (15).[23] Since both C_1 and C_4 lie along the axis of rotation, rotation about it does not contribute to the correlation time (the average time for a molecule to rotate through one radian) and thus a shorter T_1 value is observed.



15

Whenever a molecule consists of both rigid and flexible parts, the degree of motion in the flexible region will be higher than that in the rigid region, leading to shorter correlation times and thus longer T_1 values. Decane (16) exhibits segmental motion because the ends of the chain have the greatest flexibility and hence the larger T_1 values.[23]

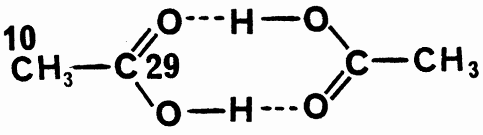


$$\overset{8.7}{CH_3}-\overset{6.6}{CH_2}-\overset{5.7}{CH_2}-\overset{5.0}{CH_2}-\overset{4.4}{CH_2}-C_5H_{11}$$

16

Compounds with a high molecular weight tend to have shorter T_1 values than low molecular weight compounds. If a molecule can associate or complex with other molecules, its effective molecular weight will increase, thus increasing the correlation time and decreasing the T_1 values. For comparison, acetic acid and methyl acetate are given as examples.[23]

The T_1 values for acetic acid (17) are smaller than those of methyl acetate (18) because acetic acid can associate and methyl acetate cannot.



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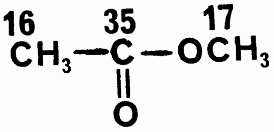


18

Molecular Orbital Calculations

Quantum mechanical calculations are frequently used to study organic compounds.[3-5,28-30] Information such as bond angles, bond distances, atomic electron densities, and reaction pathways can be obtained from such calculations. Because of its complexity, the Schrödinger equation

$$H\Psi = E\Psi$$

is not solved exactly. Instead, two types of less rigorous calculations have been performed. In the ab initio approach, the correct Hamiltonian operator is used, and all integrals are evaluated rigorously. In such calculations the variational principle ($E \geq E_{true}$) holds rigorously. In contrast, in semiempirical calculations a modified Hamiltonian is employed and some of the integrals are approximated or ignored entirely to simplify the mathematics. In such cases the variational principle is not applicable.

Both ab initio and semiempirical calculations use the LCAO-MO (linear combination of atomic orbitals-molecular orbitals) approximation. The assumption is made that the electrons in a molecule occupy a set of MO's, two in each, to satisfy the Pauli exclusion principle. Each MO (Ψ_μ) is expressed as a combination of a basis set of atomic orbitals (AO's) ϕ_i.[3] The ϕ_i can be either hydrogen-like (Slater) or Gaussian atomic orbitals.

$$\Psi_\mu = \Sigma\, a_{\mu i}\phi_i$$

The problem is to solve the Schrodinger equation for the energy of the system. The Hamiltonian (H) is known and an approximate value for Ψ can be obtained by guessing the variational coefficients ($a_{\mu i}$). The energy is then obtained as a function of $a_{\mu i}$. The total energy appears as a sum of terms representing: (1) the kinetic energy of the electrons; (2) the attractive forces between the nuclei and the electrons; (3) the repulsions between the electrons; and (4) the repulsions between nuclei. The energy is then minimized by finding the set of coefficients $a_{\mu i}$ that give the lowest total energy.

At this point ab initio and semiempirical calculations vary. Semiempirical calculations approximate or ignore some of the integrals, and in an attempt to compensate for these approximations, some experimental data are added into the calculation. In the complete neglect of differential overlap (CNDO) method, all integrals whose integrand has the form

$$\phi_{A(1)}\phi_{B(1)}d\tau_1$$

are omitted.[28] The incomplete neglect of differential overlap (INDO) method only omits part of such integrals.[28] In ab initio calculations such as Gaussian 70,[30] all integrals are retained and evaluated correctly. The results of this calculation approach the Hartree-Fock limit more closely if a larger number of AO's, a larger basis set, is used. In semiempirical calculations, however, a minimum basis set (atomic ortibals up to and including the orbitals of the valence shell of each atom of the system) is usually used to save computer time.[33]

The method used for this study was partial retention of diatomic differential overlap (PRDDO), which is intermediate in complexity compared to CNDO/INDO and *ab initio* calculations as it retains all three and four centered integrals.[3,4] PRDDO is comparable in accuracy to the more complicated Slater-type orbitals-3 Gaussian (STO-3G) calculations with respect to optimal geometries, and is comparable to CNDO/INDO with respect to the amount of computer time required (several times more).[3,4]

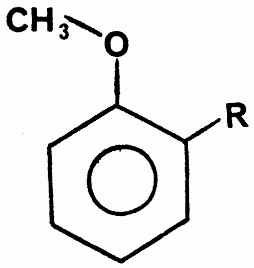
CHAPTER III

RESULTS AND DISCUSSION

NMR Studies

Since the regioselective cleavage of methoxy groups and a downfield ^{13}C NMR shift seem to be related, ^{13}C NMR spectra of some methoxybenzenes were obtained, as shown in Table V.

Methoxy carbons placed adjacent to one ortho substituent show about the same chemical shift as the methoxy carbon in methoxybenzene (54.8 ppm). The preferred orientation of these compounds must be such that the methoxy carbon is farthest from the alkyl group (shown below) because crowded carbons tend to absorb at higher fields than chemically similar but less crowded carbons.[17]



The methoxy groups flanked by 2 <u>ortho</u> substituents show a significant downfield shift, although an upfield shift is usually observed for crowded carbons. The shift increases as the substituents are increased in size. Dhami and Stothers have suggested that the ortho substituents

TABLE V

CARBON-13 NMR CHEMICAL SHIFTS OF SOME SUBSTITUTED METHOXYBENZENES (IN PPM FROM TMS)[a]

Substituent	Methoxyl Carbon		Aromatic Carbons					
	1	2	C-1	C-2	C-3	C-4	C-5	C-6
2-H	54.8	---	159.3	113.6	129.1	120.3	129.1	113.6
2-CH_3	54.9	---	157.5	126.4*	130.4	120.1	126.5	109.6
2-C_2H_5	55.0	---	157.1	132.4	128.7	120.3	126.6	109.9
2-(i-C_3H_7)	55.0	---	156.5	136.7	126.3*	120.4	125.7	110.1
2-(t-C_4H_9)	54.8	---	158.3	138.0	126.7	120.1	126.3	111.4
2,6-$(CH_3)_2$	59.3	---	156.7	130.5	128.5	123.5	128.5	130.5
2,6-$(C_2H_5)_2$	60.7	---	155.9	136.6	126.7	123.9	126.7	136.6
2,6-(i-$C_3H_7)_2$	61.9	---	154.4	141.4	123.8	124.3	123.8	141.4
2,6-(t-$C_4H_9)_2$	64.1	---	159.3	143.4	126.3	122.8	126.3	143.4
2-CH_3,4-OCH_3	55.3*	55.5*	153.1	127.4	116.7	151.7	110.4	110.5
2-OCH_3	55.2	55.2	148.5	148.5	110.9	120.3	120.3	110.9
2-OCH_3,3-CH_3	54.9	59.2	146.8	152.0	131.1	122.1	123.0	109.5
2-OCH_3,3-iC_3H_7	55.1	60.2	152.1	145.9	141.9	117.8	123.5	109.3
b	56.0	59.7	150.3	145.0	136.5	137.5	118.6	110.7
2,3-$(OCH_3)_2$	55.7	60.4	153.1	137.8	153.1	105.0	123.2	105.0

[a] 1.8 M in $CDCl_3$. [b] 4,5-Dimethoxyindane; for purposes of this table it is numbered as a substituted methoxybenzene.

*Values may be exchanged.

interfere with the methoxy group so that the electron release by the methoxy oxygen is significantly reduced.[17] No fundamental reason for the observed shift has been presented but there is now evidence for steric deshielding effects between methyl groups occupying hindered positions[34] as described for 1,8-dimethylnaphthalene. The methyl groups in this compound are deshielded by 6.6 ppm relative to methylnaphthalene.[34]

Another explanation for the deshielding of "hindered" methoxy carbons is that the methoxy group is rotated out of the aromatic ring and the C_{Ar}-O bond loses its resonance stabilized double bond character. Consequently, the methoxy carbon does not experience as great a shielding.[27,41]

The downfield shift is increased with the bulk of the alkyl groups. This shows that an ε steric factor may also be involved. It is interesting that the shifts for the alkyl carbons is greater in the 2,6-dialkyl substituted methoxybenzenes than with the 2-alkyl cases.[34] Thus, a mutual deshielding is evident.

The shift assignments of the aromatic nuclei were made by using previously assigned values,[17] additive empirical parameters,[24,34] or gated decoupled ^{13}C NMR experiments (see Appendix C).[41] The substituent effects in benzenes are nearly additive except when substituents are ortho to each other. The values obtained using the additive parameters are shown in Table VI.

For the mono-ortho substituted methoxybenzenes, the values calculated through use of additivity of the substituent effects agree well with the experimental data, especially for C-4 and C-5 (see Table VI). At

TABLE VI

PREDICTED CARBON-13 NMR CHEMICAL SHIFTS OF SOME SUBSTITUTED METHOXYBENZENES (IN PPM FROM TMS)[24,34]

Substituent	Aromatic Carbons					
	C-1	C-2	C-3	C-4	C-5	C-6
H	159.9	114.1	129.5	120.8	129.5	114.1
2-CH_3	160.7	123.4	130.3	120.8	126.6	114.1
2-C_2H_5	159.5	129.7	129.1	120.8	126.9	114.1
2-(i-C_3H_7)	157.4	134.3	127.0	120.9	127.1	114.2
2-(t-C_4H_9)	156.8	136.5	126.4	120.7	126.6	114.0
2,6-$(CH_3)_2$	161.5	123.4	127.4	120.8	127.4	123.4
2,6-$(C_2H_5)_2$	159.1	129.7	126.5	120.8	126.5	129.7
2,6-(i-$C_3H_7)_2$	154.9	134.4	124.6	121.0	124.6	134.4
2,6-(t-$C_4H_9)_2$	153.7	136.4	123.5	120.6	123.5	136.4
2-CH_3, 4-OCH_3	153.0	124.4	115.9	152.2	112.2	115.1
2-OCH_3	145.5	145.5	115.1	121.8	121.8	115.1
2-OCH_3, 3-CH_3	145.5	146.3	124.4	122.6	121.8	112.2
2-OCH_3, 3-($i$$C_3H_7$)	145.4	143.0	135.3	119.3	121.7	112.7
a	142.8	141.1	130.2	136.9	117.4	112.4
2,3-$(O\text{-}CH_3)_2$	146.5	131.1	146.5	107.4	122.8	107.4

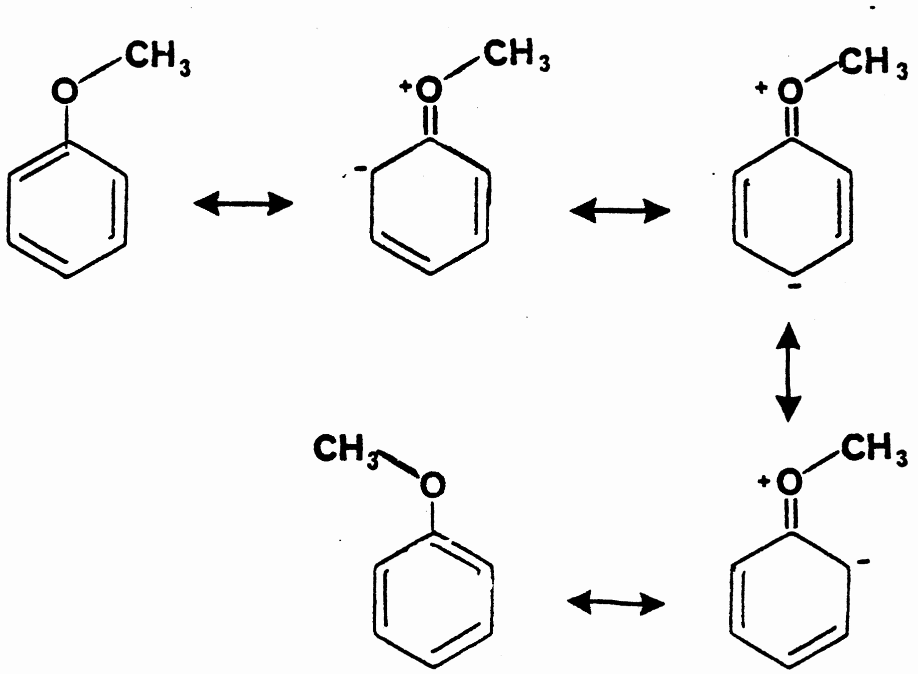
[a] 4,5-Dimethoxyindane; for purposes of this table it is numbered as a substituted methoxybenzene.

position six, the shifts are consistently at higher field than predicted. This effect can be explained by assuming that the methoxy group is in the plane of the ring away from the alkyl group, thus crowding the C-6 position and causing it to be shielded.

For C-1, no consistent deviation is observed and the shifts agree well considering that the position has an ortho neighbor. The predicted shielding for C-2 is consistently large for the series. Since the methoxy group spends most of its time around C-6, the amount of shielding at C-2 decreases. In methoxybenzene, para substituted methoxybenzenes, and meta substituted methoxybenzenes, the methoxy group causes nearly equal amounts of shielding at both ortho positions and consequently good results are obtained when assuming additivity of substituent parameters.[17]

For the 2,6-diortho-substituted methoxybenzenes, the ^{13}C chemical shifts calculated by assuming additivity of parameters do not agree well with the experimentally obtained values. The aromatic carbons ortho and para to the crowded methoxy group show less shielding than predicted. The deviations range from 1.2 to 2.8 ppm for the para position and from 1.3 to 7.5 ppm for the ortho positions. This effect has been attributed to steric inhibition of resonance.[17]

The resonance forms of methoxybenzene (below) predict that the ortho and para carbons will be shielded with respect to benzene because of the high electron densities on these positions. Since the effect is not as great as predicted for the positions ortho and para to a hindered methoxy group, the electron release from the methoxy oxygen must be hampered. This would occur if the methoxy group were rotated out of the plane of the benzene ring, lessening the conjugation with the oxygen unshared p electrons and the π cloud of the benzene ring.



In the 3-alkyl substituted catechol dimethyl ethers, the C-6 position is shifted to higher field than predicted. The methoxy group with only one ortho neighbor is forced to lie in the plane of the ring away from the other methoxy group, placing the methyl group in close proximity to C-6 and causing it to be shielded similar to the C-6 position of 2-alkylmethoxybenzenes.

The shielding of the aromatic carbon containing the hindered methoxy group in the 3-alkyl substituted catechol dimethyl ethers is greater than predicted. This is probably caused by through space factors like those causing C-2 to be shifted in the 2-alkylmethoxybenzenes as explained earlier.

Relaxation Measurements

More evidence that the hindered methoxy group is rotated out of the plane of the ring came from T_1 measurements. The major mechanism of relaxation for carbons bonded to protons is the ^{13}C-H dipole-dipole mechanism. In such cases, an increase in the rate of reorientation of ^{13}C nuclei would result in less efficient relaxation and therefore longer T_1 values. T_1 values can therefore be used as a measure of the relative rotation rates of these nuclei in solution.

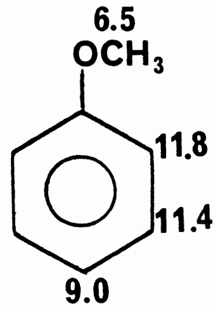
As shown in Figure 1, carbons of methoxy groups which have two ortho neighbors show a larger T_1 value ($\geq$ 6.6 in every case) than those with only one ortho neighbor ($\leq$ 5.1 in every case). The latter are forced to lie in the plane of the ring away from the ortho substituent (see the PRDDO calculations later in this chapter). In this conformation, rotation around the O-CH_3 bond is hampered by the proton ortho to it.[22]

On the other hand, rotation around the O-CH_3 bond in the former case is unhindered because the methoxy group is rotated out of the plane of the benzene ring, thus resulting in longer T_1 values. The methoxy group of methoxybenzene is relatively free to rotate around the O-C_{Ar} bond so that the rotation around the O-CH_3 bond is not substantially hampered by the ortho protons and thus a relatively long T_1 is observed.

Molecular Orbital Calculations

Since the previously mentioned characteristics of methoxy benzenes had been attributed to steric factors governing the conformation of the methoxy group, PRDDO calculations were carried out on some model methoxybenzenes to determine their most stable conformation. Other data obtained from the calculations include dipole moments and atomic electron densities.

Bond lengths and angles were obtained from literature values.[38,39] The methoxy group was rotated around the O-C_{ar} bond at 30° intervals through all possible conformations, as shown below.



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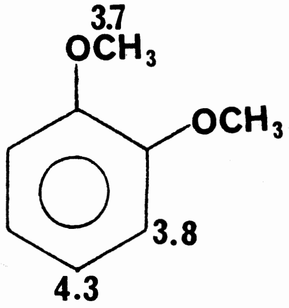
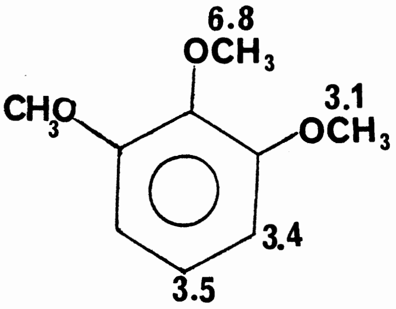


5a



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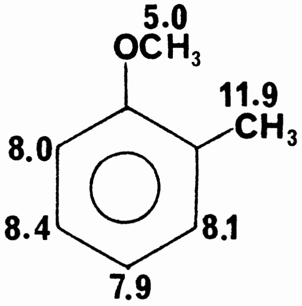
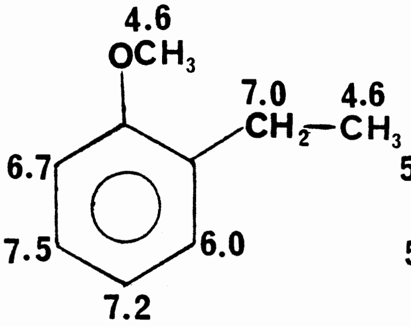
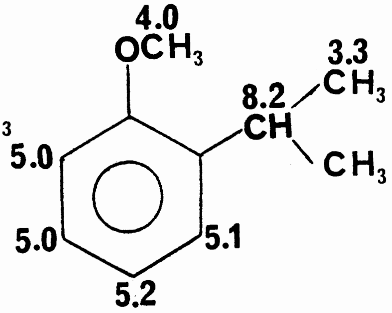


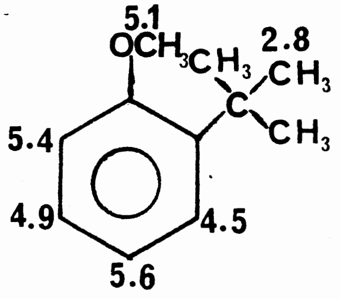
11a



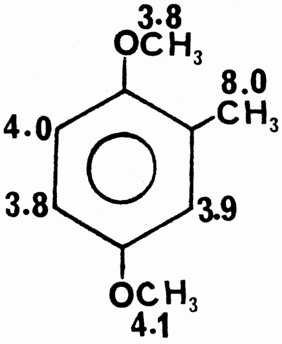
11b



11c



11d



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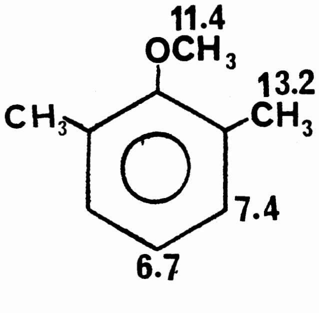
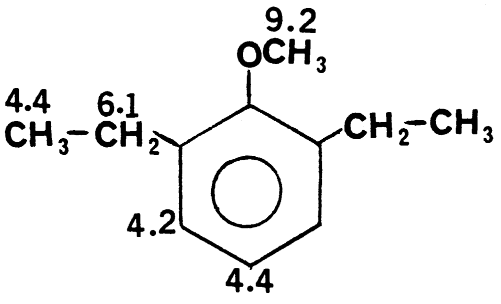


10a

Figure 1. T_1 Values (sec) as an Average of Three Consistent (±10%) Runs



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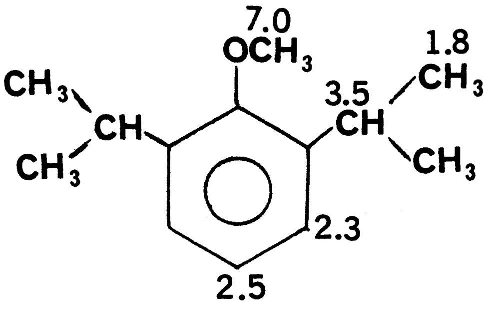
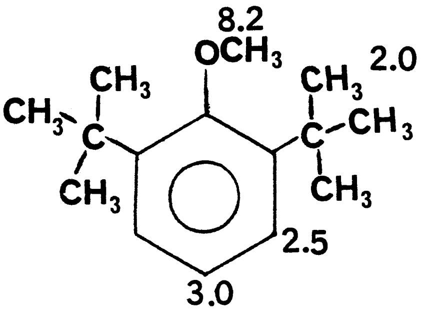
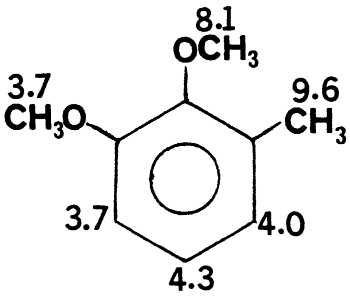


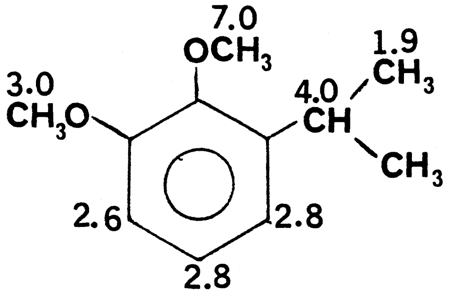
10c



10d



6b



7b

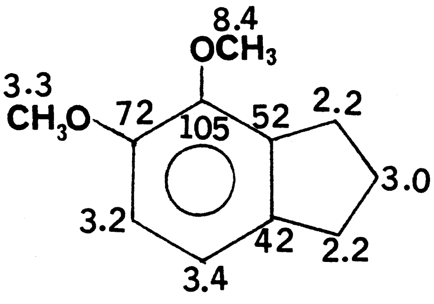


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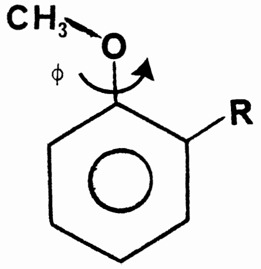
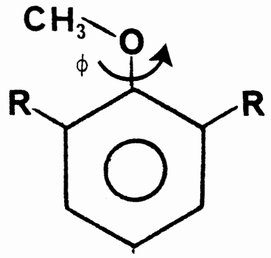
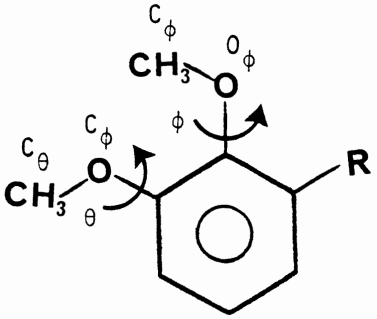
Figure 1. (Continued)







At the most stable position, the methoxy group of methoxybenzene (9) and the 2-alkylmethoxybenzenes is in the plane of the benzene ring away from the alkyl group (Table VII). Figure 2 shows the rotational barrier for 9, 2-methylmethoxybenzene (11a), and 2,6-dimethylmethoxybenzene (10a). This is consistent with the NMR data, which suggest that the methoxy carbon and C-6 are in close proximity, causing C-6 to be shielded.

Figure 3 shows how the atomic charge for 9, 10a, and 11a vary as the methoxy group is rotated out of the plane of the ring by 90°. Notice for 9, when the methoxy group is in the plane of the ring, the electron density on the ortho position closest to the methoxy carbon is higher than the electron density at the other ortho position (more negative atomic charge). In 9, naturally, the methoxy group shields C-2 and C-6 equally. In 11a, however, the methoxy group can shield only C-6, so that C-6 experiences a ^{13}C NMR shift to higher field and C-2 to lower field than predicted by assuming additivity of parameters. Since the maximum amount of overlap between the oxygen p electrons and the ring π cloud is obtained in the stable conformation, C-3, C-4, and C-5 are not greatly affected.

At the most stable conformation of 10a, the methoxy group is rotated 90° out of the plane of the benzene ring. At this position, there is minimal overlap between the oxygen unshared electrons and the benzene π

TABLE VII

PRDDO ENERGIES, ATOMIC CHARGES, AND DIPOLE MOMENTS OF ORTHO SUBSTITUTED METHOXYBENZENES

		φ	E_{rel}*	Atomic Charge		Dipole Moment
R	Compound	Degrees	Kcal/mole	Oxygen	Carbon	Debye
H	9	0	0.00	-0.288	-0.033	1.299
		30	1.03	-0.292	-0.032	1.288
		60	1.34	-0.300	-0.030	1.301
		90	1.39	-0.303	-0.029	1.323
CH_3	11a	0	0.00	-0.286	-0.033	1.161
		30	1.09	-0.290	-0.032	1.158
		60	1.55	-0.299	-0.030	1.196
		90	2.83	-0.304	-0.029	1.279
		120	15.25	-0.303	-0.041	1.414
		150	40.20	-0.299	-0.055	1.540
		180	58.35	-0.297	-0.046	1.503
C_2H_5	11b	0	0.00	-0.285	-0.035	1.071
		30	0.74	-0.290	-0.036	1.079
		60	1.13	-0.298	-0.032	1.160
		90	3.19	-0.304	-0.030	1.288
		120	15.86	-0.304	-0.041	1.465
		150	40.62	-0.301	-0.056	1.602
		180	59.09	-0.300	-0.047	1.562
i-C_3H_7	11c	0	0.00	-0.283	-0.034	1.161
		30	0.92	-0.288	-0.035	1.157
		60	1.32	-0.296	-0.032	1.184
		90	2.94	-0.303	-0.031	1.271
		120	18.06	-0.306	-0.040	1.401
		150	115.07	-0.300	-0.044	1.431
		180	100.79	-0.291	-0.064	1.399
t-C_4H_9	11d	0	0.00	-0.274	-0.041	1.331
		30	0.92	-0.280	-0.041	1.297
		60	4.05	-0.291	-0.037	1.266
		90	54.48	-0.303	-0.057	1.358
		120	1,046.68	-0.302	-0.041	1.394
		150	369.95	-0.287	-0.163	0.898
		180	952.71	-0.315	-0.205	2.664
$2,6(CH_3)_2$	10a	0	54.14	-0.296	-0.046	1.362
		30	35.95	-0.297	-0.056	1.388
		60	11.28	-0.301	-0.041	1.294
		90	0.00	-0.304	-0.029	1.220

*0.00 = -215,859.88 Kcal/mole for 9, -240,335.61 Kcal/mole for 11a, -264,802.12 Kcal/mole for 11b, -289,277.92 Kcal/mole for 11c, -313,746.85 for Kcal/mole for 11d, and -264,806.99 for Kcal/mole for 10a.

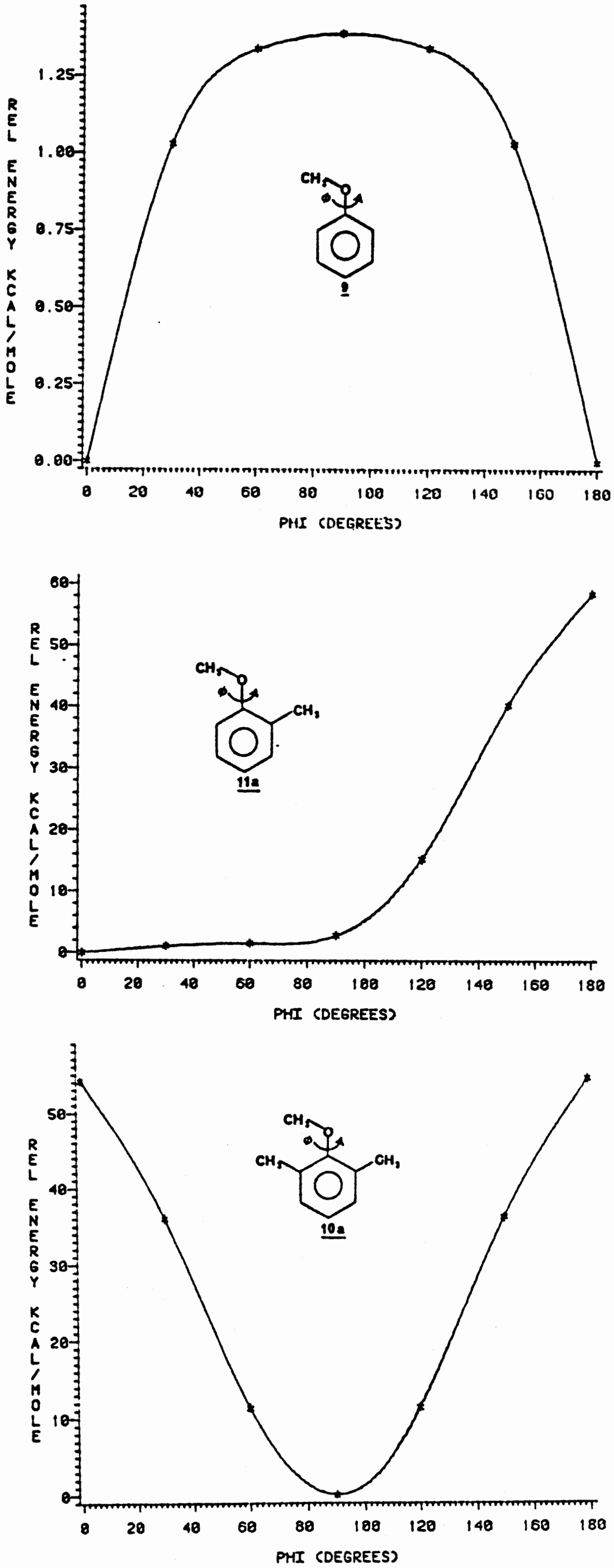
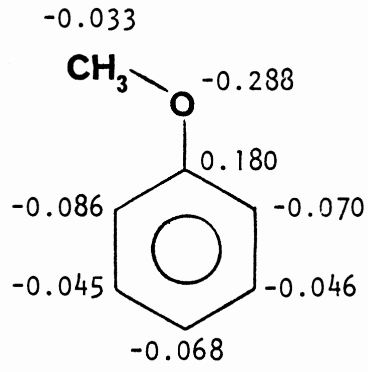


Figure 2. Rotational Barriers for
9, 11a, and 10a



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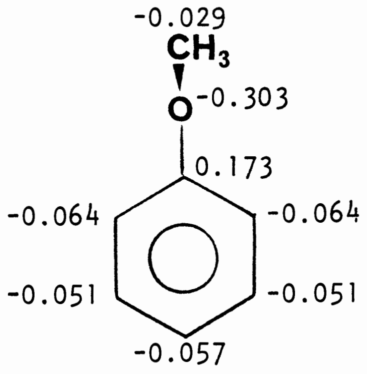

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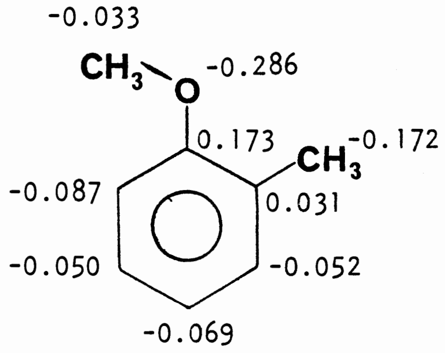
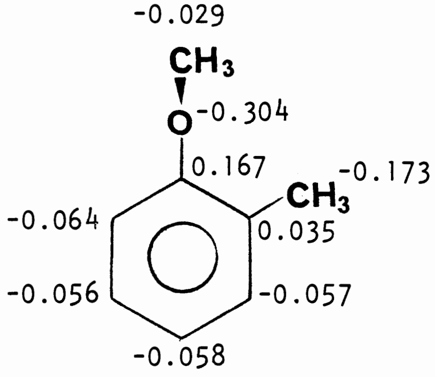
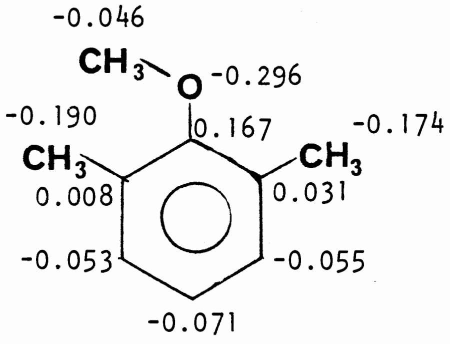


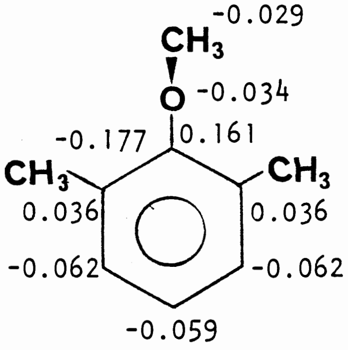
11a



11a



10a



10a

Figure 3. Atomic Charges for Positions ϕ = 0° and ϕ = 90° for 9, 11a, and 10a

cloud. Therefore, electron donation to the ring is hampered and the atomic charge on the ortho and para positions becomes more positive. This effect shows up as "unpredicted deshielding" in the ^{13}C NMR spectrum.

Interestingly, the electron density on the methoxy oxygen increases as the methoxy group is rotated out of the plane of the benzene ring, reaching a maximum at $\phi = 90°$. This effect is expressed graphically in Figure 4. The methoxy carbon shows the opposite effect as shown in Figure 5. The electron density on the methoxy carbon is sterically forced out of conjugation with the ring and is deshielded. This is indeed what is observed.[17]

Dipole moments (μ) can be used to gain information about molecular conformations.[35] Dipole moments for 9, 10a, and 11a are shown in Table VIII; 10a is the only one of the three that shows good correlation between the experimental and calculated value. Figure 6 shows how the dipole moment varies as the methoxy group is rotated out of the plane of the ring.

The minimum energy positions of 6b, 7f, and 12 were determined to be at $\theta = 0°$ and $\phi = 60°$ (Appendix A). Calculations on 7b and 7e were carried out only for this minimum energy position. A summary of the results is given in Table IX.

Figure 7 shows how the energy of 6b varies as θ is rotated through all possible positions for various values of ϕ. No matter what the value of ϕ is, the minimum energy position of θ is 0° (in the plane of the ring) "facing away" from the other methoxy group. These calculations suggest that a methoxy group "prefers" to be in the plane of the ring if possible. Notice that the energy of the system rises rapidly as a methoxy

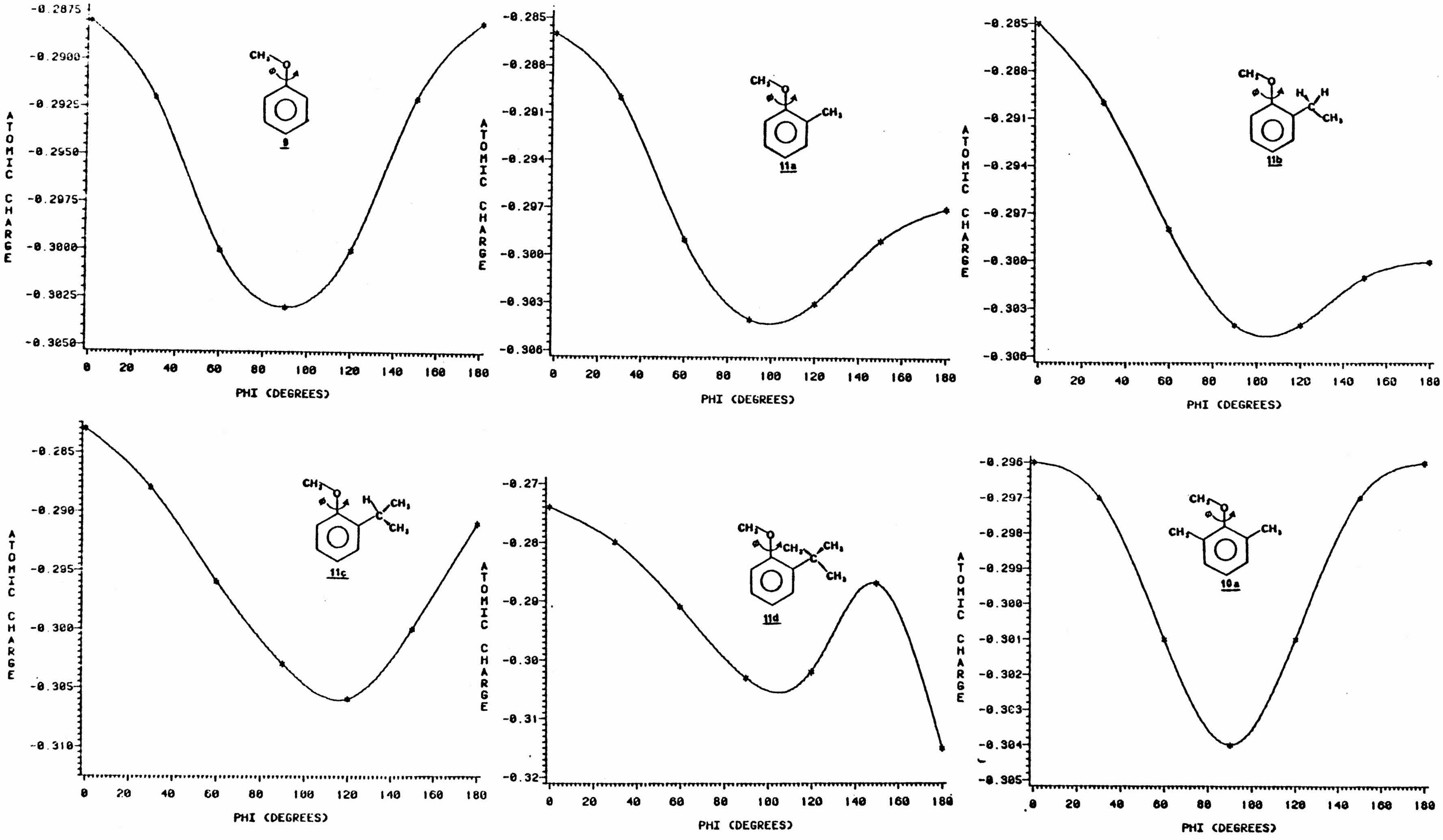


Figure 4. Atomic Charges on the Methoxy Oxygen for 9, 11a, 11b, 11c, 11d, and 10a

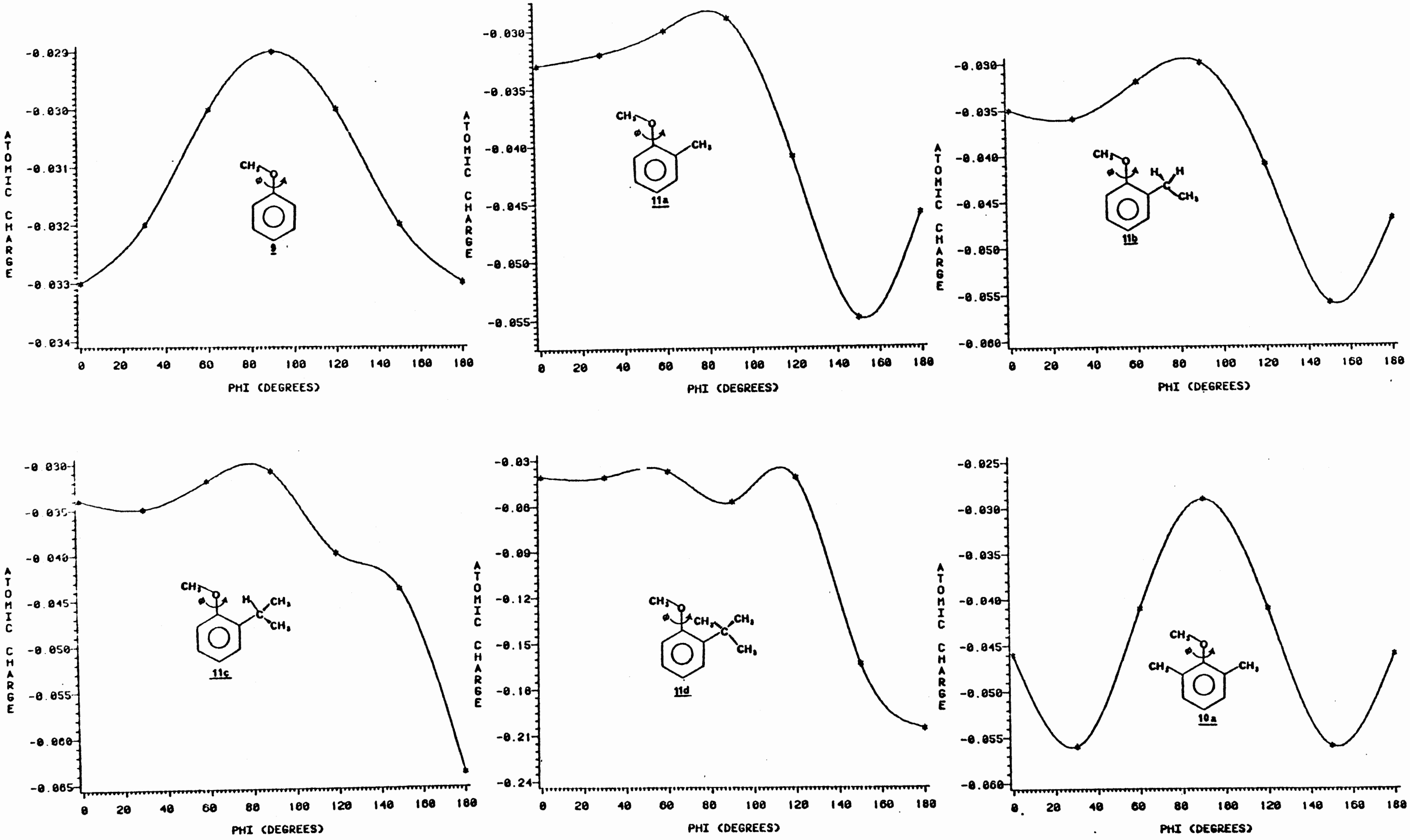


Figure 5. Atomic Charges on the Methoxy Carbon for 9, 11a, 11b, 11c, 11d, and 10a

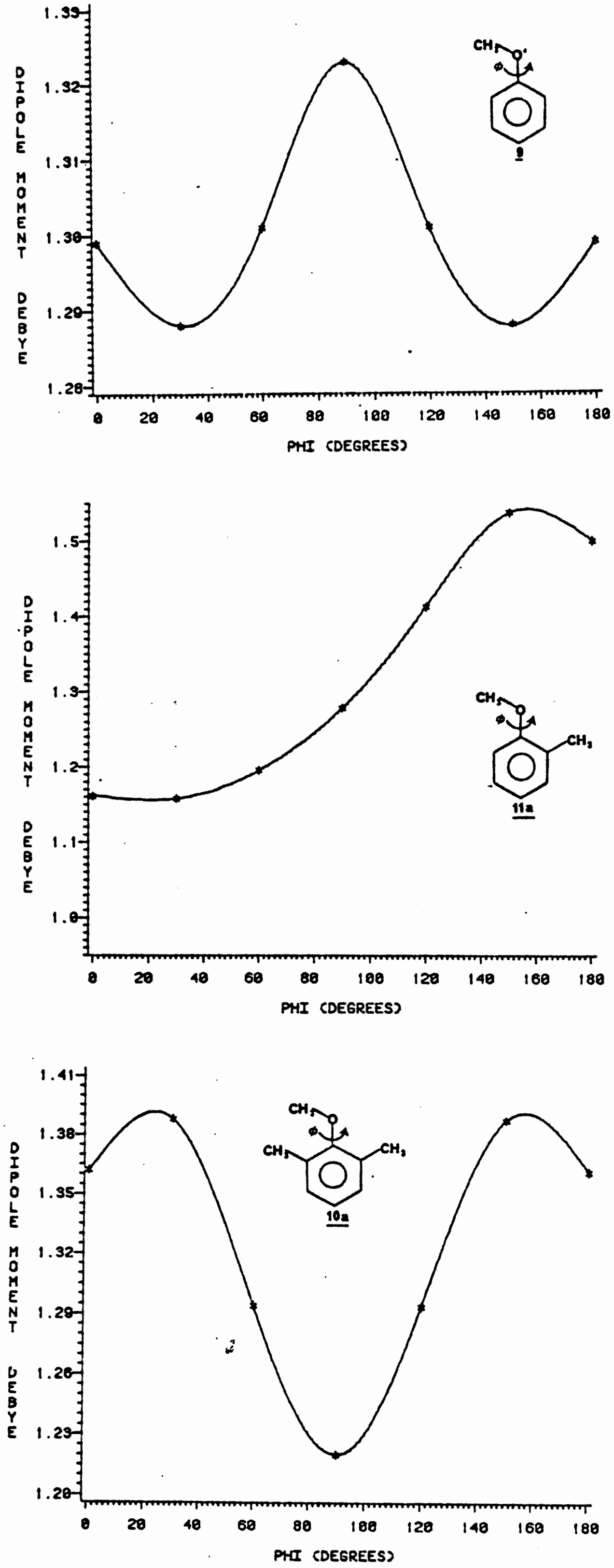


Figure 6. Dipole Moments as a Function of φ for 9, 11a, and 10a

TABLE VIII

DIPOLE MOMENTS

Compound	Literature (μ)[40]	PRDDO (μ) (Debye)
9	1.25	1.299
11a	1.00	1.161
10a	1.24	1.220

TABLE IX

PRDDO ELECTRON DENSITIES AND DIPOLE MOMENTS OF 3-ALKYL SUBSTITUTED CATECHOL DIMETHYL ETHERS AT THEIR MINIMUM POSITION

Compound	R	Electron Densities				μ
		O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
6b	CH_3	8.282	8.296	6.038	6.034	2.036
7e	C_2H_5	8.283	8.296	6.039	6.035	1.953
7b	i-C_3H_7	8.283	8.294	6.034	6.035	1.966
7f	t-C_4H_9	8.283	8.289	6.033	6.040	2.066
12	a	8.285	8.299	6.046	6.034	1.978

4,5-Dimethoxyindane.

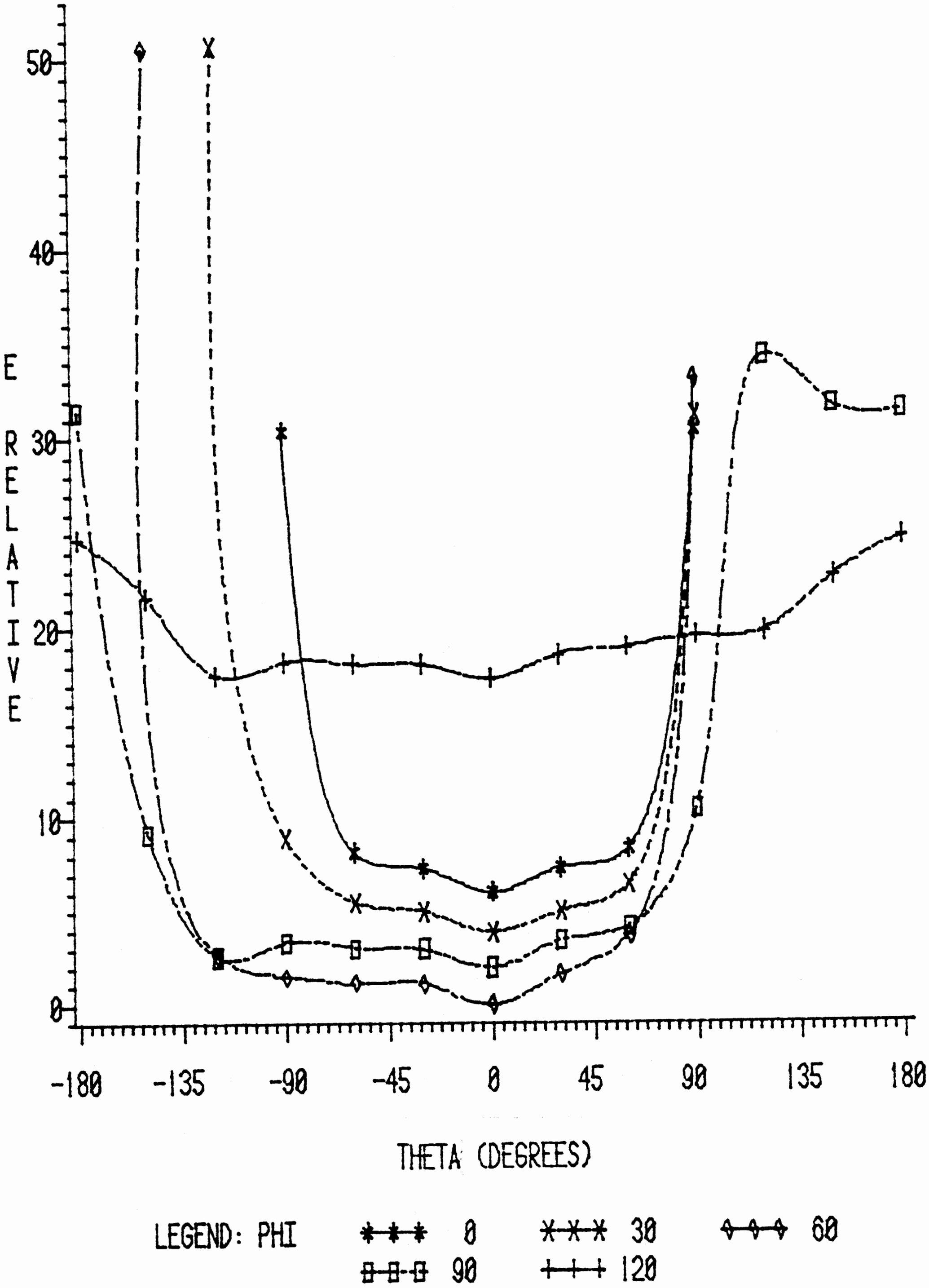


Figure 7. Relative Energy as a Function of θ for Various Values of ϕ for Dimethoxytoluene (6b)

group approaches an ortho substituent ($\theta \rightarrow 180^\circ$ and $\phi \rightarrow 0^\circ$ or 180°). Figure 8 shows the trend in a three-dimensional plot.

Consistent with the information for the monomethoxybenzenes, the oxygen atom on the methoxy group which is bent out of the plane (O_ϕ) has a higher electron density than the one lying in the plane of the ring. This fact may be partially responsible for the regioselective cleavage of this group. The Lewis acids, which are electrophiles, will be attracted toward the oxygen atom with the highest electron density, causing preferential binding to O_ϕ. O_ϕ may also be more open to attack from a steric standpoint. The orbitals of O_θ are "hidden" by the other methoxy group, whereas the orbitals on O_θ are projected above and away from the ring and thus available for preferential attack.

The calculated electron densities on the methoxy carbons predict the observed ^{13}C NMR downfield shift for C_ϕ but not the increase in the shift for larger alkyl groups. The larger alkyl group may affect the amount of time that the methoxy group is rotated out of the plane. For large R groups, the methoxy group would virtually never lie in the plane, whereas for small R groups more time would be spent in the plane.

Further information about the conformation of the "hindered" methoxy group may be gained from X-ray and light absorption studies.[32,33] In addition, kinetic studies could be used to show whether the regiospecificity observed in methoxy cleavage is actually a steric rate enhancement effect.

Summary

This study has shown that the selective demethylation of 3-alkyl-1,2-dimethoxybenzenes at C-2 is caused by steric factors forcing the

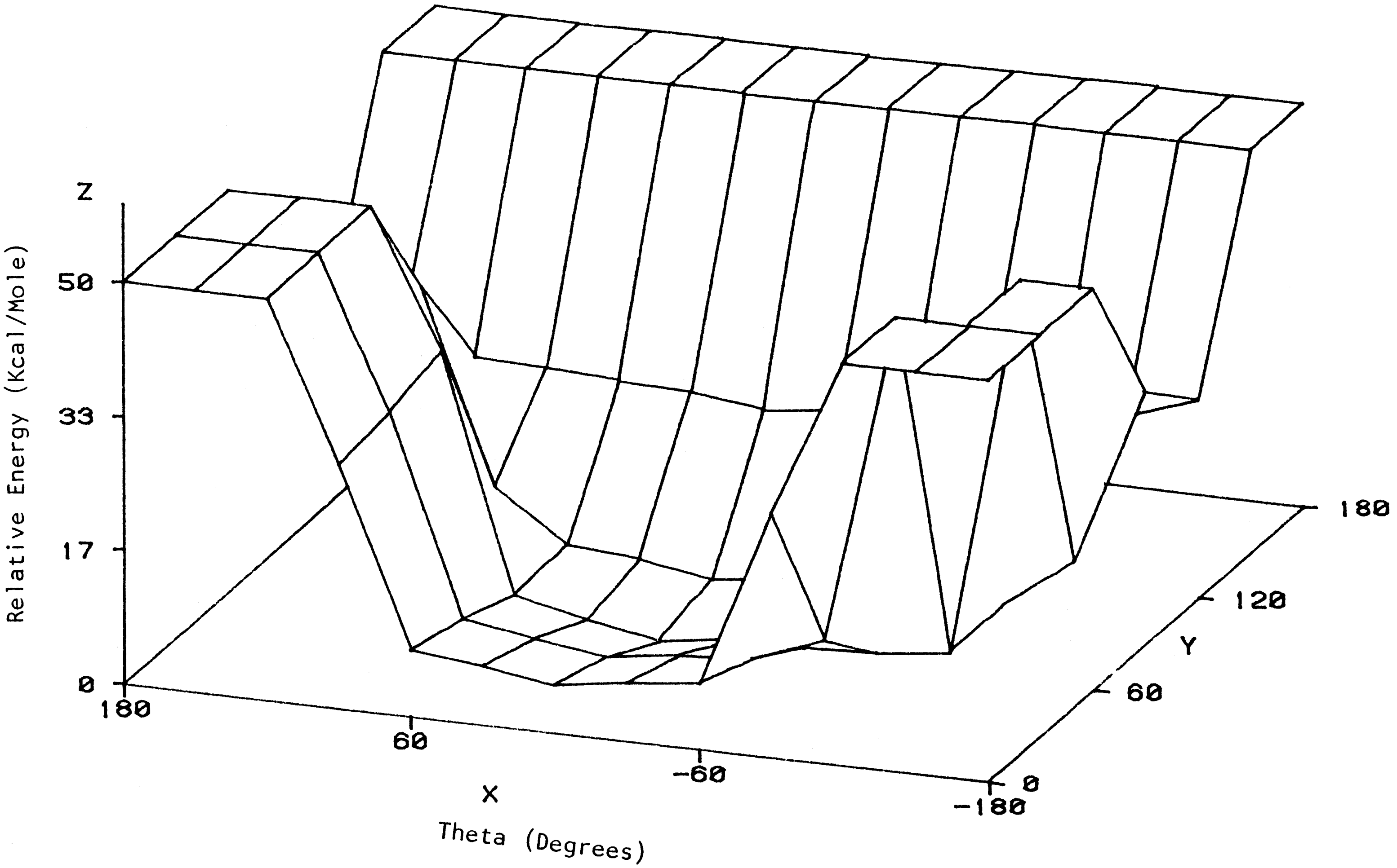


Figure 8. Relative Energy as a Function of θ and ϕ for 2,3-Dimethoxytoluene (<u>6b</u>)

methoxy group to rotate about the C-2 carbon-oxygen bond so that the methoxy group is kept out of the plane of the benzene ring. This results in an increase in the electron density on O_ϕ as compared to that of O_θ. Hence electrophiles are selectively attracted to O_ϕ. The orbitals on O_ϕ, in the least energy conformation are protruding above and away from the ring, whereas the orbitals of O_θ are "hidden." Thus, the orbitals of the former are sterically more accessible for attack.

This concept is supported by data from PRDDO calculations, ^{13}C NMR chemical shifts, and ^{13}C NMR T_1 relaxation measurements. The PRDDO calculations predict that the methoxy group with two ortho neighbors is rotated out of the plane of the ring by 60°. The calculations also show that the electron density on O_ϕ is greater than that on O_θ. ^{13}C NMR additive parameters of substituted benzenes consistently predicted greater shielding than that observed at the ortho and para positions of 2,6-disubstituted methoxybenzenes. This reduced shielding may be caused by the rotation of the methoxy group out of conjugation with the ring, thus reducing electron donation to the ring.[17]

This study shows that the methoxy groups with two ortho neighbors possessed longer T_1 values than methoxy groups with only one ortho neighbor. In the former case free rotation about the $O\text{-}CH_3$ bond is possible whereas in the latter case rotation is hindered, thus leading to shorter T_1 values.[22]

The deshielding observed for methoxy carbons with two ortho neighbors may be caused by the C_{ar}-O showing less double bond character.[41] Another possibility is a δ steric deshielding as observed in 1,8-dimethyl naphthalene.[34] The increased size of the shift, as the ortho substituent is increased in bulk, may be due to the amount of time the methoxy group is out of the plane of the benzene ring. This suggests that if the ortho substituent is small (proton), the methoxy group will spend more time in the plane of the ring than in the case where the substituent is large (*t*-butyl).

CHAPTER IV

EXPERIMENTAL

General procedure for methylation of phenols.[36] The synthesis of 2-*t*-butylmethoxybenzene (11d) is used as an example to illustrate the general procedure. A mixture of 500 mL dichloromethane, 500 mL water, 15.0 g (0.1 mole) of 2-*t*-butylphenol, 6.0 g (0.15 mole) of sodium hydroxide, 13.5 g (0.250 mole) dimethyl sulfate, and 0.9 gms (5.5 moles) N-benzyltrimethylammonium hydroxide was agitated with a Vibromixer at room temperature for 12 h. The orgnic layer was then separated and the aqueous layer extracted twice with 200 mL portions of methylene chloride. The organic extracts were combined and the solvent evaporated. The residue was mixed with water and extracted with ether. The organic extract was washed twice with 2 N ammonia to remove excess dimethyl sulfate. It was then washed with Claisen's alkali to remove the unreacted phenol. It was finally washed with H_2O, dried with magnesium sulfate, and the solvent evaporated. Kugelrohr distillation gave 20.0 g (80%) of a slightly yellow liquid. ^{13}C NMR ($CDCl_3$) ppm 158.3, 138.0, 126.7, 126.3, 120.1, 111.4 (aromatic), 54.8 ($-OCH_3$), 34.8 ($ArCR_4$), 29.7 (CH_3).

2,6-Diethylmethoxybenzene (11b). 2,6-Diethylphenol (10 g, 0.067 mole) was reacted with dimethyl sulfate as described in the general procedure. Kugelrohr distillation gave 9.3 g (85%) of a yellow liquid. Passage of the product through a column of basic alumina yielded a colorless liquid. ^{13}C NMR ($CDCl_3$) 155.9, 136.6, 126.7, 123.9 (aromatic) ^{13}C

NMR ($CDCl_3$) 155.9, 136.6, 126.7, 123.9 (aromatic), 60.7 (OCH_3), 22.7 ($ArCHR_2$), 14.9 (CH_3).

2,6-Diisopropylmethoxybenzene (10c). 2,6-Diisopropylphenol (20 g) was reacted with dimethyl sulfate as described in the general procedure. Kugelrohr distillation gave 21 g (80%) of a slightly yellow liquid. ^{13}C NMR ($CDCl_3$) 154.4, 141.4, 123.8, 124.3, 123.8, 141.4 (aromatic), 61.9 (OCH_3), 24.5 ($ArCHR_2$), 27.0 (CH_3).

2,6-Di-*t*-butylmethoxybenzene (10d). The above procedure did not work for production of 10d. Instead, the procedure of Kornblum and Seltzer was used.[37] 2,6-Di-*t*-butylphenol was recrystallized from aqueous ethanol. *t*-Butyl alcohol and diglyme were allowed to stand over calcium hydride and distilled.

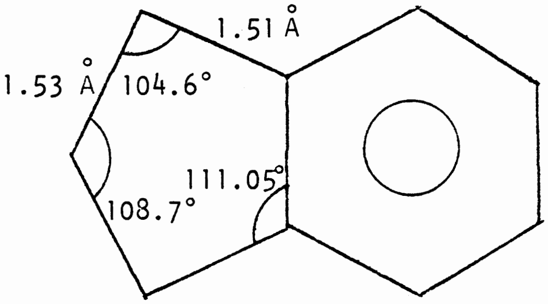
A 20 g (0.10 mole) sample of 2,6-di-*t*-butylphenol was dissolved in 50 mL of *t*-butyl alcohol. To this solution was added 100 mL (0.10 mole) of a 0.10 M solution of potassium *t*-butoxide in *t*-butyl alcohol. 50 mL of diglyme and then 25 mL of methyl iodide were added to the solution and the reaction was stirred for 12 h at room temperature.

The product was extracted with ether, washed twice with water, and dried over magnesium sulfate. The ether was evaporated leaving 17 g of a yellow liquid. The product was passed through a column of basic alumina and a colorless liquid was obtained. ^{13}C NMR ($CDCl_3$) 159.3, 143.4, 126.3, 122.8 (aromatic), 64.1 (OCH_3), 35.7 ($ArCR_3$), 32.2 (CH_3).

2,3-Dimethoxytoluene. 2,3-Dimethoxybenzaldehyde (50 g, 0.30 mole), potassium hydroxide (33 g, 0.59 mole), hydrazine (50 mL, 1.6 moles), and 430 mL of diethyleneglycol were added to a stainless steel Wolff-Kishner flask.[42] The reaction was heated at 90-100 V for 1.5 h. The product was distilled into a Dean-Stark trap as the reaction proceeded. The product was washed with 10% hydrochloric acid, extracted with ether, and distilled (Kugelrohr apparatus) to give 36 g (81%) of a colorless liquid. ^{13}C NMR ($CDCl_3$) 152.0, 146.8, 131.1, 123.0, 122.1, 109.5 (aromatic), 59.2, 54.9 (OCH_3), 15.2 (CH_3).

MO calculations. The MO calculations were carried out on a PRDDO program by Thomas Halgren using an IBM-360 computer. The convergence criteria were set at 10^{-4} rms change in the density matrix.

The calculations were carried out using the following distances and angles: C_{ar}-C_{ar}, 1.40 Å; C_{ar}-H, 1.084 Å, Cali-Cali, 1.54 Å; Car-O, 1.36 Å; O-CH_3, 1.43 Å; Cali-H, 1.101 Å; Sp^3 carbon angles, 109.5°; benzene ring angles, 120°; ether angles, 120°.[38,39] The dimensions used for the five membered ring of indane were as shown below.



All Cali-H, 1.101 Å; All H-C-H angles, 109.5°.

In the case where R = C_2H_5, the methyl carbon of the alkyl group was placed in the plane of the ring away from the methoxy group. In the case where R = *t*-C_3H_7, the hydrogen on the branched carbon was placed in the plane of the ring toward the methoxy group so that the methyls in the alkyl group were the maximum distance from the methoxy group. One of the methyl carbons of the *t*-C_4H_9 group was placed in the plane of the ring away from the methoxy group because this position proved to be of lower energy than placing the methyl carbon in the plane of the ring toward the methoxy group.

<u>^{13}C NMR</u>. The ^{13}C NMR spectra were recorded at 25.2 M Hz and 24,490 G in the FT mode on a varian XL-100-15 instrument interfaced with a TT-100 Nicolet computer. Chemical shifts are given in ppm downfield from Me_4Si. Concentrations were all 1.8 M in $CDCl_3$.

T_1 values were obtained with the following parameters: Pulse sequence, T_1IR_3; tau values, 0.1 sec, 1.0 sec, 2.5 sec, 4.0 sec, 7.0 sec, 14.0 sec, 30.0 sec, 70.0 sec, 170.0 sec; delay (D_5), 216.0 sec; acquisition time, 1.360 sec; spectra, 8 k. The samples were degassed after bubbling argon through them by repeated freezing (-78 °C) and thawing under vacuum.

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	Amberlyst-15	Amberlyst-NK-1010
Surface area, sq. m/gm	570	45
Porosity, per cent	47	32
Ion exchange capacity, meg/gm	3.3	4.6
Ion exchange capacity, meg/ml	1.0	1.8

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	C-1	Ortho	Meta	Para
H	0.0	0.0	0.0	0.0
CH_3	+9.3	+0.8	0.0	-2.9
C_2H_5	-15.6	-0.4	0.0	-2.6
iC_3H_7	+20.2	-2.5	+0.1	-2.4
t-C H_9	+22.4	-3.1	-0.1	-2.9
OCH_3	+31.4	-14.4	+1.0	-7.7

Chemical shift for benzene = 128.5; chemical shifts for the indane system, C-3a and C-7a = 143.6; C-4 and C-7 = 124.4; C-5 and C-6 = 125.8.

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APPENDIX A

PRDDO CALCULATIONS OF 3-ALKYL SUBSTITUTED CATECHOL DIMETHYL ETHERS

TABLE X

2,3-DIMETHOXY-*t*-BUTYLBENZENE (7F)

θ	φ	E_{rel}	Atomic Charge				μ
			O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
0	0	2.33	-0.283	-0.285	-0.034	-0.033	2.206
	30	0.23	-0.283	-0.286	-0.033	-0.051	2.264
	60	0.00	-0.283	-0.289	-0.033	-0.040	2.055
	90	50.67	-0.279	-0.296	-0.033	-0.055	1.840
	120	1,043.32	-0.277	-0.292	-0.032	-0.041	1.569
	150	366.40	-0.278	-0.276	-0.035	-0.166	0.638
	180	950.12	-0.277	-0.304	-0.035	-0.270	2.327
30	0	3.66	-0.288	-0.285	-0.034	-0.032	2.104
	30	1.66	-0.287	-0.285	-0.033	-0.051	2.320
	60	1.82	-0.287	-0.288	-0.033	-0.039	2.303
	90	51.81	-0.284	-0.295	-0.033	-0.055	2.237
	120	1,045.04	-0.282	-0.292	-0.030	-0.040	2.010
	150	367.85	-0.283	-0.276	-0.035	-0.164	0.946
	180	951.56	-0.283	-0.303	-0.034	-0.206	2.504
	210	367.51	-0.283	-0.276	-0.035	-0.166	0.564
	240	1,044.32	-0.282	-0.292	-0.032	-0.042	1.124
	270	51.47	-0.285	-0.295	-0.032	-0.056	1.276
	300	1.20	-0.288	-0.289	-0.033	-0.040	1.605
	330	1.45	-0.287	-0.285	-0.033	-0.051	2.009
	360	3.56	-0.288	-0.284	-0.034	-0.032	2.100
60	0	4.51	-0.297	-0.284	-0.035	-0.031	1.888
	30	2.92	-0.296	-0.284	-0.034	-0.052	2.226
	60	3.31	-0.296	-0.287	-0.034	-0.038	2.405
	90	52.80	-0.293	-0.294	-0.032	-0.055	2.503
	120	1,045.30	-0.292	-0.292	-0.031	-0.041	2.386
	150	368.14	-0.293	-0.276	-0.034	-0.165	1.332
	180	951.58	-0.292	-0.303	-0.032	-0.205	2.892
	210	367.62	-0.293	-0.276	-0.035	-0.164	0.904
	240	1,044.43	-0.293	-0.292	-0.030	-0.041	0.919
	270	51.28	-0.295	-0.296	-0.031	-0.056	0.640
	300	1.10	-0.298	-0.290	-0.033	-0.040	1.032
	330	1.89	-0.297	-0.286	-0.035	-0.050	1.627
	360	4.35	-0.297	-0.284	-0.035	-0.031	1.885
90	0	27.12	-0.304	-0.286	-0.038	-0.051	1.846
	30	27.72	-0.308	-0.283	-0.050	-0.054	2.020
	60	33.19	-0.305	-0.289	-0.047	-0.054	2.440
	90	59.19	-0.301	-0.295	-0.033	-0.059	2.631
	120	1,045.91	-0.300	-0.293	-0.028	-0.042	2.596
	150	368.31	-0.301	-0.277	-0.033	-0.166	1.709
	180	951.14	-0.301	-0.305	-0.030	-0.206	3.216
	210	367.68	-0.302	-0.278	-0.032	-0.164	1.351
	240	1,044.45	-0.302	-0.295	-0.028	-0.041	1.057
	270	52.10	-0.304	-0.298	-0.029	-0.056	0.265

TABLE X (Continued)

θ	ϕ	E_{rel}	Atomic Charge				μ
			O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
90	300	1.67	-0.306	-0.291	-0.031	-0.041	0.489
	330	5.35	-0.305	-0.287	-0.035	-0.050	1.264
	360	27.30	-0.304	-0.286	-0.038	-0.051	1.846
120	0	694.32	-0.303	-0.284	-0.034	-0.059	1.517
	30	286.22	-0.329	-0.264	-0.205	-0.177	1.970
	60	674.63	-0.304	-0.289	-0.032	-0.032	2.161
	90	83.48	-0.304	-0.300	-0.053	-0.073	2.609
	120	1,046.73	-0.302	-0.296	-0.037	-0.044	2.596
	150	368.32	-0.303	-0.280	-0.037	-0.166	1.988
	180	950.56	-0.305	-0.309	-0.039	-0.207	3.395
	210	367.10	-0.305	-0.282	-0.040	-0.166	1.748
	240	1,044.22	-0.305	-0.298	-0.036	-0.042	1.403
	270	51.67	-0.306	-0.300	-0.037	-0.057	0.810
	300	3.11	-0.308	-0.294	-0.038	-0.042	0.499
	330	48.01	-0.310	-0.293	-0.065	-0.074	1.180
	360	693.93	-0.304	-0.283	-0.033	-0.060	1.510
150	0	1,114.13	-0.292	-0.246	-0.279	-0.264	1.106
	30	1,133.56	-0.287	-0.269	-0.140	-0.129	1.987
	60	290.85	-0.282	-0.315	-0.174	-0.212	1.990
	90	82.12	-0.302	-0.304	-0.051	-0.075	2.249
	120	1,049.77	-0.303	-0.296	-0.050	-0.043	2.457
	150	371.67	-0.304	-0.280	-0.051	-0.160	2.195
	180	954.12	-0.307	-0.309	-0.051	-0.207	3.531
	210	371.35	-0.305	-0.280	-0.052	-0.165	2.089
	240	1,048.57	-0.306	-0.296	-0.048	-0.044	1.915
	270	59.08	-0.306	-0.299	-0.046	-0.061	1.529
	300	50.87	-0.312	-0.295	-0.070	-0.068	1.269
	330	608.36	-0.307	-0.287	-0.219	-0.219	1.469
	360	1,114.25	-0.292	-0.246	-0.280	-0.266	1.111
180	0	---	---	---	---	---	---
	30	---	---	---	---	---	---
	60	698.08	-0.303	-0.289	-0.060	-0.034	1.657
	90	81.44	-0.305	-0.299	-0.049	-0.063	2.094
	120	1,051.81	-0.303	-0.295	-0.030	-0.045	2.116
	150	373.66	-0.304	-0.280	-0.031	-0.167	2.134
	180	956.78	-0.307	-0.310	-0.030	-0.208	3.396

0.00 = 385,013.69 Kcal/mole.

TABLE XI

2,3-DIMETHOXY TOLUENE (6b)

θ	φ	E_{rel}	Atomic Charge				μ
			O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
0	0	5.99	-0.282	-0.297	-0.038	-0.028	2.118
	30	3.85	-0.282	-0.297	-0.038	-0.045	2.201
	40	1.81	-0.282	-0.297	-0.037	-0.044	2.176
	50	0.30	-0.282	-0.297	-0.038	-0.039	2.113
	60	0.00	-0.282	-0.296	-0.038	-0.034	2.036
	70	0.56	-0.281	-0.296	-0.038	-0.031	1.984
	80	0.91	-0.280	-0.296	-0.038	-0.030	1.925
	90	1.97	-0.278	-0.296	-0.037	-0.028	1.861
	120	17.31	-0.276	-0.294	-0.036	-0.042	1.580
	150	114.59	-0.277	-0.286	-0.036	-0.047	1.123
	180	100.22	-0.277	-0.275	-0.038	-0.072	0.564
10	60	0.20	-0.282	-0.296	-0.037	-0.034	2.153
	300	0.12	-0.283	-0.297	-0.036	-0.034	1.908
20	60	1.13	-0.284	-0.296	-0.038	-0.034	2.245
	300	0.78	-0.285	-0.297	-0.038	-0.034	1.762
30	0	7.32	-0.287	-0.296	-0.038	-0.026	2.031
	30	4.99	-0.286	-0.296	-0.037	-0.044	2.284
	60	1.64	-0.286	-0.296	-0.037	-0.033	2.311
	90	3.43	-0.283	-0.295	-0.037	-0.027	2.252
	120	18.59	-0.281	-0.294	-0.036	-0.041	2.035
	150	116.04	-0.282	-0.285	-0.035	-0.046	1.597
	180	101.45	-0.282	-0.275	-0.036	-0.070	0.931
	210	115.37	-0.282	-0.285	-0.035	-0.046	0.947
	240	18.08	-0.282	-0.294	-0.035	-0.043	1.151
	270	2.97	-0.284	-0.296	-0.036	-0.028	1.344
	300	1.12	-0.287	-0.297	-0.037	-0.034	1.590
	330	4.98	-0.286	-0.297	-0.037	-0.044	1.947
	360	7.29	-0.287	-0.296	-0.038	-0.026	2.029
60	0	8.31	-0.295	-0.296	-0.035	-0.026	1.808
	30	6.44	-0.295	-0.295	-0.034	-0.045	2.197
	60	3.67	-0.295	-0.295	-0.034	-0.033	2.421
	90	4.15	-0.292	-0.295	-0.033	-0.027	2.504
	120	18.96	-0.291	-0.293	-0.031	-0.041	2.416
	150	115.93	-0.291	-0.285	-0.030	-0.046	2.100
	180	101.29	-0.291	-0.274	-0.032	-0.069	1.557
	210	115.15	-0.291	-0.285	-0.032	-0.045	1.253
	240	18.12	-0.291	-0.294	-0.032	-0.042	0.979
	270	3.03	-0.294	-0.297	-0.032	-0.028	0.787
	300	1.17	-0.297	-0.298	-0.033	-0.034	1.003
	330	5.49	-0.295	-0.298	-0.035	-0.043	1.540
	360	8.15	-0.295	-0.296	-0.035	-0.026	1.807

TABLE XI (Continued)

			Atomic Charge				μ
θ	ϕ	E_{rel}	O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
90	0	30.35	-0.301	-0.297	-0.034	-0.045	1.753
	30	31.15	-0.305	-0.294	-0.046	-0.047	1.993
	60	33.04	-0.302	-0.297	-0.044	-0.049	2.448
	90	10.43	-0.298	-0.296	-0.029	-0.031	2.605
	120	19.57	-0.297	-0.294	-0.025	-0.042	2.634
	150	116.04	-0.297	-0.286	-0.024	-0.047	2.458
	180	101.26	-0.298	-0.276	-0.025	-0.070	2.077
	210	115.38	-0.298	-0.287	-0.025	-0.045	1.675
	240	18.21	-0.299	-0.296	-0.026	-0.042	1.155
	270	3.36	-0.301	-0.299	-0.026	-0.028	0.480
	300	1.52	-0.303	-0.300	-0.027	-0.035	0.411
	330	8.91	-0.302	-0.299	-0.031	-0.045	1.137
	360	30.56	-0.301	-0.297	-0.034	-0.045	1.752
120	0	697.44	-0.300	-0.295	-0.028	-0.054	1.392
	30	289.82	-0.325	-0.274	-0.201	-0.170	1.980
	60	647.48	-0.300	-0.296	-0.025	-0.027	2.167
	90	34.29	-0.300	-0.301	-0.046	-0.046	2.542
	120	19.80	-0.298	-0.297	-0.030	-0.044	2.644
	150	115.03	-0.299	-0.298	-0.030	-0.047	2.633
	180	101.03	-0.300	-0.280	-0.031	-0.070	2.443
	210	114.69	-0.300	-0.291	-0.031	-0.047	2.034
	240	17.50	-0.301	-0.299	-0.031	-0.042	1.488
	270	2.57	-0.303	-0.301	-0.032	-0.031	0.803
	300	2.64	-0.305	-0.302	-0.034	-0.036	0.382
	330	50.70	-0.306	-0.304	-0.060	-0.067	1.022
	360	697.55	-0.300	-0.295	-0.028	-0.054	1.387
150	0	1,117.07	-0.288	-0.256	-0.274	-0.257	1.088
	30	1,137.35	-0.282	-0.279	-0.129	-0.130	1.949
	60	289.97	-0.277	-0.322	-0.186	-0.205	1.793
	90	31.75	-0.297	-0.304	-0.045	-0.049	2.153
	120	22.70	-0.298	-0.297	-0.043	-0.043	2.516
	150	118.70	-0.299	-0.289	-0.041	-0.047	2.693
	180	104.15	-0.300	-0.279	-0.043	-0.070	2.724
	210	118.31	-0.300	-0.290	-0.042	-0.047	2.417
	240	21.64	-0.301	-0.298	-0.040	-0.044	1.984
	270	9.19	-0.302	-0.299	-0.040	-0.035	1.456
	300	50.53	-0.307	-0.303	-0.065	-0.062	1.229
	330	611.65	-0.302	-0.298	-0.212	-0.214	1.309
	360	1,117.56	-0.288	-0.256	-0.274	-0.257	1.084
180	30	1,117.80	-0.295	-0.285	-0.253	-0.277	0.922
	60	697.72	-0.298	-0.297	-0.053	-0.030	1.616
	90	31.46	-0.300	-0.300	-0.043	-0.036	1.992
	120	24.73	-0.299	-0.297	-0.023	-0.045	2.185

TABLE XI (Continued)

θ	ϕ	E_{rel}	Atomic Charge O_θ	O_ϕ	C_θ	C_ϕ	μ (Debye)
180	150	120.72	-0.299	-0.290	-0.023	-0.048	2.486
	180	106.59	-0.300	-0.297	-0.026	-0.070	2.678

0.00 = 311,605.11 Kcal/mole.

TABLE XII

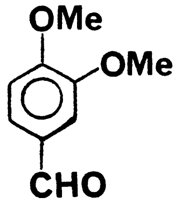
4,5-DIMETHOXYINDANE (12)

			Atomic Charge				μ
θ	ϕ	E_{rel}	O_θ	O_ϕ	C_θ	C_ϕ	(Debye)
0	0	5.63	-0.285	-0.297	-0.046	-0.027	1.980
	30	2.74	-0.285	-0.298	-0.045	-0.044	2.084
	60	0.00	-0.285	-0.299	-0.046	-0.034	1.978
	90	2.01	-0.282	-0.299	-0.045	-0.027	1.875
	120	6.78	-0.280	-0.295	-0.044	-0.036	1.707
	150	16.49	-0.280	-0.291	-0.045	-0.044	1.484
	180	22.23	-0.280	-0.289	-0.046	-0.041	1.344
30	0	6.67	-0.290	-0.297	-0.048	-0.026	1.901
	30	4.41	-0.289	-0.297	-0.047	-0.044	2.174
	60	1.52	-0.289	-0.298	-0.048	-0.033	2.256
	90	3.54	-0.286	-0.298	-0.047	-0.027	2.253
	120	7.99	-0.285	-0.295	-0.046	-0.035	2.125
	150	17.46	-0.285	-0.290	-0.046	-0.043	1.853
	180	23.35	-0.285	-0.289	-0.047	-0.040	1.536
	210	17.28	-0.285	-0.290	-0.044	-0.040	1.399
	240	7.69	-0.285	-0.295	-0.046	-0.037	1.363
	270	3.15	-0.287	-0.299	-0.046	-0.028	1.423
	300	0.90	-0.291	-0.299	-0.048	-0.035	1.556
	330	4.26	-0.290	-0.298	-0.047	-0.044	1.839
	360	6.67	-0.290	-0.297	-0.048	-0.026	1.901
0	0	7.22	-0.298	-0.296	-0.043	-0.025	1.679
	30	5.73	-0.298	-0.296	-0.041	-0.045	2.093
	60	3.38	-0.298	-0.297	-0.041	-0.033	2.382
	90	4.50	-0.295	-0.298	-0.040	-0.027	2.521
	120	8.50	-0.294	-0.295	-0.039	-0.035	2.503
	150	17.66	-0.294	-0.290	-0.038	-0.043	2.298
	180	23.04	-0.294	-0.288	-0.040	-0.038	1.967
	210	17.06	-0.294	-0.290	-0.040	-0.043	1.647
	240	7.59	-0.294	-0.295	-0.039	-0.036	1.232
	270	2.94	-0.297	-0.300	-0.039	-0.028	0.955
	300	1.14	-0.300	-0.300	-0.040	-0.034	0.983
	330	4.93	-0.298	-0.299	-0.042	-0.043	1.429
	360	7.55	-0.298	-0.296	-0.042	-0.025	1.678

0.00 = -359840.64 Kcal/Mole.

APPENDIX B

GLOSSARY OF STRUCTURES



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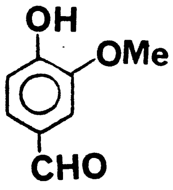

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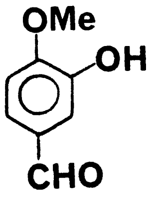

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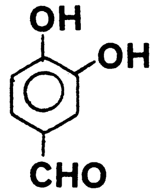

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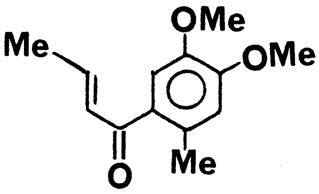

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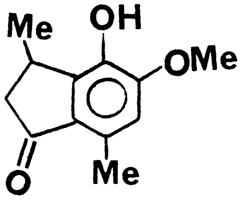

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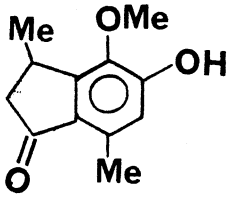

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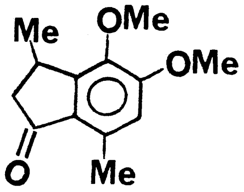

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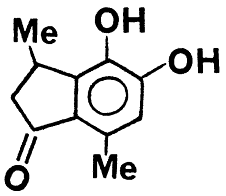

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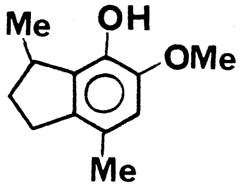

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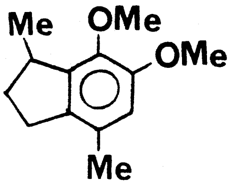

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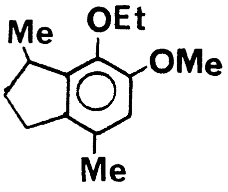

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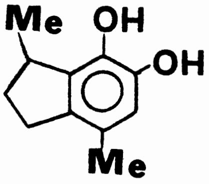

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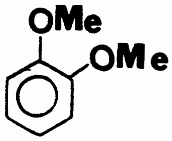

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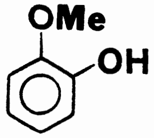

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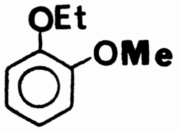

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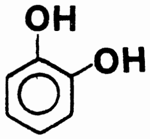

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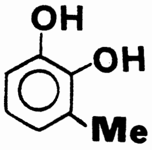

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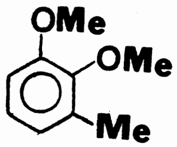
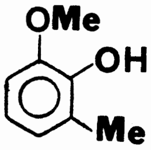


6b



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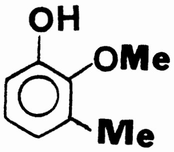

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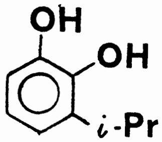

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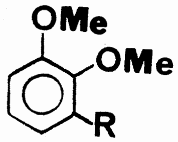
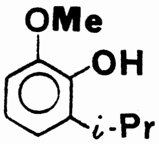


7b, R = *i*-Pr
7e, R = Et
7f, R = *t*-Bu



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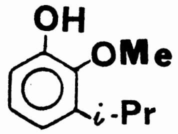
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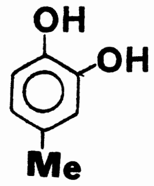
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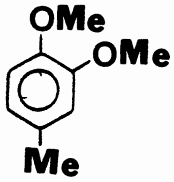
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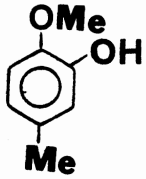
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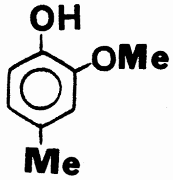
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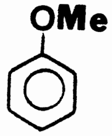
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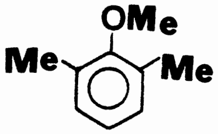
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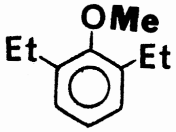
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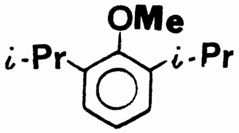
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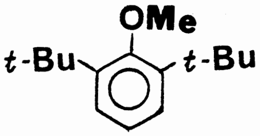
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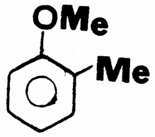
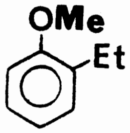

11a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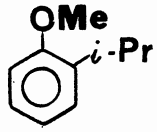

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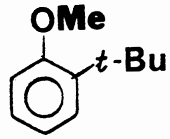

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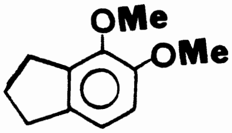

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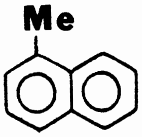

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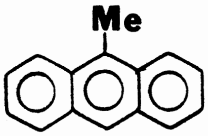
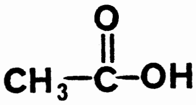


14

15

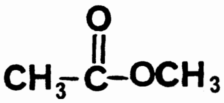
$CH_3(CH_2)_8CH_3$

16



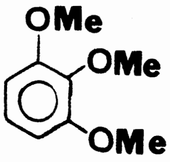
$CH_3{-}\overset{O}{\overset{\|}{C}}{-}OH$

17

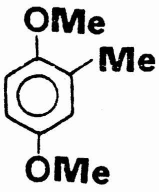


$CH_3{-}\overset{O}{\overset{\|}{C}}{-}OCH_3$

18



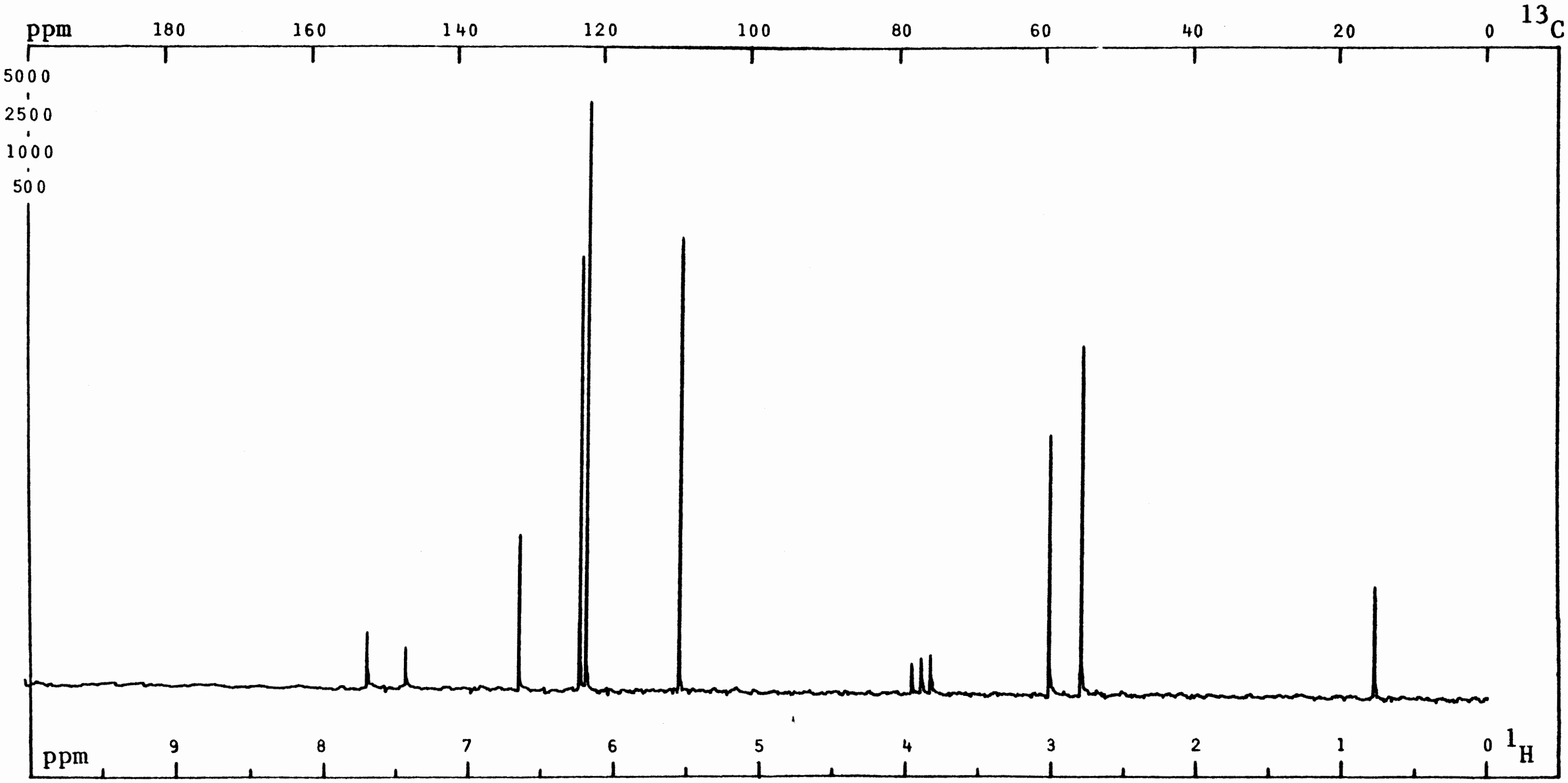
19



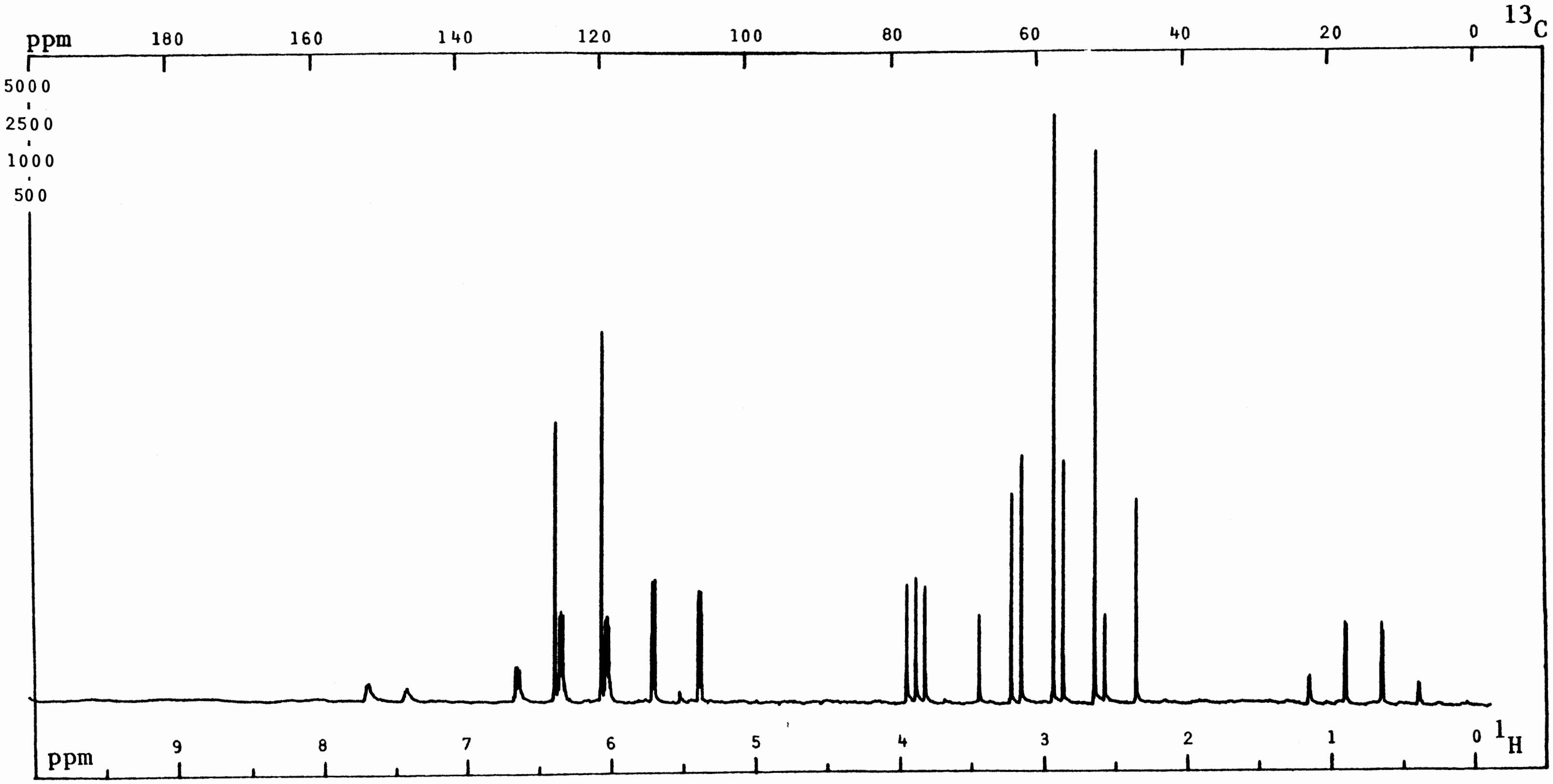
20

APPENDIX C

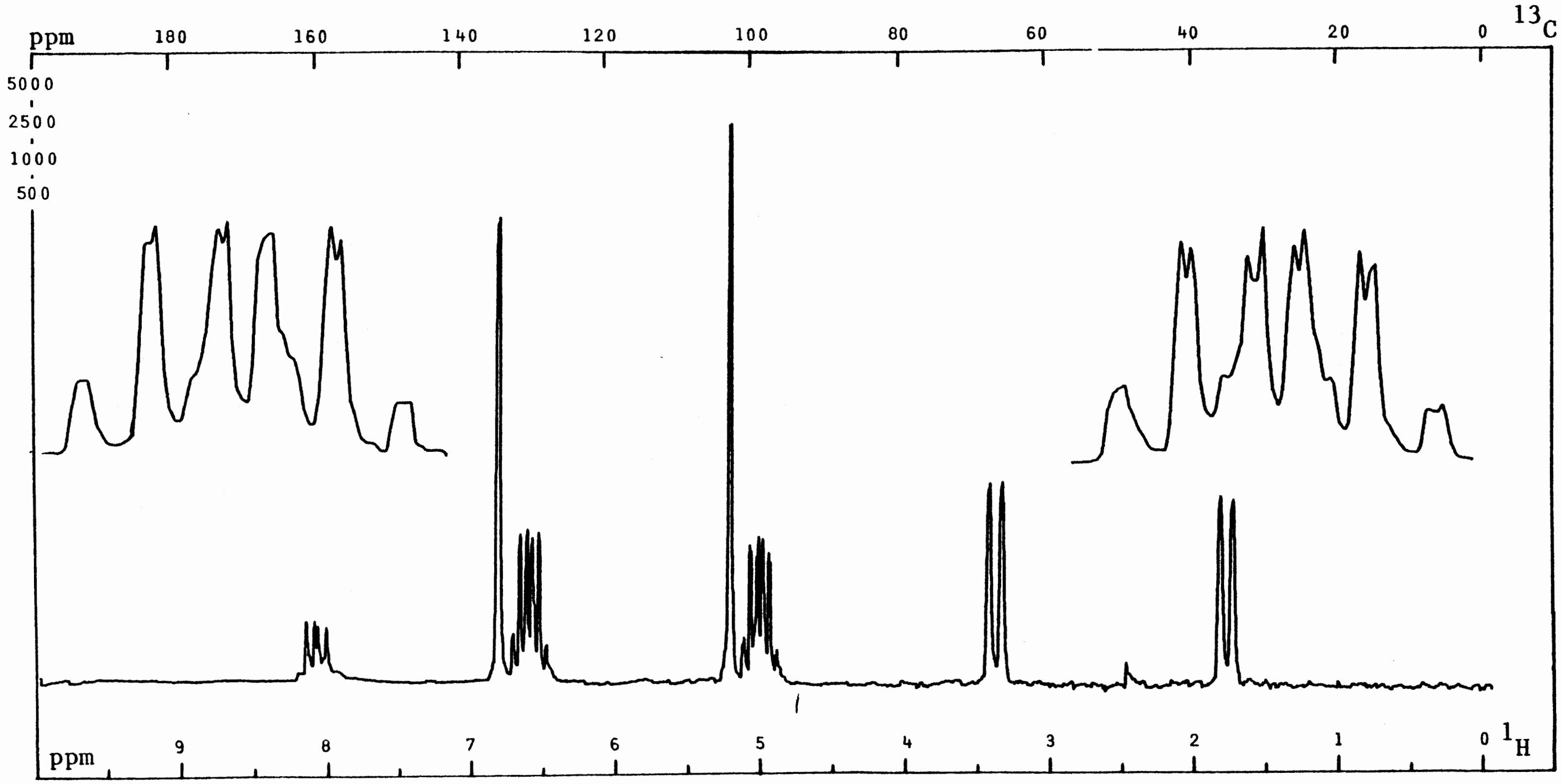
SELECTED SPECTRA



Spectrum 1. Fully Decoupled ^{13}C NMR Spectrum of 2,3-Dimethoxytoluene (6b)



Spectrum 2. Gated Decoupled ^{13}C NMR Spectrum of 2,3-Dimethoxytoluene (6b)



Spectrum 3. Gated Decoupled ^{13}C NMR Spectrum of 2,3-Dimethoxytoluene (6b) (2,500 Hz-3,500 Hz)

VITA

Phillip Walter Jardon

Candidate for the Degree of

Master of Science

Thesis: MOLECULAR ORBITAL CALCULATIONS AND ^{13}C NMR STUDIES TO EXPLAIN THE SELECTIVE DEMETHYLATION OF 3-ALKYL-1,2-DIMETHOXYBENZENES

Major Field: Natural Science

Biographical:

Personal Data: Born in Council Bluffs, Iowa, September 18, 1957, the son of Mr. and Mrs. Robert A. Jardon.

Eduation: Graduated from Farragut Community High School, Farragut, Iowa, in May, 1976; received the Bachelor of Science degree in Chemistry from Northwest Missouri State University, Maryville, Missouri, in May, 1980; completed requirements for the Master of Science degree at Oklahoma State University, Stillwater, Oklahoma, in July, 1982.

Professional Experience: Farm worker and manager, Jardon Holstein Farm, birth to present; undergraduate teaching assistant, Northwest Missouri State University, 1978-1980; environmental instructor, Iowa Youth Conservation Corps, summers of 1978 and 1979; graduate teaching assistant, Oklahoma State University, Department of Chemistry, 1980-1981; graduate research assistant, Oklahoma State University, Department of Chemistry, 1981-1982.

Professional Societies: Phi Lambda Upsilon, American Chemical Society.