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MULTINUCLEAR MAGNETIC RESONANCE AND MOLECULAR MECHANICS STUDIES ON THE CONFORMATIONS AND THE DYNAMIC BEHAVIORS OF α-ALKYL-SUBSTITUTED *o*-METHOXYBENZYL ALCOHOLS

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The conformations and the dynamic behaviors of α-monoalkyl- and α,α-dialkyl-*o*-methoxybenzyl alcohols are discussed on the basis of their ^{1}H, ^{13}C and ^{17}O NMR spectra and MM3 calculations. The conformations of α-monoalkyl derivatives are shown to be different from those of α,α-dialkyl derivatives and unfavorable to form intramolecular OH···O hydrogen bonds. The trends of substituent effects on the restricted rotation about the C_{ipso}—C_α bond could be reproduced fairly well by MM3 calculations. © 1997 John Wiley & Sons, Ltd.

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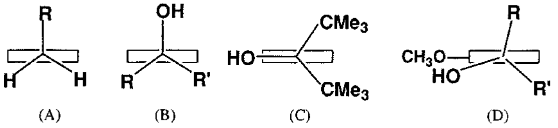
INTRODUCTION

Rotational barriers about the C_{sp^2}—C_{sp^3} single bonds are usually lower than those about C_{sp^3}—C_{sp^3} single bonds.[1] Alkenes usually take a conformation in which one of the alkyl groups or hydrogen on the α-carbon atom eclipses the C=C double bond (synperiplanar) so as to take advantage of the stabilization by hyperconjugation. In alkyl-substituted aromatic compounds, the alkyl groups tend to fold over the aromatic π-electron cloud. This favors the alkyl-perpendicular conformation (A).[2] Thus, 1,3,5-tri(neopentyl)benzene was shown to take a conformation in which all three neopentyl groups lie on the same side and just above the aromatic ring.[3–5]

The conformations of several benzyl alcohols have been elucidated by IR and NMR spectroscopic methods. In connection with the hydrogen-bond-like interaction between the hydroxyl and the aromatic π-system, a conformation (B) in which the OH group orients itself to the direction perpendicular to the plane of the aromatic ring was proposed.[6] On the other hand, the highly crowded α,α-di-*tert*-butylbenzyl alcohol molecule was shown to take conformation C, in which the crossing of *tert*-butyl groups over the plane of the aromatic ring is hindered. Owing to slow rotation, the *ortho* (2 and 6) protons become non-isochronous even at room temperature.[7, 8] The six-membered intramolecular hydrogen bond in the *o*-methoxybenzyl alcohol confines its α-hydroxyl groups to be coplanar to the aromatic ring and is expected to favor the OH-coplanar conformation (D).



In order to clarify the conformational effect on hydrogen bonding, the conformations of α-substituted *o*-methoxybenzyl alcohols have been studied by IR spectroscopy.[9] The hydrogen bond shifts $\Delta\nu_{OH}$ could not be correlated with the enthalpies of hydrogen bond formation when the α-monoalkyl- and the α,α-dialkyl-*o*-methoxybenzyl alcohols were treated together. From this discrepancy and other facts, it was suspected that the conformations of the α-monoalkyl derivatives are considerably different from those of the α-unsubstituted and the α, α-dialkyl derivatives. It is expected that the α-monoalkyl derivatives take a conformation (similar to A) in which α-alkyl group is stretching nearly perpendicular to the plane of the aromatic ring. However, this conformational preference has not yet been rationalized.

In order to elucidate further the stable conformations and the dynamic behaviors of α-substituted *o*-methoxybenzyl

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alcohols, the effects of α-alkyl substituents on their ^{1}H, ^{13}C and ^{17}O NMR chemical shifts, and also their ^{1}H DNMR spectra, were measured and are discussed in comparison with the MM3 geometries of these molecules. As pointed out by Bartlett *et al.*,[8] the internal rotation about the C_{ipso}—C_{α} bond becomes slow as the substituent becomes bulky. This allows us to observe the signals of the rotational isomers separately at low temperatures. Thus, DNMR[10] measurments on these compounds provide further information concerning the dynamic behaviors of their conformations.

EXPERIMENTAL

Materials. α,α-Dialkyl-*o*-methoxybenzyl alcohols were prepared by reaction of the corresponding ketones with *o*-methoxyphenylmagnesium bromide in THF.[11, 12] α-Alkyl-*o*-methoxybenzyl alcohols were prepared by reaction of the corresponding alkylmagnesium halides with *o*-methoxybenzaldehyde.[13] All of these alcohols are known and have been characterized by their spectral data and by comparing their boiling points with those reported in the literature.[11–14] Solvents for NMR measurements and other materials were commercially available and used without further purification.

Spectral measurements. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL EX-270 spectrometer at 25 °C, except for the DNMR measurements. A JEOL FX-90Q spectrometer was also employed for ^{17}O measurements. Chemical shifts form internal TMS standard are given for ^{1}H and ^{13}C spectra. The ^{17}O chemical shifts are given in reference to the signal of $H_2{}^{17}O$.[15] Variable-temperature measurements were carried out by using a JNM VT variable-temperature apparatus. Rotational barriers ($\Delta G^{\ddagger}$) were calculated from the coalescence temperature (T_c) by the following equation:[16]

$$\Delta G^{\ddagger} = 2.303RT_c[10.32 + \log(T_c/k)] \qquad (1)$$

The rate k was, in turn, obtained from the spectra at T_c by the equation $k = \Delta\delta/\sqrt{2}$.

IR spectra were measured with a JASCO FT-IR5M spectrophotometer in dilute CCl_4 solutions. The concentration of the solutions were kept within 3×10^{-3} -5×10^{-3} mol l^{-1} so a to avoid the effect of intermolecular association.[17] The temperature of the sample was controlled to within ±0·1 °C by using an Advantec TE-105M circulating thermostat. The enthalpy of intramolecular hydrogen bond formation (ΔH) was obtained by measuring the ν_{OH} intensities of the free (ε_f) and the hydrogen-bonded (ε_b) species at various temperatures (within the range 288–315 K). The gradient of the $\ln(\varepsilon_f/\varepsilon_b)$ vs $1/T$ plot gave ΔH. Some of the ΔH data had been reported previously.[9] New data are given in Table 1.

Calculations. Molecular force field calculations were done by using the MM3 program written by Allinger and co-workers.[18] the dielectric parameter D was set to be 1·5. The CONFLEX 3 program[19] and Dihedral Driver option were employed in the search for stable rotamers.

RESULTS AND DISCUSSION

In general, the ^{1}H signal of the hydroxyl group in the $OH\cdots O$ hydrogen-bonded system moves towards lower field as the hydrogen bond becomes stronger.[20] Thus, δ_{OH} in inert solvents (e.g. chlorofom) can be a measure of the strength of intramolecular hydrogen bonding. On the other hand, the ^{17}O chemical shift of the hydrogen-accepting alkoxyl group shows a high-field shift when the hydrogen bond is strengthened.[21] Thus, the ^{1}H, ^{13}C and ^{17}O chemical shifts related to the intramolecular hydrogen bond of α-substituted *o*-methoxybenzyl alcohols are given, together with $\Delta\nu_{OH}$, $\varepsilon_h/\varepsilon_f$ and ΔH from IR spectroscopic measurements, in Table 2. Here, $\Delta\nu_{OH}$ is the hydrogen bond shift,[22] which is defined as the difference in the absorption frequencies of the free and the hydrogen-bonded species [$\Delta\nu_{OH} = \nu_{OH(free)} - \nu_{OH(H\text{-}bonded)}$]; $\varepsilon_h/\varepsilon_f$ and ΔH denote the ratio

Table 1. Infrared OH stretching absorption spectra of unsymmetrically α-substituted *o*-methoxybenzyl alcohols ($2\text{-}MeOC_6H_4CR^1R^2OH$) and enthalpies of hydrogen bond formation[a]

Compound	ν_f (cm^{-1})	ε_f ($l\ mol^{-1}\ cm^{-1}$)	ν_b (cm^{-1})	ε_b ($l\ mol\ cm^{-1}$)	$\Delta\nu$ (cm^{-1})	ΔH ($kJ\ mol^{-1}$)
12	3622	22·1	3564	68·7	50	3·3
13	3626	26·8	3557	84·9	69	3·4
15	3611	26·3	3541	131·2	70	2·3
17	3626	27·7	3553	52·4	67	4·6
18	3614	24·9	3541	144·6	73	3·8
19	3614	32·4	3530	89·9	84	3·9
20	3607	20·0	3525	51·9	82	4·2
21	3611	19·7	3549	130·2	62	3·0
22	3611	21.4	3530	141.5	81	2.9

[a] ν_f, ε_f, $\sigma\lambda + = \nu_b$ and ε_b were measured at 25 °C in carbon tetrachloride solutions.

of the intensities of the hydrogen-bonded (ε_h) and the free (ε_f) OH stretching bands and the enthalpy difference between the hydrogen-bonded and the free species, respectively.

Substituent effects on the hydrogen bonds as evidenced by NMR and infrared studies

The chemical shift of the OH proton signal $\delta(^1H)_{OH}$ of a hydrogen-bonded system depends both on the strength of the hydrogen bond per molecule and on the abundance of the hydrogen-bonded species relative to the total number of molecules. As a result, $\delta(^1H)_{OH}$ moves towards low field as the hydrogen bond is strengthened and as the hydrogen-bonded species becomes abundant. However, we cannot observe the two effects separately by NMR spectroscopy.

In contrast, IR spectroscopy provides information about the strength and abundance individually, since the absorption bands of the free and the hydrogen-bonded species can be observed separately in the IR OH spectrum. Hence the hydrogen bond shift $\Delta\nu_{OH}$ can be a measure of the intrinsic strength of a hydrogen bond without the effect of the abundance. On the other hand, the intensity ratio $\varepsilon_h/\varepsilon_f$ can be a relative measure of the abundance of the hydrogen-bonded species.

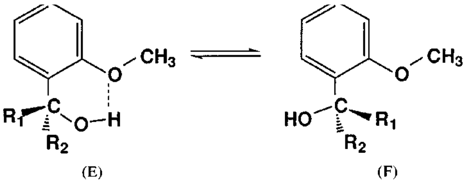
Generally, the abundance of the hydrogen-bonded species increases as the hydrogen bond is strengthened. In fact, the $\delta(^1H)_{OH}$ values in chloroform-*d* are well correlated with $\Delta\nu_{OH}$ ($r = 0.902$). It can also be correlated equally well with the $\varepsilon_h/\varepsilon_f$ ratio and the steric energy difference (ΔSE) between the free and the hydrogen-bonded conformers ($r = 0{\cdot}920$ and $0{\cdot}885$, respectively). Thus, the low-field shift of $\delta(^1H)_{OH}$ in chloroform-*d* (Table 2) implies that the equilibrium given by equation (2) moves towards the left-hand side or, in other words, that the intramolecularly hydrogen-bonded OH/MeO *syn*-conformer (E) is favored. In solvents capable of forming hydrogen bonds (dimethyl sulfoxide, acetone and methanol), the intramolecular hydrogen bond should be destroyed at least partly and, alternatively, an intermolecular hydrogen bond is formed

Table 2. Some chemical shifts (ppm) of α-substituted o-methoxybenzyl alcohols ($2\text{-}MeOC_6H_4CR^1R^2OH$) relevant to intramolecular hydrogen bonding

			$\delta(^1H)_{OH}$			$\delta(^{13}C)$					
Compound	R_1	R^2	In $CDCl_3$	In DMSO	$\Delta\delta$	$C(2)_{ar}$	OMe	$\delta(^{17}O)$[a] OMe	$\Delta\nu_{OH}$ (cm^{-1})	ΔH ($kJ\ mol^{-1}$)	$\varepsilon_h/\varepsilon_f$
1	H	H	2·40	5·06	2·66	157·4	55·3	42 (−5)	30	4·72[e]	1·97
2	H	Me	2·67	5·00	2·33	156·5	55·2	48 (+1)	36	1·25[e]	0·53
3	H	Et	2·22	4·44	2·22	156·6	55·2	52 (+5)	48	0·79[e]	0·55
4	H	Pr^i	2·57	4·69	2·12	156·7	55·2	50 (+3)	42	1·00[e]	0·51
5	H	Bu^t	2·68	4·84	2·16	157·0	55·1	32 (−15)	60	0·42[e]	0·50
6	Me	Me	4·25	4·89	0·64	156·9	55·2	45 (−2)	58	6·40[e]	4·29
7	Et	Et	3·88	4·39	0·51	157·2	55·4	41 (−6)	64	2·59[e]	1·64
8	Pr	Pr	3·74	4·43	0·69	157·1	55·4	37 (−10)	62	2·88[e]	1·58
9	Pr^i	Pr^i	5·70	4·40	−1·30	158·6	55·9	34 (−13)	74	5·48[e]	5·47
10	Bu	Bu	3·74	4·35	0·61	157·0	55·4	37 (−10)	62	2·51[e]	1·65
11	Bu^t	Bu^t	6·59	6·54	−0·05	158·4	57·3	29 (−18)	108	5·85[e]	5·70
12	Me	Et	4·09	4·67	0·58	156·9	55·3	48 (+1)	50		3·11
13	Me	Pr^i	4·11	4·50	0·39	156·8	55·4	43 (−4)	69	2·93	3·17
14	Me	Bu^i	3·78	4·66	0·88	156·0	54·4	46 (−1)			
15	Me	Bu^t	5·57	4·77	−0·80	158·3	55·9	27 (−20)	70	3·63	4·99
16	Me	Pe^n	3·43	4·58	1·15	156·1	54·3	51 (+4)			
17	Et	Pr^i	3·78	4·21	0·43	157·3	55·5	42 (−5)	67		1·89
18	Et	Bu^t	5·65	4·75	−0·90	158·1	55·7	33 (−14)	73	2·98	5·81
19	Pr^i	Bu^t	5·98	4·98	−1·00	158·4	56·4	35 (−11)	84	3·77	5·78
20	Me	Ph	4·64	5·35	0·71	157·0	55·5	46 (−1)			
21	Pr^i	Ph	4·92	5·09	0·17	157·5	55·7	39 (−8)			
22	Bu^t	Ph	5·05	5·15	0·10	158·2	55·9	34 (−13)			
23[b]	Me	Me	4·59	4·87	0·28	154·2	61·2	45 (−2)	82	4·19	2·60
24[c]	Me	Bu^t	5·37	4·67	−0·70	158·2	55·5	31 (−16)	62	2·88	6·61
25[d]	Me	Bu^t	5·64	4·81	−0·83	153·0	55·6	33 (−14)	81	4·33	6·61

[a] Differences from the chemical shift value (47 ppm) of *o*-methylanisole are given in parentheses.
[b] 3,5-Dimethyl-substituted derivative.
[c] 4-Methoxy-substituted derivative.
[d] 5-Methoxy-substituted derivative.
[e] ΔH values reported in Ref. 9.

between the hydroxyl group of the benzyl alcohol and the acceptor atom in the solvent molecule. The intermolecular hydrogen bond is expected to stabilize the free OH/MeO *anti*-conformer (F) relative to conformer E. This trend was revealed in the solvent effect on the conformational free energy difference ΔG given in Table 5.



The large solvent shifts $\Delta\delta$ [$= \delta_{OH(DMSO)} - \delta_{OH(CDCl_3)}$] (Table 2) of the OH proton signal for the unsubstituted and the α-monosubstituted alcohols **1**–**5** can be rationalized on the basis that the intramolecular OH · · · O hydrogen bond in the inert solvent is replaced by the much stronger and more favorable intermolecular hydrogen bond with DMSO. In contrast, the sterically enforced and protected hydrogen bonds in the crowded α,α-dialkyl alcohols **9**, **11**, **15**, **18**, **19**, **24** and **25** are insensitive to the effect of the hydrogen-accepting solvent; the high-field solvent shifts of these alcohols must arise from the fact that the intermolecular hydrogen bond is weaker than the intramolecular hydrogen bond in these alcohols.

The IR OH frequency shift $\Delta\nu_{OH}$ can be correlated well with the steric substituent constant Ωs,[23, 24] as shown in Figure 1. Thus, the magnitude of the frequency shift $\Delta\nu_{OH}$ can be primarily determined by the steric hindrance between the α-alkyl group(s) and other parts of the molecule in conformer E, which enforces a close OH · · · distance. This type of steric effect is often called steric compression. A large steric compression can be expected from the large MM3 steric energies (Table 3) of the alcohol molecules bearing two bulky α-alkyl groups (**19** and **11**). The short distances between the hydrogen-bonded H · · · O in these molecules also suggest the presence of steric compression. As a matter of course, the steric compression results in the additional stabilization of the intramolecular hydrogen bond.

On the other hand, the populations of the intramolecularly hydrogen-bonded (E) and the free (F) conformers are determined by the energy difference between them. In highly crowded α,α-dialkyl-*o*-methoxybenzyl alcohols, the very severe steric crowdedness between the α-alkyl groups and *o*-methoxyl moiety will disfavor conformer F. As a result, the equilibrium moves far towards conformer E as the substituent becomes bulky.

In accordance with the general trends reported pre-

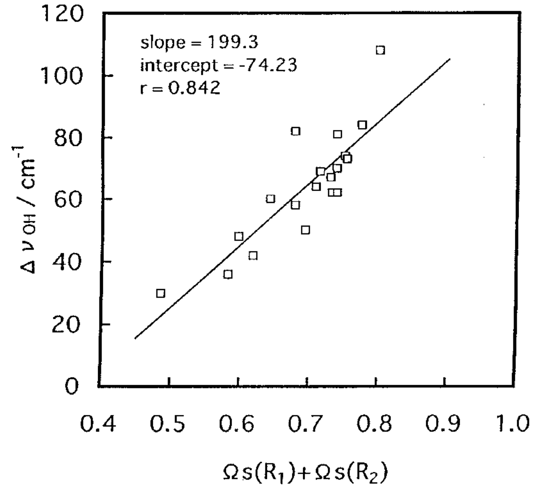


Figure 1. Results of correlation analyses: $\Delta\nu_{OH}$ vs Ωs plot. The sum of the Ωs values of the two α-substituents [$\Omega s(R_1)+\Omega s(R_2)$] was chosen as the abscissa

Table 3. Steric energies from MM3 of the energy-minimal conformations and the rotational barriers of α-substituted *o*-methoxybenzyl alcohols ($2\text{-}MeOC_6H_4CR^1R^2OH$)[a]

			Conformer I (E)[b]		Conformer II (F)[b]		Transition state I		Transition state II		
Compound	R¹	R²	ω (ω′) (°)	*SE* *(kJ mol⁻¹)*	ω (°)	Δ*SE* (kJ mol⁻¹)	ω (°)	Δ*SE* (kJ mol⁻¹)	ω (°)	Δ*SE* (kJ mol⁻¹)	H-bonded *d*(O · · · H) (Å)
1	H	H	− 62·0 (− 59·4)	*28·12*	78·8	4·66	20·1	12·4	142·3	13·0	2·201
2	H	Me	− 45·1 (76·8)	*30·17*	137·2	0·92	28·1	18·8	− 156·2	20·6	1·995
6	Me	Me	− 42·2 (− 77·8)	*39·29*	159·6	8·71	94·6	15·5	− 112·4	21·5	1·950
5	H	Bu^t	− 38·3 (87·7)	*55·19*	139·1	− 1·90	26·1	37·0	− 147·9	55·7	1·942
15	Me	Bu^t	− 28·5 (94·0)	*83.43*	152·8	8·28	91·6	60·6	− 88·2	70·0	1·938
18	Et	Bu^t	− 24·8 (96·8)	*92·84*	158·0	8·13	93·7	77·5	− 90·1	83·6	1·927
19	Pr^i	Bu^t	− 19·9 (106·3)	*128·87*	164·9	14·1	92·7	80·8	− 90·5	90·0	1·937
11	Bu^t	Bu^t	− 8·4 (110·2)	*181·38*	170·9	17·0	91·7	110·1	− 91·7	110·1	1·895

[a] ω refers to the torsional angle C(2)—C(*ipso*)—C(α)—O(hydroxyl) of the *S*-isomer. ω′ is the C(2)—C(*ipso*)—C(α)—C(R²) torsional angle of conformer I.

[b] Conformers I and II refer to the OH/MeO *syn*-conformer (E) and the OH/MeO *anti*-conformer (F), respectively. Steric energy difference Δ*SE* is given with reference to the *SE* (italicized in the table) of conformer I.

viously,[21] the ^{17}O signals of the methoxyl groups of the *o*-methoxybenzyl alcohols showed a high-field shift when the hydrogen bond was stengthened. For example, for di-*tert*-butyl derivative (**11**), which has the largest $\Delta\nu_{OH}$ value, the methoxyl ^{17}O signal appears at 13 ppm higher field than the signal of the unsubstituted derivative (**1**), which, in turn, is 18 ppm higher field than that of the parent anisole. In order to correlate the ^{17}O chemical shift (δ^{17}O) of the hydrogen-accepting methoxyl group with the strength of hydrogen bonding, it was plotted against the proton chemical shift of the alcoholic OH group (δ_{OH}), against the hydrogen bond shift of the IR OH stretching frequency ($\Delta\nu_{OH}$) and against the enthalpy of intramolecular hydrogen bond formation (ΔH). The δ_{OH} vs δ^{17}O and $\Delta\nu_{OH}$ vs δ^{17}O correlations are fairly good [$r = 0.829$ ($n = 20$) and $r = 0.782$ ($n = 16$), respectively]. These two correlations support the fact that the high-field shift of the δ^{17}O is an indication of the intramolecular hydrogen bonding.

However, ΔH could not be correlated with δ^{17}O at all. As reviewed briefly in the Introduction, the preferred conformations of α-substituted benzyl alcohols are considerably different from each other depending on the bulkiness and number of the α-substituents.[9] The unexpectedly low ΔH vs δ^{17}O correlation coefficient must originate from the differences in geometries among the hydrogen-bonded conformers (E) of variously substituted benzyl alcohols. In addition, as suggested by the variation in the torsional angle C(2)—C(*ipso*)—C(α)—O(α)-O(hydroxyl) (ω) in Table 3, the conformation of the reference free conformer (F) can differ among the benzyl alcohols in Table 2. Thus, the enthalpy difference ΔH ($= H_{\text{H-bonded}} - H_{\text{free}}$) must be perturbed by the conformational changes in both conformers *E* and *F*.

Discussion of stabilities and geometries of the conformers on the basis of molecular mechanics results

In order to evaluate the steric hindrance due to the α-alkyl substituents more quantitatively and to elucidate further the geometries and the dynamic behaviors of the conformers of these alcohols, MM3[18] calculations were carried out on some of these alcohols. Stable rotational isomers about the C_{ipso}—C_α bond were searched by use of the CONFLEX 3 program.[19] As an example of conformation searching by the combined use of the Dihedral Driver option and CONFLEX 3, the *SE* vs ω plot for α-*tert*-α-methyl-*o*-methoxybenzyl alcohol (**15**) is shown in Figure 2, where ω denotes the torsional angle about the C_{ipso}—C_α bond. The thus obtained stable and transition-state conformations (the torsional angle ω corresponding to the minima and the maxima in Figure 2) are given together with their steric energies (*SE*) in Table 3.

The MM3 calculations showed that the hydrogen-bonded conformer (E) is more stable than the free conformer (F) for the series of unsubstituted and α,α-disubstituted *o*-methyoxybenzyl alcohols. ΔSE ($= SE_2 - SE_1$) is the calculated equivalent for the energy difference. In the cases of α-monosubstituted *o*-methoxybenzyl alcohols, the calculation showed that the free conformer (F) is slightly more stable than the hydrogen-bonded conformer (E). Qualitatively this conclusion is compatible with the results from the experiments. The experimentally obtained enthalpy of hydrogen bond formation (ΔH in Table 2) actually measures the energy difference between E and F conformers. In accordance with the calculated ΔSE, the ΔH for the α-monoalkyl-*o*-methoxybenzyl alcohols **2**–**5** from IR spectroscopy are also smaller than those of the unsubstituted

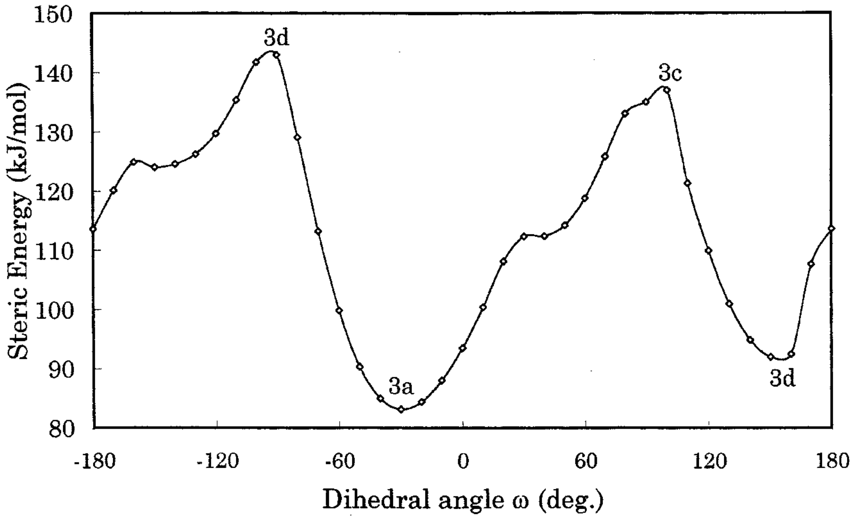


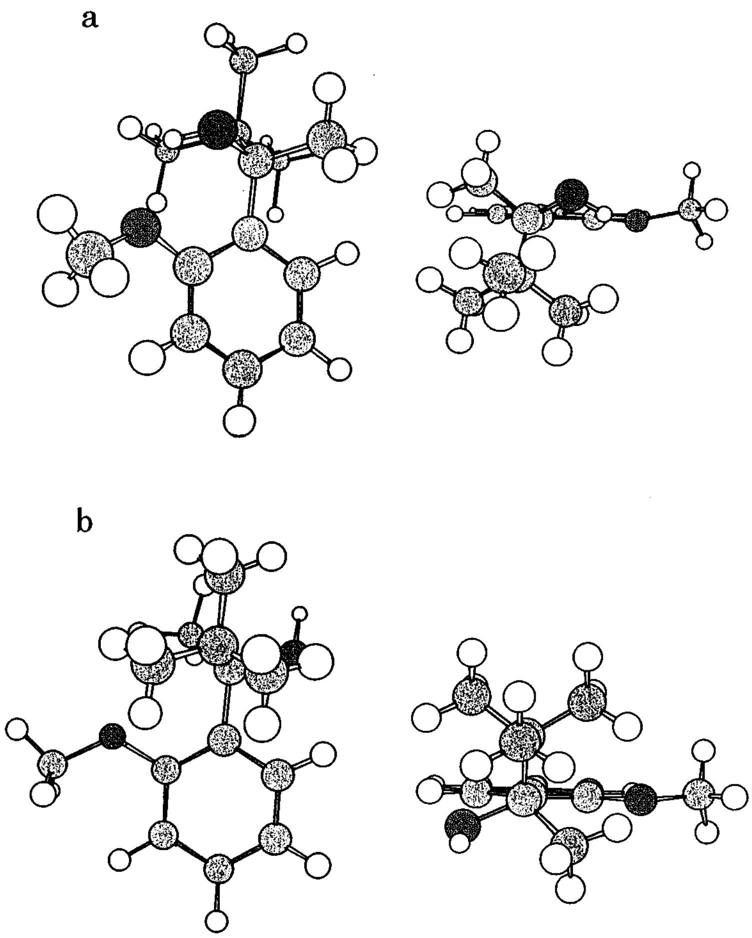
Figure 2. Steric energy (*SE*) vs torsional angle (ω) plot for α-*tert*-butyl-α-methyl-*o*-methoxybenzyl alcohol (**15**)

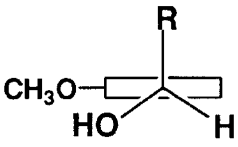
and α,α-di-substituted derivatives. However, in contrast to the ΔSE from MM3, the ΔH values for these alcohols are still negative, showing that conformer E of the α-monoalkyl derivatives is slightly more stable than conformer F.

The intensity ratio $\varepsilon_h/\varepsilon_f$ can also be a simple experimental measure of the abundance of the hydrogen-bonded species, and was well correlated with ΔSE from MM3 ($r = 0.894$).

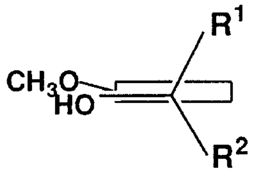
As discussed before, the OH proton signals of the α-monoalkyl derivatives **2**–**5** appear at relatively high fields in comparison with the α,α-dialkyl derivatives. The ^{17}O chemical shifts of the hydrogen-accepting methoxyl group of the α-monoalkyl derivatives **2**–**4** were observed at lower fields than that of the parent *o*-methoxybenzyl alcohol. The $\Delta\nu_{OH}$ values for these alcohols are also small. All this spectroscopic evidence leads to the conclusion that the $OH \cdots O$ hydrogen bonds in the α-monoalkyl derivatives are considerably weaker and less favorable than those in the α,α-dialkyl derivatives.

In the preferred conformations of α-monoalkyl and unsymmetrical α,α-dialkyl derivatives, the bulkier alkyl group prefers to take a position perpendicular to the aromatic ring plane due to the steric repulsion between the alkyl group and the hydrogen atom at the 6-position of the aromatic ring. Thus, in the cases of the combinations of two α-substituents of considerably different size (H and alkyl, Me and *t*-Bu, etc.), the bulkier alkyl group occupies the perpendicular position and takes conformation A′ preferably [see the MM conformations in Figure 3(a) and (e)]. In contrast, the α,α-dialkyl derivatives bearing two alkyl groups of similar size take the most stable conformation (D′) in which the OH group lies on the plane of the aromatic ring and the R^1—C_α—R^2 angle is bisected by the plane [the MM3 conformation of Fig. 3(f)]. Thus, the preferred conformations of α-alkyl-substituted *o*-methoxybenzyl alcohols were shown to be considerably different depending on the number and the bulkiness of the α-substituents.





(A')

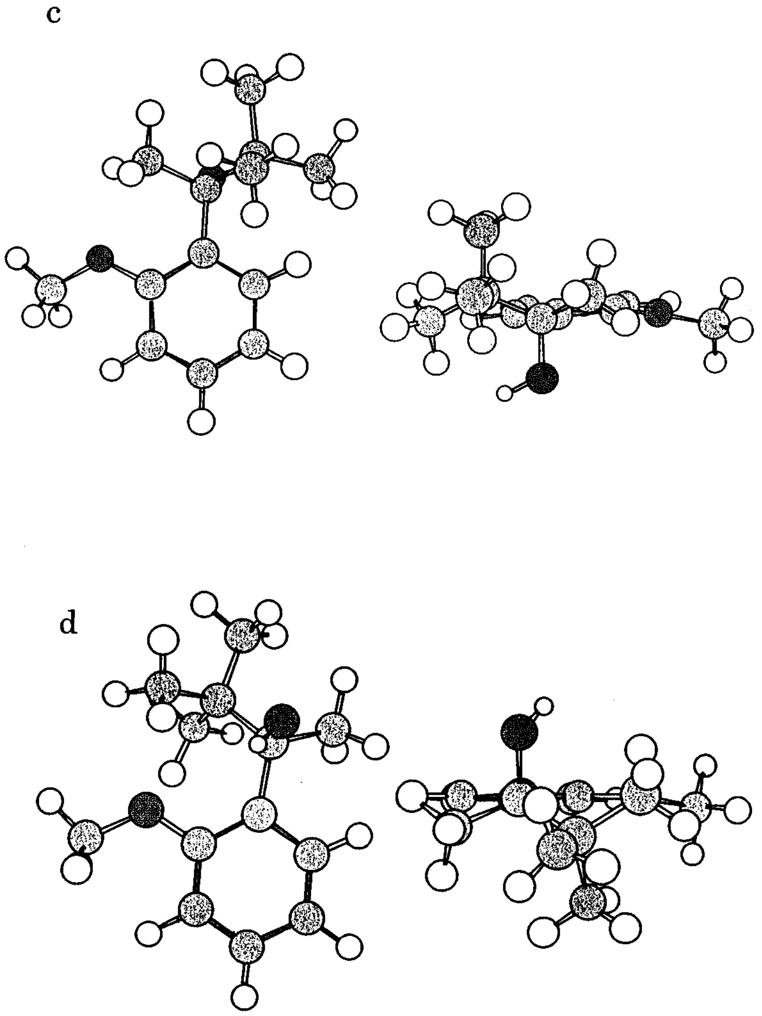


(D')

Rotational barriers and free energy difference between the conformers from NMR spectroscopy—comparison with those from MM

The energy profiles of **15** (Figure 2) showed that the molecule has the maximum energy and reaches the transition state when both alkyl groups come close to the plane of the aromatic ring, taking conformation B. In this conformation (two conformations when $R^1 \neq R^2$), the hydroxyl group occupies a position nearly perpendicular to the plane (as illustrated in Figure 3(c) and (d)]. Thus, the rotational barrier ($\Delta G^{\ddagger}$) concerning this torsional motion is influenced by the size of the second less bulky alkyl group (R^2) in addition to the bulkier alkyl group (R^1), and tends to be augmented as the second alkyl group R^2 becomes bulkier in a case when the substituent R^1 is similar.

This was actually observed in the DNMR experiments on a series of α-substituted *o*-methoxybenzyl alcohols. NMR signals of *o*-methoxybenzyl alcohols bearing one or two bulky groups on the α-carbon atom sometimes showed exchange broadening, and the variable-temperature measurements gave their rotational barriers ($\Delta G^{\ddagger}$). The results are given in Table 4. The observed $\Delta G^{\ddagger}$ of α-alkyl-α-*tert*-butyl-*o*-methoxybenzyl alcohols becomes higher as the second alkyl group becomes bulkier. As expected, the $\Delta G^{\ddagger}$ for **15** is considerably higher than the reported value for an



α-tert-butyl-*α*-methylbenzyl alcohol without an *o*-methoxyl group (39·5 kJ mol^{-1} for *α-tert*-butyl-3,4,5-trimethoxy-*α*-methylbenzyl alcohol[25]).

Comparison of the calculated Δ*SE* (in Table 3) with the observed Δ*G* (in Table 4) revealed a tendency to overestimate the population of the OH/MeO *syn*-conformer (E). The comparison of ΔG_{obs} (in acetone-d_6) with Δ*SE* showed that Δ*SE* is 3–8 kJ mol^{-1} more favorable to conformer E. This apparent anomaly cannot be ascribed to mere overestimation of the stabilization energy by the hydrogen bond formation. The Δ*G* values were measured using polar solvents such as acetone or methanol, because of the convenience for NMR measurements. In these solvents, the isometric ratio is near 50 : 50 and is convenient to determine the ratio precisely. Under these conditions, the lineshape analysis could also be performed with higher accuracy.

The solvent effect on the isomeric ratio is significant; the equilibrium significantly moves to the OH/MeO *syn*-conformer (E) as the solvent becomes less polar. Thus, in acetone–chloroform mixtures, both Δ*G* and $\Delta G^{\ddagger}$ of the *α*-methyl-*α-tert*-butyl derivative **15** were shown to vary regularly as a function of the composition of the solvent (Table 5). As expected, the intramolecularly hydrogen-bonded conformer (E) becomes more predominant as the proportion of chloroform increases. Even if Δ*G* and $\Delta G^{\ddagger}$ in chloroform could not be determined by the measurement, the extrapolated values for Δ*G* (7.37 kJ mol^{-1}) and $\Delta G^{\ddagger}$ (61·4 kJ mol^{-1}) agree very well with those from MM3 (8.22 and 60·6 kJ mol^{-1}, respectively). The lower $\Delta G^{\ddagger}$ in hydrogen-accepting solvents can be rationalized by the calculated

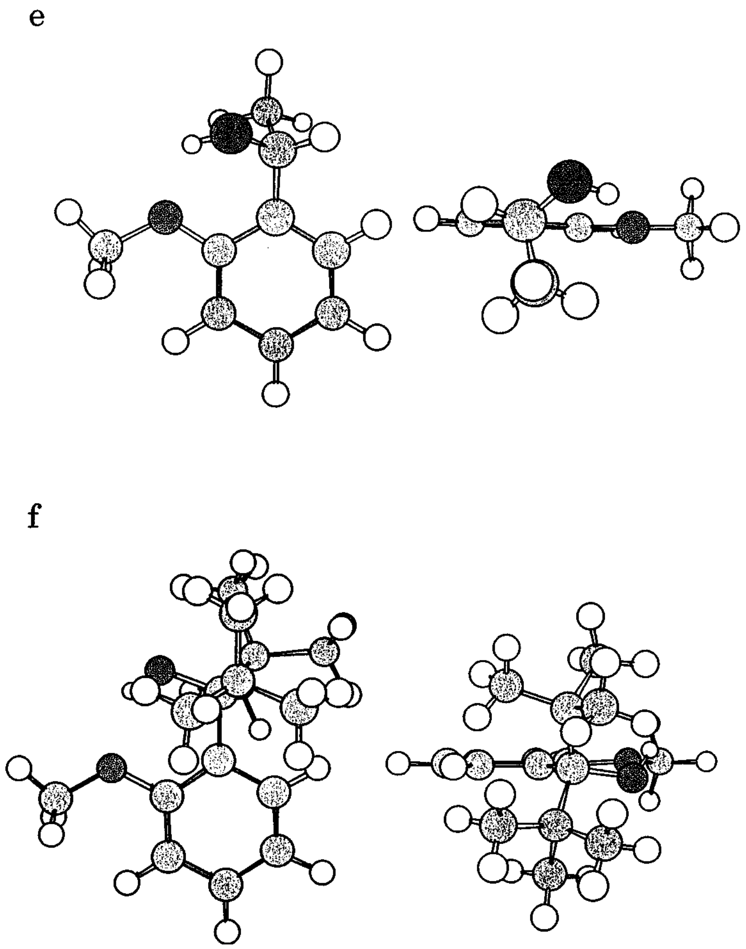


Figure 3. Ball-and-stick presentations of some important conformations from MM3/CONFLEX 3 calculations: (a)–(d) the most stable (intramolecularly hydrogen-bonded) conformer, the next stable free conformer and the lower and the higher transition state conformations, repsectively, of *α-tert*-butyl-*α*-methyl-*o*-methoxybenzyl alcohol (**15**). These conformations correspond, respectively, to the torsinal angles indicated by 3a–3d in Figure 2. (e), (f) The stable intramolecularly hydrogen-bonded conformers of *α*-methyl-*o*-methoxybenzyl alcohol (**2**) and *α*,*α*-di-*tert*-butyl-*o*-methoxybenzyl alcohol (**11**), respectively

Table 4. Rotational barriers ($\Delta G^{\ddagger}$) and conformational free energy differences (ΔG) of congested α-substituted o-methoxybenzyl alcohols

							$\Delta G^{\ddagger}$ (kJ mol^{-1})[b]		ΔG (kJ mol^{-1})	
Compound	Solvent	Signal	T_c (K)	$\Delta\nu$ (Hz)	(Z):(E)	k (s^{-1}[a]	Values	Av.	Values	Av.
9	Acetone	$\mathrm{OC}H_3$	258·5	37·8	67:33	36·6	53·1		1·18	
		Pr^i-CH	262·7	118·8	65:35	126·1	53·6	53·3	1·04	1·11
9	Chloroform	$\mathrm{OCH_3}$	246·2	40·9	84:16	15·7	54·3		3·07	
		Pr^i-CH	252·6	105·2	82:18	46·8	53·5	54·9	2·81	2·94
15	Acetone	$\mathrm{OC}H_3$	263·4	42·9	53:47	76·9	54·7		0·22	
		$\mathrm{C}H_3$	268·3	64·3	55:45	105·3	55·1	54·9	0·31	0·27
15	Methanol	$\mathrm{OC}H_3$		254·9	40·5	54:46	69·5	53·1	0·30	
		$\mathrm{Bz\text{-}CH_3}$	256·2	54′1	56:44	87·4	52·8	53·0	0·45	0·38
18	Acetone	$\mathrm{OC}H_3$	299·3	40·5	56:44	67·4	62·8		0·45	
		$\mathrm{Et\text{-}C}H_3$	279·5	5·9	53:47	26·7	64·2	61·8	0·26	0·36
19	Acetone	$\mathrm{Bu}^t\mathrm{\text{-}C}H_3$			59:41				0·92	(0·92)
19	Methanol	$\mathrm{Bu}^t\mathrm{\text{-}C}H_3$	329·3	7·2	60:40	9·0	73·3		0·11	(0·11)
		$\mathrm{Pr}^t\mathrm{\text{-}C}H$			61:39					
19	DMSO	$\mathrm{OC}H_3$	337·5	32·1	77:23		74·7		2·99	
		$\mathrm{Pr}^i\mathrm{\text{-}C}H$	339·5	1·4	72:28		74·1	74·4	2·38	2·69
21	Acetone	$\mathrm{Bz\text{-}CH_3}$	258·5			77·4	53·7		0·37	(0·37)
22	Acetone	$\mathrm{Bz\text{-}CH_3}$	268·2	64·8	56:44	129·2	54·6		0·41	(0·41)

[a] Rates at T_c.
[b] Rotational barriers at T_c.

transition-state conformation (B) in which the OH group occupies the position nearly perpendicular to the aromatic ring. This conformation is more susceptible to form a hydrogen bond with the solvent than the ground-state conformer. As the transition state (B) is stabilized by the intermolecular hydrogen bond formation with the solvent, the interconversion between the conformers proceeds more rapidly. The solvent effect on ΔG is reflected in the populations of the conformers. When the ^{1}H spectrum was measured in chloroform, the equalibrium between the two conformers lay very far to conformer E, whch made it impossible to detect the signal of conformer F.

Table 5. Rotational barriers ($\Delta G^{\ddagger}$) and conformational free energy differences (ΔG) of **15** in acetone-d_6–chloroform-d mixed solvent of various compositions

Composition (mol% of $\mathrm{CD_3COCD_3}$)	$\Delta G^{\ddagger}$ (kJ mol^{-1})[a]	ΔG (kJ mol^{-1})
100	54·9	0·27
86·7	55·9	1·33
73·3	56·5	2·03
66·3	56·9	2·53
52·4	57·5	3·10
45·0	58·1	3·78
30·4	59·6	4·82
20·7	59·6	5·89
10·7	61·2	7·22
0	(61·4)[b]	(7·37)[b]

[a] Rotational barriers at T_c.
[b] Values estimated by extrapolation.

In conclusion, the discrepancy between the calculated and observed $\Delta G^{\ddagger}$ and ΔG values in hydrogen-accepting solvents such as acetone and methanol can be ascribed, for the most part, to the destruction of the hydrogen-bonded chelate structure by the solvents capable of participating in intermolecular hydrogen bonding.

CONCLUSION

The conformational preferences and the dynamic behaviors of α-substituted o-methoxybenzyl alcohols are governed both by the intramolecular OH · · ·OMe hydrogen bonding and by the steric hindrance caused by the α-substituents.

Their stable conformations in non-polar solvents can be predicted farly well by MM calculations. The OH/MeO *syn*-conformer is usually estimated to be far favorable than the OH/MeO *anti*-conformer. However, the conformations are significantly perturbed in polar solvents capable of forming hydrogen bonds. As a result, the second-most stable OH/MeO *anti*-conformer increases in polar solvents.

In the transition states, the molecule takes a conformation in which both α-alkyl groups come close to the plane of the aromatic ring. In this conformation, the hydroxyl group occupies a position nearly perpendicular to the aromatic plane and is susceptible to hydrogen bonding with solvents.

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