Conformational Analysis. A Nuclear Magnetic Resonance Study of the Conformations of *ortho*-Disubstituted Benzenes

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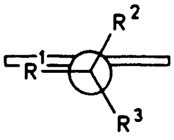
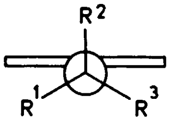
Results pertinent to the determination of the conformation of the side chain $R^1R^2R^3C$ attached to a benzene ring with or without an *ortho*-methyl substituent are reported and discussed. Results comprise dynamic n.m.r., carbon-13 chemical shift, and lanthanide-shift reagent data. When R^1 is particularly large, the preferred conformation is concluded to be close to R^1-perpendicular. In two cases two such conformations with either R^2 or R^3 *syn* to the *ortho*-substituent are observed.

WHILE much is known about the dynamics of rotation and conformational preferences about *sp*³–*sp*³ carbon-bonds,[1] there is relatively little information for *sp*³–*sp*² carbon bonds,[2] such as that joining a phenyl group to an alkyl chain. In contrast to the negligible barrier hindering rotation in toluene,[3] barriers in ααα-trisubstituted toluenes,[4,5] *i.e.* toluene with each of the methyl hydrogens replaced by a substituent, may be as high as 20 kcal mol^{-1}. Such barriers mean that in α-substituted toluenes, in contrast to toluene itself, there are some conformations that are much more stable than others, and the question of which are the unusually stable conformations is of particular interest.

There are two limiting conformations of a substituted toluene, one ***parallel*** with one of the three α-groups in the plane of the phenyl ring (1), and the other ***perpendicular*** (2) where one of the three α-groups is rotated 90° out of the plane of the ring. When the substituents are different, it is necessary to specify which group is parallel or perpendicular. It should be remembered that these two kinds of conformation may be very similar in terms of energies and interactions since rotation of only 30° in either sense converts a parallel to a perpendicular conformation, and *vice versa*. Further it may happen that the conformational energy minimum is not precisely one of these limiting forms, but is best described as the ' close-to-parallel ' or ' close-to-perpendicular ' conformation. This reservation should always be taken as implicit in our use of ' perpendicular ' and ' parallel '.



(1)



(2)

[1] (*a*) A recent general review is given by J. P. Lowe, *Progr. Phys. Org. Chem.*, 1968, **1**, 6; (*b*) For a review dealing with n.m.r. only see I. O. Sutherland, *Ann. Rep. NMR Spectroscopy*, 1971, **4**, 71; (*c*) J. E. Anderson and H. Pearson, *J. Amer. Chem. Soc.*, 1975, **97**, 764.

[2] See, however, G. J. Karabatsos and D. J. Fenoglio, *Topics Stereochem.*, 1971, **5**, 167.

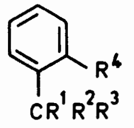
[3] C. A. Wulff, *J. Chem. Phys.*, 1963, **39**, 1227.

[4] G. P. Newsoroff and S. Sternhell, *Tetrahedron Letters*, 1967, 2539.

[5] R. E. Gall, D. Landman, G. P. Newsoroff, and S. Sternhell, *Austral. J. Chem.*, 1972, **25**, 109.

It appears that in ethyl- and isopropyl-benzene the preferred conformations are parallel[6,7] but in both cases substantial amounts of two different conformations coexist in solution. In ethylbenzene the methyl-parallel conformation is of slightly lower enthalpy than the hydrogen-parallel one.[6] In isopropylbenzene[6,7] the preferred conformation is the hydrogen-parallel one, but a second conformation, probably the methyl-parallel one, is of very similar enthalpy. These results certainly do not allow any generalisation about conformations.

There is no firm evidence for the occurrence of perpendicular conformations in simple cases although these do occur in some molecules where there are two *ortho*-substituents in the phenyl ring,[8] and might be expected for toluenes with one α-substituent much larger than any other. We have previously considered some molecules of this latter type[9] and have found little certain evidence to support a perpendicular conformation. However such conformations have been predicted by calculations of conformational energies,[10] so it would be rash to preclude the possibility of their occurrence.

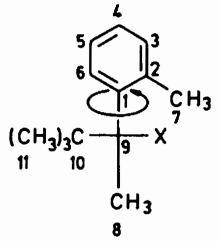


(3)

When there is a substituent *ortho* to the side chain, (3), the conformation will be modified and one of us has recently shown[11] that the preferred conformation in *o*-ethyltoluene has the methyl of the ethyl group turned away from the *ortho*-substituent. We now look at some more highly substituted examples of (3).

Dynamic N.m.r. Spectroscopy.—Our interest in this area arose from our recent observation,[9] that on the basis of its ^{1}H n.m.r. spectrum, 2-methoxy-3,3-dimethyl-2-(*o*-tolyl)butane (4) exists in two discrete conformations. Below room temperature rotation about the phenyl–carbon bond is slow on the n.m.r. timescale, so that the aromatic methyl, *O*-methyl, and *C*-methyl signals, all singlets at 30°, appear at −30° as unequal doublets of intensity ratio *ca.* 2.6 : 1. The more intense of the unequal doublet signals is upfield in the case of the *C*-methyl, and downfield for the other two. The aromatic region is complex, although different from the ambient temperature pattern, while the t-butyl resonance remains a singlet presumably because of accidentally isochronous signals in the two conformers.

The corresponding hydroxy-compound (5) and the parent hydrocarbon (6) have now been studied. Table 1 gives the ^{1}H n.m.r. data for these three compounds. The n.m.r. spectrum of (5) shows changes with temperature analogous to those for (4), the two conformations being in the proportion 3.3 : 1 in this case.



(4) X = OCH$_3$
(5) X = OH
(6) X = H

In contrast the n.m.r. spectrum of the hydrocarbon (6) on cooling exhibits no changes that may be ascribed to slow rotation about the phenyl–carbon bond. At extremely low temperatures (*ca.* −150°) the t-butyl signal undergoes changes due to the expected slow rotation about the C_α–C_β bond.[12] We prefer to conclude from this that one conformation of (6) is particularly favoured, rather than the alternative, that there is a particularly low barrier to rotation about the phenyl–carbon bond. It would be difficult to explain why the barrier in (6) should be lower than in (4) or (5), since the reverse effect is observed in analogues of these without an *ortho*-methyl substituent.[5] Further, since changing from methoxy to hydroxy [(4) to (5)] reduces the fractional population of the less stable isomer, this conclusion for (6) seems a reasonable extrapolation of observed behaviour.

TABLE 1

^{1}H Chemical shifts (δ) for compounds (4)—(6) at ambient and low temperature [a]

	Shift				
Signal	(4) *b*		(5) *b*		(6)
Bu^t	0.91		0.94		0.91
Me	1.60	(1.58) (1.64)	1.63	(1.62) (1.72)	1.20 [c]
o-Me	2.54	(2.63) (2.42)	2.56	(2.65) (2.49)	2.33
Aromatic	*ca.* 7.07		*ca.* 7.1		*ca.* 7.06
X	3.08	(3.11) (3.02)	1.53		2.94 [d]

[a] *ca.* 0.3M solutions, CDCl$_3$ solvent. [b] Values in parentheses are at −30° [compound (4)] or −57° [compound (5)], the upper value is for the major conformation. [c] Doublet (*J* 7.3 Hz). [d] Quartet (*J* 7.3 Hz).

Lanthanide Shift Reagent.—The n.m.r. spectrum of the hydroxy-compound (5) recorded at −57° shows separate signals for two conformations as described above. In the presence of trisheptafluorodimethyloctanedionatoeuropium [Eu(fod)$_3$] the relative amounts of isomers appear to be unaltered but all peaks in the aliphatic region move to lower field. The signal most displaced and most broadened by the shift reagent is that of the *ortho*-methyl group of the major isomer, which

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[9] J. E. Anderson and H. Pearson, *J.C.S. Perkin II*, 1974, 1779.

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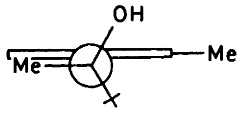
in a typical experiment has a linewidth of 20 Hz and a displacement of 0.53 p.p.m. when the same signal for the minor isomer has a linewidth of 7 Hz and a displacement of only 0.12 p.p.m. At the same time the peaks of the remaining aliphatic methyl group moved 0.28 and 0.26 p.p.m. for the major and minor isomers respectively. The t-butyl signal moved 0.32 p.p.m.

The broadening of the *ortho*-methyl signal is much greater in the major conformation than in the minor, suggesting that in the major conformation, the hydroxy-group is close to the *ortho*-methyl group. Insofar as the chemical shift displacement induced by the europium reagent depends principally on the distance from the metal atom to the nucleus considered, the particularly large shift induced in the *ortho*-methyl signal of the major conformation confirms this assignment. The evidence suggests then, that the major conformer is one like (7), (8), or (9), while the minor conformer must be like (10), (11), or (12).* Evidently and reasonably the molecule prefers to adopt a conformation with the smallest moiety attached to the sp^3 carbon *syn* to the *ortho*-substituent.

In the major conformer of the methoxy-compound (4) the OMe group presumably adopts a position corresponding to the OH position in (7)—(9) assuming that a methoxy-group is smaller than a methyl group; certainly the order of intensities of signals are the same for the two compounds. In the hydrocarbon (6) the one conformer present is then probably like (13), (14), or (15).



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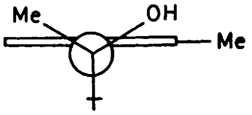

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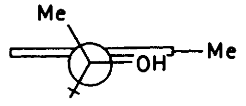

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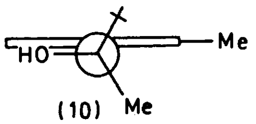

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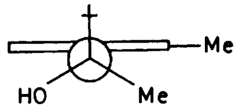

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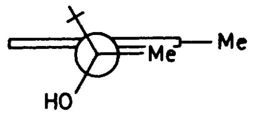

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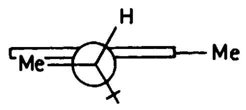

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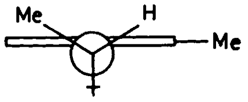

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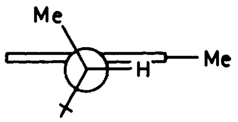
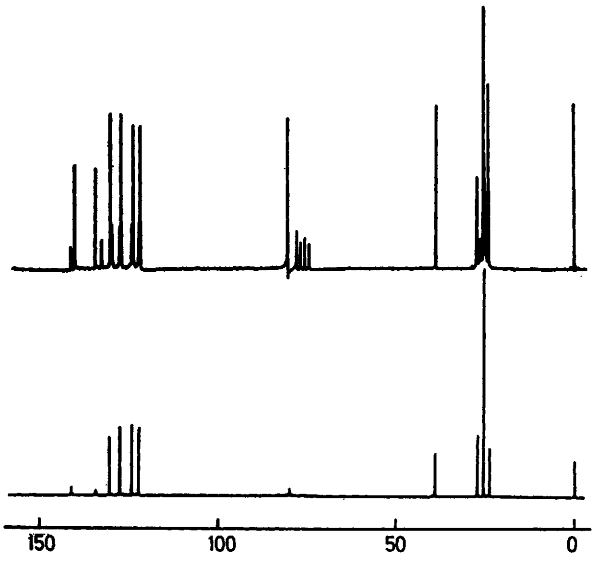


(15)

Carbon-13 *Data*.—The C-13 spectra of compounds (4)—(6) were determined at ambient and in the case of (4) and (5) low temperatures. Compound (6) was not examined at low temperatures since the ^1H n.m.r. spectrum down to −150° indicated that there are no significant changes. Spectra for the alcohol (5) are shown in the Figure and spectral data are in Table 2.



^{13}C N.m.r. spectra of compound (5) at ambient temperature (lower) and at *ca.* −55° (upper)

TABLE 2

^{13}C Chemical shifts [a] for compounds (4)—(6)

	Shift				
	(4)		(5)		(6)
Signal	Ambient	Low [b]	Ambient	Low [c]	Ambient
C-1	140.4	140.3 139.2	143.2	142.7 143.9	143.9
C-2	137.3	137.3 136.9	136.5	136.8 135.1	136.0
C-3	132.5	132.2 132.2	132.6	132.5 132.0	130.0
C-4	126.4	126.1 126.4	126.3	126.0 126.5	125.2
C-5	124.4	124.3 124.3	124.2	124.1 124.5	125.2
C-6	131.1	131.1 130.7	129.6	129.5 129.9	127.4
C-7	23.0	22.2 24.5	24.4	24.5 24.7	20.8
C-8	22.0	22.2 21.7	27.8	27.8 26.8	16.7
C-9	86.1	86.4 83.8	81.3	81.9 79.3	42.9
C-10	40.5	40.1 40.5	39.8	39.4 39.5	34.8
C-11	26.3	26.4 25.7	26.0	25.9 25.6	27.8
OMe	50.5	50.7 50.2			

[a] In p.p.m. from internal tetramethylsilane in $CDCl_3$ solution at ambient temperature of *ca.* 35°. Diagram (4) shows numbering of peaks. [b] *ca.* −30°, the upper value is the major isomer. [c] *ca.* −55°, the upper value is the major isomer.

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* For molecules of compounds (4)—(6) with absolute configuration the reverse of that displayed in diagrams (7)—(12), the preferred conformation will be the mirror image of the one shown.

Low temperature spectra of (4) and (5) show the presence of two conformations for each molecule, separate signals almost always being observed for corresponding atoms in different molecules. It is interesting that in both compounds it is the quaternary α-carbon whose signals are most different at low temperature: it is not clear why this should be so.

A significant feature of the data is the chemical shift of the *ortho*-methyl group. In the parent hydrocarbon this shift is 20.8 p.p.m. Substitution of a hydrogen atom, which is δ to the methyl in question, by a methoxy- or hydroxy-group causes downfield shifts of 2.2 and 3.6 p.p.m. respectively. Although δ effects are usually negligible, it is now clear that when the groups in question are close to each other in space then a significant downfield shift ensues,[11,13-16] so the hydrocarbon (6) must exist in a conformation with the hydrogen atom syn to the *ortho*-methyl group, that is one of, or a mixture of (13)—(15). Introduction of a further substituent inevitably leads to steric interaction with the *ortho*-methyl group that manifests itself as a substantial downfield shift.

It is clear then that in accord with the findings in the europium shift reagent experiment the carbon-13 chemical shift data support the view that the molecule prefers to adopt a conformation with the smallest substituent close to the *ortho*-methyl group.

Conclusions.—From these observations we conclude that the most stable conformation of (4)—(6) is one like (7)—(9) where X is near the *ortho*-methyl group. Conformation (7) is least likely since there is a strong interaction of the t-butyl group with the *ortho*-methyl substituent; conformation (9) has a similar but lesser interaction with the other *ortho*-position. The most likely stable conformation is close to (8), any deviation being in the direction of (9).

For similar reasons, the minor conformation for (4) and (5) is likely to be close to (11), any deviation being towards (12).

In an earlier paper [9] we presented evidence interpreted as tending to favour parallel conformations in other compounds similar to (4)—(6). Considering these results, present results, and the literature on simpler molecules, we conclude that while for molecules with small substituents in the side chain, close-to-parallel conformations are preferred, when there is one large substituent, a conformation with that substituent close-to-perpendicular is more likely.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Varian HA100 spectrometer as described previously.[17] C-13 Spectra were obtained on a Varian XL100 spectrometer operating at 25.2 MHz. In (4) differentiation between the peaks at δ 22.0 and 23.0 p.p.m. was made on the basis that the latter peak is broad and weak at ambient temperature (34°) but sharpened at *ca.* 50°. This is due to a large frequency separation of the interconverting conformers. In the ^{1}H spectrum the frequency separation between signals for the separate conformers is significantly greater (see Table 2) for the methyl attached to the aromatic ring. It is reasonable then to assign the peak at δ 23.0 p.p.m. to the aromatic methyl group; the peak at δ 22.0 p.p.m. is, by elimination, the methyl at the α-position. This assignment was confirmed by single frequency on-resonance decoupling; irradiation, at low power, at the aromatic methyl hydrogen frequency collapsed the peak at δ 23.0 p.p.m. to a singlet (this experiment was carried out at *ca.* 55°). The signal for the quaternary carbon bearing the methoxy-group also appears as a weak broad hump similar to that shown at δ 81.3 p.p.m. for (5) (in fact this peak appears to be at 'coalescence') at ambient temperature but sharpens considerably at *ca.* 50°.

3,3-Dimethyl-2-(*o*-tolyl)butan-2-ol (2) was prepared as described previously [9] (Found: C, 80.6; H, 10.5. Calc. for $C_{13}H_{20}O$: C, 81.25; H, 10.4%). 3,3-*Dimethyl*-2-(o-*tolyl*)-*butane*, (6), was prepared by catalytic hydrogenation of 3,3-dimethyl-2-(*o*-tolyl)but-1-ene and had b.p. 243° (Found: C, 88.3; H, 10.8. $C_{13}H_{20}$ requires C, 88.65; H, 11.35%). The preparation and characterisation of (4) has been described previously.[9]

At −30° the conformational equilibrium constant for (4) is *ca.* 2.6 which corresponds to a free energy difference of *ca.* 460 cal mol^{-1} between conformations. Similarly for (5) at −57° the equilibrium constant is *ca.* 3.3 and the free energy difference of *ca.* 510 cal mol^{-1}. From the coalescence of the *ortho*-methyl signals in the ^{1}H spectra of (4) and (5) at −34 and +5.5 °C respectively it can be calculated that the barrier to rotation about the phenyl α-carbon bond is 12.2 and 14.2 kcal mol^{-1} at the coalescence temperature respectively.

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