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SUBSTITUENT EFFECTS ON THE MAGNETIC NONEQUIVALENCE IN THE PMR SIGNALS OF ISOPROPYL Me PROTONS OF 2-ARYL-3-METHYL-2-BUTANOLS

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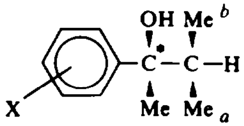
Abstract—The influence of substituents in the aromatic nucleus of 2-aryl-3-methyl-2-butanols (**1**) on the magnetic nonequivalence of the isopropyl Me protons was investigated. Quantitative correlations were obtained with the aid of the Hammett-Yukawa and Taft equations. The origin of the phenomena is discussed in terms of preferred conformations of **1** and the diamagnetic anisotropy of the aromatic nucleus.

INTRODUCTION

IN 2-aryl-3-methyl-2-butanols (general formula **1**) the isopropyl Me groups are diastereotopic by internal comparison due to the chiral centre at C-2. Variation of the nature and position of the substituent X at the aromatic nucleus may result, *in principle*, in a variation of anisochronism of the isopropyl Me protons.



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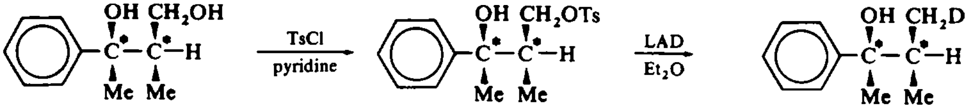
Although magnetic nonequivalence of diastereotopic atoms or groups has received growing attention in recent years,[1] we are not aware of any systematic study of the effect as a function of the electronic nature of one of the groups attached to the chiral center.

In this paper we communicate the results of such a study by variation of X in **1**; the anisochronism of the isopropyl Me protons is found to be a satisfactory function of the Hammett-Yukawa or Taft substituent constants. Considerations with respect to both the preferential conformations of compounds **1** and the diamagnetic anisotropy of the aromatic nucleus are presented in order to elucidate the origin of the anisochronism.

RESULTS AND DISCUSSION

The PMR spectrum of **1**, X = H shows two doublets ($J = 6{\cdot}8$ Hz) at $\delta = 0{\cdot}76$ and 0·86 ppm (CCl_4, relative to TMS) corresponding with the isopropyl Me^b and Me^a protons, respectively. This assignment was based on comparison with the PMR data of *threo*-4-deutero-3-methyl-2-phenyl-2-butanol (4), which was prepared from *threo*-2-methyl-3-phenyl-1,3-butanediol[2] (2) according to



2 **3** **4**

The PMR spectrum of 4 (CCl_4) shows a doublet ($J = 6·8$ Hz) at 0·84 ppm and a doublet ($J = 7·0$ Hz) of a triplet ($J = 1·9$ Hz) at 0·73 ppm corresponding with the isopropyl CH_3 and CH_2D protons, respectively.

The results for a number of substituted **1** have been arranged in Table 1 on the assumption of no change in the order of the Me^a and Me^b PMR signals.

TABLE 1. PMR DATA OF THE ISOPROPYL Me PROTONS OF 2-ARYL-3-METHYL-2-BUTANOLS (1)[a]

Substituent	ν_a	ν_b	ν_a–ν_b
H	51·8	45·6	6·2
m-Me	51·8	45·4	6·4
p-Me	49·7	44·5	5·2
p-Et	50·6	45·7	4·9
p-isoPr	50·8	45·7	5·1
p-*tert*-Bu	52·9	47·3	5·6
m-F	52·8	45·7	7·1
p-F	51·8	46·2	5·6
m-Cl	52·8	45·7	7·1
p-Cl	51·8	45·3	6·5
m-Br	53·3	45·6	7·7
p-Br	52·9	45·8	7·1
m-OMe	51·4	45·0	6·4
p-OMe	48·3	45·8	2·5
m-NMe_2	51·7	45·9	5·8
p-NMe_2	47·5	47·5	0·0
m-CF_3	54·0	45·3	8·7
m-NMe_3^+ I^-	52·1[b,e]	40·7[b,e]	(10)[c,e]
p-(N)[d]	55·1	45·3	9·8
p-(N)H^+ CF_3COO^-	58·2[b,e]	41·2[b,e]	(15)[c,e]

[a] 60 MHz; 10% (wt/vol) in CCl_4; chemical shifts in Hz relative to TMS

[b] 10% (wt/vol) in DMSO-d_6

[c] Estimated value from the relation $(\nu_a - \nu_b)_{DMSO} = 1·1\ (\nu_a - \nu_b)_{CCl_4}$, based on H, *m*-Br, and *m*-CF_3

[d] 2-(4-pyridyl)-3-methyl-2-butanol

[e] Not included in the quantitative correlations

The data show that the difference in chemical shift of the isopropyl Me protons, $\nu_a - \nu_b$, is influenced by the substituents. It appears that electron-donation by the substituents causes a decrease, and electron-withdrawal an increase in the magnitude of $\nu_a - \nu_b$. Although the same picture holds for ν_a, the variations in ν_b are rather small and irregular. Quantitative correlation of the data of Table 1 by the Yukawa extension[3] of the Hammett equation[4] gives

$$\begin{aligned} \nu_a - \nu_b &= 3{\cdot}64\,\sigma^n + 3{\cdot}78\,\Delta\bar{\sigma}_R^+ + 6{\cdot}21 \quad (r = 0{\cdot}985) \\ \nu_a &= 3{\cdot}28\,\sigma^n + 2{\cdot}71\,\Delta\bar{\sigma}_R^+ + 51{\cdot}81 \quad (r = 0{\cdot}921) \\ \nu_b &= -\,0{\cdot}36\,\sigma^n - 1{\cdot}06\,\Delta\bar{\sigma}_R^+ + 45{\cdot}60 \quad (r = 0{\cdot}594) \end{aligned}$$

in which σ^n is the substituent constant,[3, 5] $\Delta\bar{\sigma}_R^+$ the resonance parameter for *para* + M substituents,[3] and r the correlation coefficient. The first constants in each of these relations agree well with the rho values of the Hammett equation leaving out the *para* + M substituents,[5] *viz.* 3·76, 3·58, and −0·18, respectively. Obviously, the $\Delta\bar{\sigma}_R^+$ parameter is very useful for the quantitative correlation of the PMR data, despite the fact that no mesomeric *para* interaction occurs.

For comparison, the data for H, Me, F, Cl, Br, CF_3, OMe and NMe_2 are further correlated by the Taft equation,[6] yielding for the *para* substituents

$$\begin{aligned} \nu_a - \nu_b &= 6{\cdot}14\,\sigma_I + 12{\cdot}85\,\sigma_R^0 + 6{\cdot}42 \quad (r = 0{\cdot}994) \\ \nu_a &= 5{\cdot}87\,\sigma_I + 9{\cdot}00\,\sigma_R^0 + 51{\cdot}35 \quad (r = 0{\cdot}957) \\ \nu_b &= -\,0{\cdot}27\,\sigma_I - 3{\cdot}85\,\sigma_R^0 + 44{\cdot}93 \quad (r = 0{\cdot}764) \end{aligned}$$

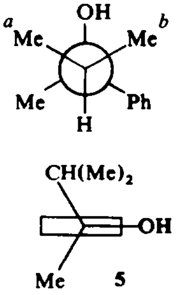
and, for the *meta* substituents

$$\begin{aligned} \nu_a - \nu_b &= 2{\cdot}86\,\sigma_I + 2{\cdot}59\,\sigma_R^0 + 6{\cdot}69 \quad (r = 0{\cdot}931) \\ \nu_a &= 2{\cdot}87\,\sigma_I + 2{\cdot}28\,\sigma_R^0 + 52{\cdot}15 \quad (r = 0{\cdot}907) \\ \nu_b &= 0{\cdot}01\,\sigma_I - 0{\cdot}31\,\sigma_R^0 + 45{\cdot}46 \quad (r = 0{\cdot}242) \end{aligned}$$

Here, σ_I and σ_R^0 are the inductive and resonance substituent parameters,[7] respectively.

The results show that the substituent effect on the anisochronism of the isopropyl Me protons is almost solely caused by variation in chemical shift of the Me^a protons. If the electronic effects were transmitted exclusively through the σ-bonds they should be equally felt at the isopropyl Me^a and Me^b protons. Therefore, we may conclude that field effects are responsible for the variations in proton chemical shifts, in accordance with the recent observations of Hamer and Reynolds.[8]

In order to interpret these phenomena we consider the possible conformations of **1**. Since the substituents at the aromatic nucleus will not interfere sterically with the other groups of the molecule, it will suffice to discuss the preferred conformations for **1**, X = H. In principle, there are three important conformations, *viz.* **5**, **6** and **7**:



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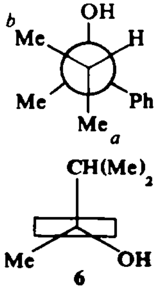

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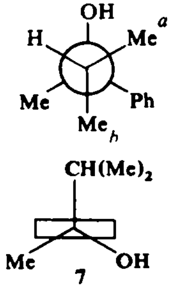

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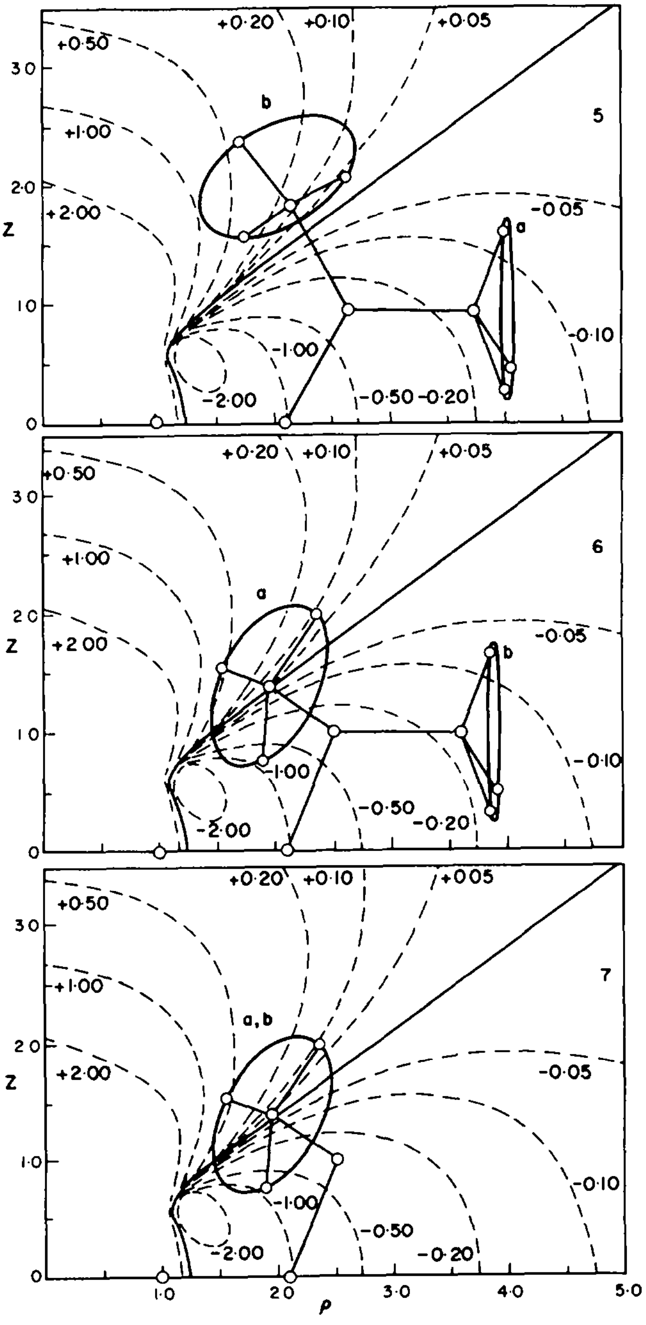

Fig 1. Positions of the isopropyl Me protons of **1**, X = H as function of the shielding zones about the benzene nucleus for the conformations **5**, **6** and **7**, respectively; z and ρ are expressed in ring radii (1·39 Å) and σ_s in ppm, according to Johnson and Bovey.[11]

The preferred conformations of the benzene ring were determined according to the method of Baas.[9] Using the *skew*-butane van der Waals repulsion energies (kcal/mole) OH,Me = 0·4, Me,Me = 0·9, Ph,Me = 1·3, Ph,H = 0·0, and Me, H = 0·0,[10] the equilibrium composition of these conformers at 37° will be approximately 60, 26, and 14% for **5**, **6** and **7**, respectively. The positions of the isopropyl Me protons in these preferred conformations are illustrated in Fig 1, in addition to the isoshielding lines of the benzene nucleus according to Johnson and Bovey.[11] Beforehand, we assume that effects other than those arising from the magnetic anisotropy of the benzene nucleus are negligible. In conformation **7** the isopropyl Me groups are situated symmetrically with respect to the benzene nucleus, so that **7** will not give an important contribution to the variation in nonequivalence. On the other hand, the Me^a and Me^b groups are quite differently situated in **5** and **6**. Since these groups have approximately interchanged position in **5** and **6** with respect to the benzene nucleus, we may consider just conformation **5** for the interpretation of the results, taking into account that the magnitudes of shielding derived from this model have to be reduced to about one third. Using this model we obtain $\nu_a > \nu_b$, in accordance with the experimental result from the PMR spectrum of **4**, while the estimated value for $\nu_a - \nu_b = \frac{1}{3}$ (0·3 ± 0·1) ppm agrees well with the value of 0·1 ppm found for **1**, X = H.

At first sight, the much stronger substituent effect on ν_a than on ν_b seems to be in contradiction with the longer distance (~1 Å) between the Me^a protons and the benzene nucleus. Therefore, instead of direct field effects of the substituents, we have to describe substituent effects in terms of alteration of the shielding and deshielding zones about the benzene ring. Whereas the average position of the Me^b protons is very close to the nodal plane of these zones, *i.e.* will be only slightly influenced, the Me^a protons are very definitely situated in the deshielding zone. Furthermore, the opposite substituent effects on ν_a and ν_b are easily understood, because the Me^a and Me^b protons lie in different zones, *viz.* the deshielding and shielding zones, respectively. In this respect, the substituent effects on the Me^a protons, for instance, may be interpreted as a change of shielding in the region $\rho = 4$, $z = 1 \pm 0{\cdot}5$, which may be expressed quantitatively by

$$(\sigma_g)_X - (\sigma_g)_H = -0{\cdot}55\,\sigma^n - 0{\cdot}45\,\Delta\bar{\sigma}_R^+$$

with σ_g denoting the shielding factor in ppm. This relation is equivalent to the Hammett–Yukawa relation for ν_a.

In conclusion, we may state that the phenomenon of magnetic nonequivalence of the isopropyl Me protons in **1** and the influence of the substituents on this phenomenon is completely understood by the occurrence of the preferred conformations **5**, **6** and **7**, and the large diamagnetic anisotropy of the aromatic nucleus. Therefore, the difference in chemical shift of the isopropyl Me protons originates only to a slight extent in the asymmetric center as such.

EXPERIMENTAL

The PMR spectra were measured on a Varian T-60 or XL-100-15 spectrometer at about 37° with CCl_4 as the solvent (10% wt/vol) unless otherwise stated.

The preparation of a number of 2-aryl-3-methyl-2-butanols (**1**) has been described recently.[12] In the same way 2-(4-*pyridyl*)-3-*methyl*-2-*butanol*, b.p. 100°/0·9 mm, n_D^{25} 1·5214, and 2-(m-*fluorophenyl*)-3-*methyl*-2-*butanol*, b.p. 116°/17 mm, n_D^{25} 1·4965 were obtained.

Threo-4-*deutero*-3-*methyl*-2-*phenyl*-2-*butanol* (**4**). TsCl (1·90 g, 10·0 mmole) in pyridine (6 ml) was added dropwise with stirring to a soln of *threo*-2-methyl-3-phenyl-1,3-butanediol[2] (**2**, 1·70 g, 9·5 mmole) in pyridine (6 ml) at 0°. The resulting mixture was stored for 16 hr at 0°, acidified with HCl aq and extracted with ether (100 ml). The dried ($MgSO_4$) extract was evaporated to yield 2·88 g (91%) of a colourless oil (**6**). A soln of **6** in dry ether (60 ml) was added to a stirred suspension of LAD (1·0 g, 24 mmole) in dry ether (40 ml) under reflux. The mixture was heated for an additional 8 hr, hydrolyzed with NaOH aq (25%, 30 ml) and extracted with ether (60 ml). The dried ($MgSO_4$) extract was evaporated and the residue distilled *in vacuo*; yield of **4** 0·54 g (43%), b.p. 111–113°/15 mm, n_D^{25} 1·5139, containing 1·00 d (MS).

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