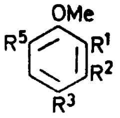
Shielding Effects of the Diphenylmethanol Substituent in Certain Anisole Derivatives: a Method for Determination of the Site of Metallation

By D. W. SLOCUM* and C. A. JENNINGS

(*Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, Illinois* 62901)

Summary A potentially valuable tool for isomer identification of lithio-aromatics consists of condensation of the lithio-intermediate with benzophenone and examination of the effect on the chemical shift of various alkyl substituent protons in the molecule: alkyl protons adjacent to the diphenylmethanol substituent invariably experience a significant upfield shift.

THE fact that aromatic molecules possess high diamagnetic susceptibilities has been demonstrated by a number of studies[1] which indicate the central region above and below the plane of the aromatic ring is strongly shielded. Although most treatments of anisotropic shielding by aromatic nuclei have involved fairly rigid molecular structures,[2] shielding effects might be expected to contribute even in non-rigid systems. For example, the diphenylmethanol substituent, although freely rotating in the derivatives studied, might be expected to shield protons situated near the aromatic nuclei. That this was the case was demonstrated by ^{1}H n.m.r. spectra of compounds (1a, b, and 2—8), and others where it was found that the position of the diphenylmethanol substituent could be predicted on the



(1)—(8)

basis of differences between the chemical shifts of protons in the parent anisole derivative and those of the anisole derivative containing the diphenylmethanol substituent. For example, the difference in chemical shift of the methylene protons in *o*-diphenylhydroxymethyl-*p*-methoxy-*NN*-dimethylbenzylamine (1a) and *p*-methoxy-*NN*-dimethylbenzylamine (1) was +24·5 Hz. The difference in chemical shift of the methoxy-resonances of these two compounds was only +8·5 Hz. Isomer (1b), however, had chemical-shift differences for the methylene and methoxy-resonance in comparison to (1) of +7·5 Hz and +14·0 Hz, respectively. Other data are listed in the Table; it is evident that larger upfield shifts occur for the protons on substituents located *ortho* to the diphenylmethanol substituent in every case.

Chemical-shift differences (Hz) *of various protons of substituted anisoles after introduction of diphenylmethanol substituent*[a,b]

Compound	R^1	R^2	R^3	R^5	CH$_2$	OMe	NMe$_2$	NMe
(1a)	H	CPh$_2$OH	CH$_2$NMe$_2$	H	+*24·5*	+ 8·5	+ 7·0	—
(1b)	CPh$_2$OH	H	CH$_2$NMe$_2$	H	+ 7·5	+*14·0*	+ 6·0	—
(2)	CPh$_2$OH	H	H	CH$_2$NMe$_2$	+ 1·0	+*39·0*	+ 0·5	—
(3)	CPh$_2$OH	H	(CH$_2$)$_2$NMe$_2$	H	—	+*14·0*	+ 8·5	—
(4)	CPh$_2$OH	H	NMe$_2$	H	—	+*11·5*	+10·5	—
(5)	CPh$_2$OH	NMe$_2$	H	H	—	+*28·5*	+22·0	—
(6)	CPh$_2$OH	H	H	NMe$_2$	—	+*34·0*	+13·5	—
(7)	H	CPh$_2$OH	CONHMe	H	—	+ 8·0	—	+*29·5*
(8)	H	CPh$_2$OH	SO$_2$NHMe	H	—	+12·0	—	+*25·0*

[a] Italicised chemical shifts are those of methylene or methyl protons adjacent to the diphenylmethanol substituent. The sign of the chemical shift indicates the direction of variation of chemical shift (+, upfield) after introduction of diphenylmethanol substituent. In each case the assignment has been verified by an alternative technique.

[b] All n.m.r. spectra were recorded on a Varian A-56/60 Spectrometer operating at 60 MHz using Me$_4$Si as an internal standard and CDCl$_3$ as solvent.

Some effects appear noteworthy. An upfield shift is extremely pronounced for 1,2,3-trisubstituted benzenes where the diphenylmethanol substituent is at the 1-position. This may be attributed to a buttressing effect (probably conformational) forcing the methyl protons to spend more time on the average in the shielding region of the benzene rings [*cf.* compounds (2) and (6)]. It is interesting to note that for compounds (1a), (2), (5), (6), (7), and (8), *ortho*-shifts of from 22 to 39 Hz are observed. The remaining compounds, (1b), (3), and (4) experience much lower *ortho*-shifts. This may be attributed to hydrogen bonding of the diphenylhydroxymethyl hydrogen to the methoxy-oxygen in the latter group of compounds. This would amount to conformational restriction of the methyl away from the shielding effect of the phenyl groups with a consequent lessening of the observed shift.

Admittedly, other effects must be considered in order to make a quantitative assessment of the anisotropic shielding of the benzene nucleus in such non-rigid systems Factors to be considered include steric effects, inductive effects, and conformational preferences. However, from the cases studied it appears that a valuable tool for isomer identification of lithio-aromatics may consist of reaction of the lithio-intermediate with benzophenone and examination of the change in chemical shift of various protons in the product.

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[1] L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd edn. Pergamon, New York, 1969, ch. 2, and refs. cited therein.

[2] For a relevant example, *cf.* F. J. Petracek, N. Sugisaka, M. W. Klohs, R. G. Parker, J. Bordner, and J. D. Roberts, *Tetrahedron Letters*, 1970, 707.