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AN ANALYSIS OF THE CHEMICAL SHIFT POSITIONS OF THE AROMATIC PROTONS OF PHENOLIC COMPOUNDS AS A GUIDE TO ORIENTATION

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Abstract—The chemical shift positions of the aromatic protons of some 450 phenolic compounds have been examined and the results were analysed in terms of additive substituent shielding values. The accuracy to which the resulting values can be used to predict the chemical shift positions, and hence the orientation, of unknown polysubstituted phenols has been examined statistically.

During the course of investigations within this department into the modes of biosynthesis of phenolic compounds a large number of phenols and their derivatives have been handled, from both natural and synthetic sources. PMR spectroscopy has proved invaluable during these studies as a guide to structural determination. However, one of the major problems associated with the determination of structure has been the definition of the orientation of the various substituents around the aromatic ring. It was considered that PMR spectroscopy should be able to furnish some information of value for the definition of the orientation of these substituents. The chemical shift positions of the aromatic protons, in particular, should carry information about the orientation of substituents in the ring system.

Over the past few years a great deal of effort has been expended in searching for an adequate theoretical understanding of the effects of substituents upon the chemical shift positions of the aromatic protons; as illustrated in a recent review.[1] It has been established[2–4] that the chemical shift positions of the aromatic protons in mono- and di-substituted benzene derivatives bear some relationship to the electron density of the ring position to which the hydrogen atom is attached and that the chemical shift position is concentration[3] and solvent dependent.[5] Carbon 13 magnetic resonance has been used[6–8] to establish that the substituent effects in simple mono- and di-substituted compounds were substantially additive. Several workers[2,3,9–11] have

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[1] J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution NMR Spectroscopy* Vol. 2, p. 749. Pergamon Press (1966)

[2] P. L. Corio and B. P. Dailey, *J. Am. Chem. Soc.* **78**, 3043, (1956).

[3] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.* **35**, 731 (1961).

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[9] A. A. Bothner-By and R. E. Glick, *J. Am. Chem. Soc.* **78**, 1071 (1956).

[10] R. W. Taft, S. Ehrenson, I. C. Lewis and R. E. Glick, *J. Am. Chem. Soc.* **81**, 5352 (1959).

[11] M. Charton-Koechlin and M. A. Leroy, *J. Chim. Phys.* **56**, 850 (1959).

attempted to relate substituent shielding effects in mono- and di-substituted compounds to the Hammett σ constants for substituents but these efforts have met with mixed success.

Diehl[12] was able to establish that in dilute solution in cyclohexane it was possible to determine experimental values for the substituent shielding effects (S *ortho*, S *meta* and S *para*), using the assumption that the substitutent shielding effects were substantially additive in disubstituted compounds. Reasonable agreement was achieved when calculated chemical shifts were compared with experimental data. This technique was extended by Smith[13] who obtained *ortho* and *meta* substituent shielding values from a more extensive examination of *para*-disubstituted compounds.

Three other Tables of substituent shielding values have appeared[14–16] but little information is available as to the types of compounds investigated, the number of examples used or the solvents and concentrations used. In our hands these Tables have had only limited success in the prediction of orientation and it was decided to investigate the PMR parameters of the large number of spectra which we had at our disposal and those reported in the recent literature, in order to determine whether it was possible to obtain a more useful set of substituent shielding values.

Substituent shielding values are presumably the net result of contributions from resonance, inductive, steric and magnetic anisotropic effects and the theoretical prediction of these values is clearly not possible at present. However, figures can

TABLE 1 SUBSTITUENT SHIELDING VALUES MEASURED IN PPM FROM BENZENE*

Substituent	S *ortho* ppm	S *meta* ppm	S *para* ppm
—OH	0·45 (78)	0·10 (69)	0·40 (45)
—OAlkyl	0·45 (449)	0·10 (340)	0·40 (184)
—OCOR	0·20 (60)	-0·10 (52)	0·20 (41)
$—NH_2$	0·55 (3)	0·15 (4)	0·55 (1)
$—CH_3$	0·15 (80)	0·10 (36)	0·10 (14)
$—CH_2—$	0·10 (80)	0·10 (104)	0·10 (43)
—CH<	0·00 (45)	0·00 (69)	0·00 (15)
—CH=CH—R	—0·10 (80)	0·00 (86)	—0·10 (30)
—CHO	-0·65 (16)	-0·25 (11)	-0·10 (1)
—COR	0.70 (54)	0·25 (129)	0.10 (10)
—COOH(R)	0.80 (6)	- 0.25 (7)	- 0.20 (2)
—Cl	0.10 (16)	0.00 (44)	0.00 (2)
—Br	0.10 (6)	0.00 (5)	0.00 (2)
$—NO_2$	—0.85 (6)	—0.10 (4)	-0.55 (1)

* 10% solution of benzene in $CDCl_3$ absorbs at 2·70 τ. A negative sign indicates a shift to lower field and the figures in brackets indicate the number of examples used to arrive at each value.

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[12] P. Diehl, *Helv. Chim. Acta* 44, 829 (1961).

[13] G. W. Smith, *J. Mol. Spect.* 12, 146 (1964); and Ref. 1., p. 1140.

[14] D. W. Mathieson, *Interpretation of Organic Spectra* p. 58. Academic Press, New York (1965).

[15] W. S. Brey and K. D. Lawson, Ref. 1., p. 1140.

[16] G. V. D. Tiers, Ref. 1., p. 1140.

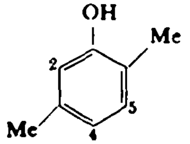
easily be determined experimentally and if a large enough number of examples are examined the significance of the figures can be analysed statistically.

Most of the PMR spectra of phenolic compounds which were available to us were examined in $CDCl_3$ or CCl_4 in 5–10% w/v solutions, and it seemed most relevant to us to examine data for these conditions only. The solvent effects of $CDCl_3$ and CCl_4 have been shown to be very similar[17] and hence data from these two solvents is substantially interchangable. The dilute solutions used for this investigation should minimize intermolecular effects upon the chemical shift positions.

The PMR spectra of 450 phenolic compounds and their derivatives were examined and the chemical shift data of the aromatic protons were tabulated. It was considered that an accuracy of ±0·05 ppm. was consistent with the aims of the project. The chemical shift values were then analysed in terms of additive substituent shielding values S *ortho*, S *meta* and S *para*. The substituent shielding values of Mathieson[14] were used as a first approximation and the data were examined by the method of successive approximations in order to refine the substituent shielding constants to find the best fit with the data available. The values obtained for the substituent shielding constants are tabulated in Table 1.

The data in Table 1 can conveniently be used to calculate the τ values of polysubstituted aromatic compounds by using the assumption that the contributions from each of the substituent shielding values are additive. The following two examples illustrate the method used:

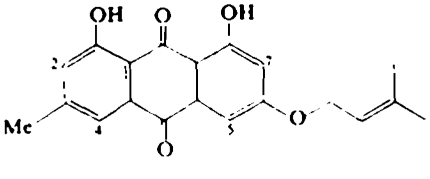
Example A[18]



OH $6CH_3$ $3CH_3$

Calc. τ for 5H = 2·70 + 0·10 + 0·15 + 0·10 = 3·05 Found τ = 3·00
Calc. τ for 4H = 2·70 + 0·40 + 0·10 + 0·15 = 3·35 Found τ = 3·30
Calc. τ for 2H = 2·70 + 0·45 + 0·10 + 0·15 = 3·40 Found τ = 3·40

Example B[19]



OH CH_3 9CO 10CO

Calc. τ for 2H = 2·70 + 0·45 + 0·15 − 0·25 − 0·10 = 2·95 Found τ = 3·00
Calc. τ for 4H = 2·70 + 0·40 + 0·15 − 0·25 − 0·70 = 2·30 Found τ = 2·50

OH OR 9CO 10CO

Calc. τ for 7H = 2·70 + 0·45 + 0·45 − 0·25 − 0·10 = 3·25 Found τ = 3·40
Calc. τ for 5H = 2·70 + 0·40 + 0·45 − 0·25 − 0·70 = 2·60 Found τ = 2·70

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[17] L. M. Jackman, *Applications of N.M.R. Spectroscopy in Organic Chemistry* p. 48. Pergamon Press, London (1962).

[18] R. J. Highet and P. F. Highet, *J. Org. Chem.* 30, 903 (1965).

[19] E. Ritchie and W. C. Taylor, *Tetrahedron Letters* 1431 (1964).

Table 2. Non fused phenolic ring systems

Phenolic Substitution Type	Mono-hydric	Catechol	Resorcinol	Hydro-quinone	Pyrogallol	Hydroxy-hydro Q	Phloro-glucinol	Totals
No of τ values examined	115	76	26	6	11	7	13	254
No. of τ values calc. within ±0·1 ppm	75 (65%)	55 (72%)	10 (38%)	6 (100%)	5 (45%)	3 (43%)	5 (38%)	159 (62%)
No. of τ values calc. within ±0·2 ppm	102 (89%)	70 (92%)	13 (50%)	6 (100%)	8 (72%)	6 (85%)	10 (77%)	215 (84%)
No. of τ values calc. within ±0·3 ppm	108 (94%)	74 (97%)	19 (73%)	6 (100%)	10 (91%)	7 (100%)	11 (85%)	235 (92%)

Table 3. Complex fused phenolic ring systems

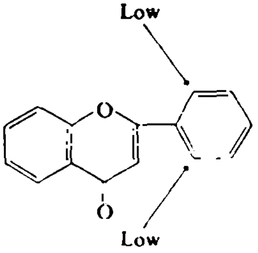
Phenolic Substitution Type	Mono-hydric	Catechol	Resorcinol	Hydro-quinone	Pyrogallol	Hydroxy-hydro Q	Phloro-glucinol	Totals
No. of τ values examined	50	47	118	3	43	38	86	385
No. of τ values calc. within ±0·1 ppm	25 (50%)	18 (38%)	58 (49%)	1 (33%)	3 (7%)	17 (44%)	27 (31%)	149 (39%)
No. of τ values calc. within ±0·2 ppm	38 (76%)	38 (81%)	83 (70%)	1 (33%)	20 (46%)	24 (63%)	67 (78%)	271 (70%)
No. of τ values calc. within ±0·3 ppm	44 (88%)	43 (91%)	101 (85%)	3 (100%)	32 (74%)	30 (79%)	81 (94%)	334 (89%)

The probability of success in using the substituent shielding constants in Table 1 to determine the chemical shift positions of aromatic protons was examined statistically. The 450 phenolic compounds were subdivided into two main classes; (a) non fused benzenoid systems and (b) fused ring systems containing the benzene ring but not inclusive of polynuclear aromatic systems. The compounds within each group were examined in relation to their phenolic substitution patterns and the rate of success tabulated in Table 2 and Table 3.

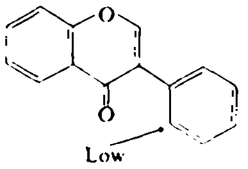
The results indicated in Tables 2 and 3 clearly show that although the substituent shielding values do not give an exact result in many cases, there is a greater than 70% probability that the calculated value will lie within ±0·20 ppm of the experimental result. Furthermore, there is a 90% probability that the difference will lie within ±0·30 ppm.

This degree of agreement has proved sufficient to enable the substituent shielding values to be used successfully for the definition of the orientation of unknown phenolic compounds.

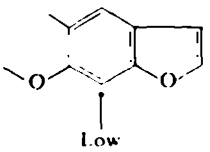
Most of the compounds whose τ values differed substantially from the calculated values belonged to certain distinguishable structural types in which long range magnetic anisotropic effects were clearly in operation. Examples of these structural types and the effects observed are illustrated by Structures I, II and III.



I



II



III

As a result of this investigation a few errors have come to light in the assignment of published PMR spectra.

The coumarin columbianetin[30] IV has been given the wrong assignment for the 5 and 6 positions. It can clearly be seen from the comparisons in Table 4 that the assignments for the 5 and 6 protons should be interchanged.

TABLE 4

Compound	5 Proton τ Assigned	5 Proton τ Calc.	6 Proton τ Assigned	6 Proton τ Calc.	8 Proton τ Assigned	8 Proton τ Calc.
IV	3·2	2·70	2·7	3·45	—	—
V	2·6	2·60	3·1	3·35	3·2	3·35
VI	2.5	2.60	3.2	3·35	3·3	3·35
VII	2·7	2·60	—	—	—	—

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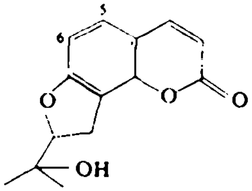
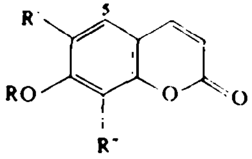
[30] Varian NMR Spectra Catalogue, No. 310.



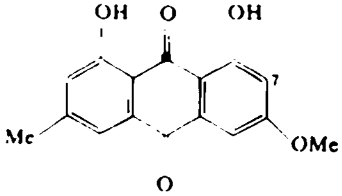
IV



V[21] R = R′ = R″ = H

VI[22] R = Et, R′ = R″ = H

VII[23] R = COMe, R′ = CH_2-CH = CH_2, R″ = Me



VIII

The anthraquinone VIII[19] has been assigned the τ value of 2·29 at position 7. While other calculated values are in agreement with experimental values, that for the 7 position differs by almost exactly 1·0 τ. The calculated value is 3·25 τ and a comparison with similar compounds would suggest that the literature value is a misprint.

Acknowledgment.—The authors are grateful to the Science Research Council for a research studentship to one of us (C. T. P.).

[21] T. J. Batterham and J. A. Lamberton, *Austral. J. Chem.* 17, 1305 (1964).

[22] Varian NMR Spectra Catalogue, No. 294.

[23] Varian NMR Spectra Catalogue, No. 323.