The Nuclear Magnetic Resonance Spectra of Some 4, 6-Disubstituted *o*-Cresols*

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In the application of the NMR technique to the organic structure determination, it is a useful principle that chemical shifts of aromatic ring protons can be estimated by using several substituent parameters. Many studies have been carried out in order to obtain such substituent parameters. Spiesecke and Schneider¹⁾ determined the shielding parameters of substituents from their study of a series of partially-deuterated monosubstituted benzenes. Diehl²⁾ also evaluated these parameters by an indirect method, in which he assumed that two equal or different substituents in the meta or the para position behave additively with respect to the chemical shift of a ring proton. The discrepancies between the two results, which probably reflect the approximate validity of the additivity rule, are less than 0.1 p. p. m. The utility of these substituent parameters has been demonstrated for several *m*- and *p*-disubstituted benzenes.³⁾ Martin and Dailey⁴⁾ showed that the ring-proton chemical shifts of a number of polysubstituted benzenes can be represented by simple sums of substituent-shielding constants with an accuracy of about 0.1 p. p. m., except for ring protons adjacent to substituents which are ortho to each other. In these positions, the large deviations observed presumably arise from strong interaction between the neighboring substituents separated approximately by the sum of van der Waals radii. They discussed the shielding mechanism and concluded that the proton chemical shifts in the disubstituted benzenes appear to arise primarily from changes in the π-electron density in the ring due to substituent perturbation. Other factors, for example, electric field and magnetic anisotropy of substituents, have minor effects upon ring proton chemical shifts.

Since it is not obvious whether or not the shielding parameters remain unchanged in the case of tetrasubstituted benzenes, it is of interest to test the additivity of shielding parameters in some 4, 6-disubstituted *o*-cresols. In addition, these compounds are suitable for studying the correlation between ring proton-coupling constants and the electronegativities of substituents, because there are only meta proton couplings.

On the other hand, the broadening of the NMR signals of methyl-substituted benzenes has been ascribed to the spin-spin coupling between methyl and ring protons (hereafter referred to as "benzylic coupling"). Quite recently, Nair and Gopakumar⁵⁾ studied the correlation between the variation in the benzylic coupling and changes in the π-electron distribution in some methyl-substituted aromatic compounds. They reported that the values of benzylic couplings in 2-methylnaphthalene and 2-methylanthracene are 0.7 and 0.8 c. p. s. respectively, and that the well-known difference in the bond order for the 1–2 bonds in naphthalene and anthracene is reflected in the observed splittings. The coupling to the 3-protons was reported to be weak. The following conclusion was drawn regarding the possibility of the splitting of the NMR signal of a methyl group attached to an aromatic ring with protons in both ortho positions. When the bond order values of the two bonds adjacent to a C–CH_3 bond are comparatively small and not very different from each other, no splitting can be expected for its resonance peak. On the other hand, when there is a considerable difference between the bond-order values or when the bond order values are both quite large, clear splittings should be observable. Shoolery⁶⁾ presented a good example, showing a close relation between the benzylic coupling and the bond-order values of the ring. Whereas a benzenoid thymol system shows no resolvable benzylic coupling, a thymoquinone system shows clear splittings in the signals. Regarding this point, it is suggestive that the coupling between methyl and ring protons is observed in heteroaromatic compounds, such

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

2) P. Diehl, *Helv. Chim. Acta*, **44**, 829 (1961).

3) B. Bak, J. B. Jensen, A. L. Larsen and J. Rastrup-Andersen, *Acta Chem. Scand.*, **16**, 1031 (1962).

4) J. S. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1722 (1963).

5) P. M. Nair and G. Gopakumar, *Tetrahedron Letters*, No. **13**, 709 (1964).

6) J. N. Shoolery, *Varian Associates, Tech. Bull.*, **2**, 8 (1957); J. D. Roberts, "Nuclear Magnetic Resonance—Applications to Organic Chemistry," McGraw-Hill Inc., New York (1959), p. 54.

as 2-methylthiophenes[7], methylfurans,[8] and methyl-substituted *N*-heteroaromatic compounds.[9,10] These facts seem to indicate that the benzylic coupling might be observed when a ring system is less aromatic, i. e., when π-electrons are much localized in a C–C bond involving a carbon atom to which a methyl group is bonded.

Experimental

Materials.—Commercial products were available for 4,6-dinitro-, 4,6-dichloro-, α,4,6-tribromo-, and 4,6-dimethyl-*o*-cresol. The bromination in acetic acid[11a] of 4-nitro-*o*-cresol, derived from 2-amino-5-nitrotoluene by boiling it in 30% aqueous sodium hydroxide for 20 hr.,[11b] yielded 4-nitro-6-bromo-*o*-cresol. Two halogenated compounds, 4,6-dibromo-*o*-cresol and 4,6-diiodo-*o*-cresol,* were prepared by the bromination and by the iodination of *o*-cresol respectively.[11c,11d] All the materials used were purified by recrystallization from appropriate solvents.

Measurements of NMR Spectra. — The NMR spectra were obtained with a Varian A-60 spectrometer in dilute deuterochloroform solutions (ca. 8 mol. %) containing a small amount of tetramethylsilane as an internal standard. Chemical shifts were read on standardized charts calibrated with the signal of chloroform. The resolution was checked with acetaldehyde. The accuracies of the chemical shifts and of the coupling constants are within about ±0.02 p. p. m. and ±0.2 c. p. s. respectively.

Results and Discussion

All the spectra of the examined compounds show simple first-order patterns. As an example, the spectrum of 4,6-dichloro-*o*-cresol is illustrated in Fig. 1. Each of the ring proton signals A and B consists of a pair of quartets. The methyl signal is composed of three peaks with a relative intensity of about 1 : 2 : 1. The middle component is somewhat broader than the outer components, suggesting the superposition of two signals. These features of the spectrum reveal the spin-spin coupling between the two ring protons and the methyl protons. Of the two signals A and B, the signal B, indicating a stronger coupling with the methyl protons, was assigned to the proton 3, while the signal A was assigned to the proton 5.

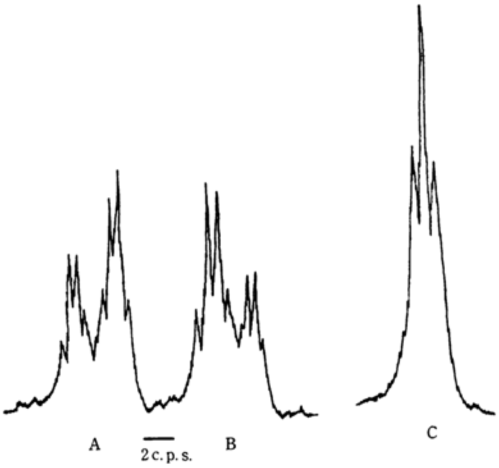

Fig. 1. The NMR spectrum of 4,6-dichloro-*o*-cresol.
A : ring proton 5, B : ring proton 3, C : methyl protons

The positions of the signals of various kinds of protons are given in Table I in p. p. m. relative to the internal standard.

Chemical Shifts. — The signals of the ring protons 5 are always observed at lower fields than are those of the protons 3, except for 4,6-dimethyl-*o*-cresol (2,4,6-trimethyl phenol), in which the two ring protons are magnetically equivalent. It appears reasonable that the proton 5, which is ortho to both of the electronegative substituents, 4 and 6, is more deshielded than is the proton 3, which is ortho to 4 and para to 6, because the deshielding effects of the substituents in question are strongest on the ortho proton (see Table II).

If the effects of substituents on the chemical shift of a ring proton are simply additive, the shift should be equal to the algebraic sum of substituent constants. In the present case, the chemical shifts of protons 3 and 5 should be :

$$\delta(3) = d_o(\mathrm{CH_3}) + d_m(\mathrm{OH}) + d_o(\mathrm{Y}) + d_p(\mathrm{Z}) + \delta(\text{benzene})$$

$$\delta(5) = d_p(\mathrm{CH_3}) + d_m(\mathrm{OH}) + d_o(\mathrm{Y}) + d_o(\mathrm{Z}) + \delta(\text{benzene})$$

Therefore, the proportional relationship between these chemical shifts should be observed, provided that the proportional relationship is observed between substituent parameters, $d_o(\mathrm{R})$

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[7] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, **16**, 563 (1960) ; *Chem. Abstr.*, **55**, 26682 (1961).

[8] G. S. Reddy and J. H. Goldstein, *J. Phys. Chem.*, **65**, 1539 (1961).

[9] B. D. N. Rao and J. D. Baldeschwieler, *J. Chem. Phys.*, **37**, 2473 (1962).

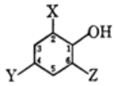
[10] K. Tori, M. Ogata and H. Kano, *Chem. Pharm. Bull.*, **11**, 235 (1963).

[*] The magnitude of the spin-spin coupling constant, 2.2 c.p.s., between two ring protons of the diiodo-*o*-cresol indicates that the two ring protons are in meta positions to each other. The infrared spectrum reveals that one of the two iodine atoms exists at the position 6; the observed OH stretching vibration frequency coincides with the value reported by Baker[12] for the cis (hydrogen bonded) form of *o*-iodophenol.

[11] a) *Beilstein* **6**, 367 ; b) ibid., 366 ; c) ibid., 360 : d) ibid., 364.

[12] A. W. Baker, *J. Am. Chem. Soc.*, **80**, 3598 (1958).

TABLE I. CHEMICAL SHIFT (IN P. P. M. FROM TMS) OF PROTONS OF SOME *o*-CRESOLS



	X	Y	Z	CH_3	H(3)	H(5)	OH
I	CH_3	NO_2	NO_2	2.48	8.38	8.95	11.4
II	CH_3	NO_2	Br	2.38	8.05	8.30	6.25
III	CH_3	Cl	Cl	2.27	7.03	7.18	5.57
IV	CH_3	Br	Br	2.27	7.25	7.45	5.57
V	CH_3	I	I	2.23	7.38	7.78	5.32
VI	CH_3	CH_3	CH_3	2.22	6.83	6.83	4.55
VII	CH_2Br	Br	Br	4.53	7.45	7.60	5.83

TABLE II. COMPARISON BETWEEN THE OBSERVED AND CALCULATED CHEMICAL SHIFTS OF RING PROTONS

		Proton 3			Proton 5		
Y	Z	Obs.	Calcd.*	Obs.-Calcd.	Obs.	Calcd.*	Obs.-Calcd.
NO_2	NO_2	−1.00	−0.96	−0.04	−1.57	−1.69	+0.12
NO_2	Br	−0.67	−0.60	−0.07	−0.92	−0.85	−0.07
Cl	Cl	+0.35	+0.48	−0.13	+0.20	+0.30	−0.10
Br	Br	+0.13	+0.23	−0.10	−0.07	−0.02	−0.05
I	I	0.00	+0.03	−0.03	−0.40	−0.43	+0.03
CH_3	CH_3	+0.55	+0.67	−0.12	+0.55	+0.67	−0.12

* Martin and Dailey's parameters⁴⁾ were used except for $d_m(OH)$.

$d_o(NO_2) = -0.995$ $d_o(Cl) = 0.000$ $d_o(Br) = -0.159$
$d_p(NO_2) = -0.29$ $d_p(Cl) = +0.16$ $d_p(Br) = +0.07$
$d_o(I) = -0.363$ $d_o(CH_3) = +0.183$ $d_m(OH) = +0.14$**
$d_p(I) = +0.07$ $d_p(CH_3) = +0.16$

** F. Langenbucher, E. D. Schmid and R. Mecke, *J. Chem. Phys.*, **39**, 1901 (1963).

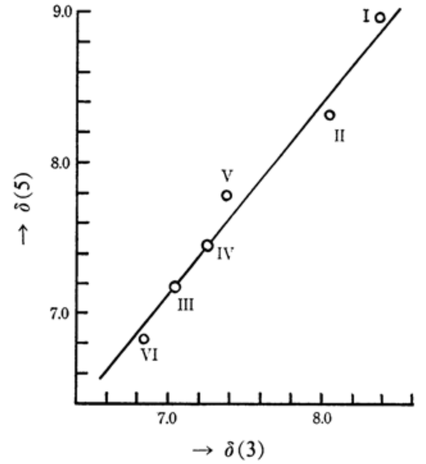


Fig. 2a. Correlation of δ(3) with δ(5).

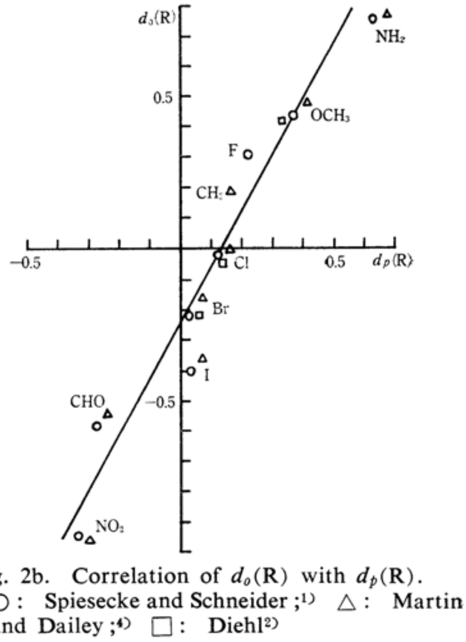


Fig. 2b. Correlation of d_o(R) with d_p(R).
○ : Spiesecke and Schneider ;¹⁾ △ : Martin and Dailey ;⁴⁾ □ : Diehl²⁾

and d_p(R). This is the case, as Fig. 2 shows. Comparisons of the observed and calculated chemical shifts were made in order to ascertain the validity of the additivity rule. Table II gives the values relative to the chemical shift of benzene in deuterochloroform. The agreement among them is good in view of the rough approximation used. This fact indicates that the additivity rule holds in the case of tetrasubstituted benzenes. A good agreement is again observed in the case of durene. The observed chemical shift of the ring protons in durene[13] (6.741 p. p. m.) agrees well with that estimated from the assumed additivity rule (6.716 p. p. m.).

The OH proton signal of 4, 6-dinitro-*o*-cresol was observed at an extraordinarily low field. This observation can be ascribed to the formation of an intramolecular hydrogen bond between OH and NO_2 groups. It has been pointed out that the OH proton signal of 2, 4-dinitrophenol appears at a field lower than that of 2, 4-dichlorophenol by about 5.6 p. p. m. because of the formation of strong intramolecular hydrogen bonds.[14] The OH proton signal of α, 4, 6-tribromo-*o*-cresol was observed at a field lower than that of 4, 6-dibromo-*o*-cresol. This downfield shift results from the formation of intramolecular hydrogen bonds between CH_2Br and OH groups, in addition to that between OH and Br groups.*

Methyl signals are shifted to lower fields with the increasing electronegativities of substituents. In the case of 4, 6-dinitro-*o*-cresol, it appears at a field lower than that of the parent compound by 0.21 p. p. m. Yamaguchi[15] studied the shielding effect of nitro groups and observed that a nitro group deshields methyl protons at the meta position of *m*-nitrotoluene by 0.12 p. p. m. The chemical shift of the methyl protons described above on 4, 6-dinitro-*o*-cresol is in good agreement with the calculated value, $2\times0.12=0.24$ p. p. m.

Spin-Spin Coupling.—The spin-spin coupling constants obtained are summarized in Table III.

TABLE III. SPIN-SPIN COUPLING CONSTANTS

	J(3-5) c. p. s.	J(3-CH_3) c. p. s.	J(5-CH_3) c. p. s.
I	2.9	0.9	0.6
II	2.7	0.8	0.5
III	2.5	0.7	0.5
IV	2.4	0.7	0.5
V	2.2	0.8	0.6
VI	—	—	—
VII	2.4	—	—

The coupling constants between two ring protons are in the 2.2—2.9 c. p. s. range. The coupling constant is larger when substituents at the positions 4 and 6 are more electronegative. Figure 3 shows the correlation between the meta coupling and the sum of the electronegativities of substituents 4 and 6. This proportional relationship indicates the additive effect of substituents on the ring proton coupling. A similar situation of meta coupling was reported for some *m*-[16] and *p*-disubstituted benzenes.[17] It was reported[17] that proportionality exists between the proton-proton coupling and the electronegativity of substituents, although no detailed discussion of coupling mechanism has yet been undertaken.

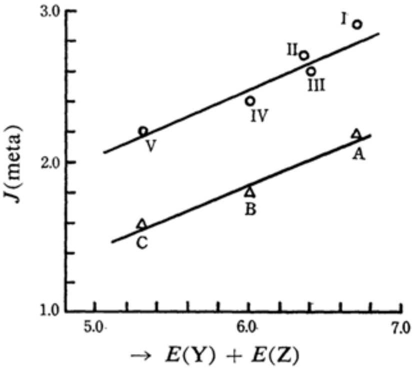


Fig. 3. Correlation between the meta coupling and the sum of electronegativities of the substituents 4 and 6.
-○-: J(3-5) for 4, 6-disubstituted *o*-cresols
-△-: J(2-6) for *m*-disubstituted benzenes[16]
A: *m*-dinitrobenzene; B: *m*-dibromobenzene; C: *m*-diiodobenzene

Proton-proton coupling constants are, in general, affected by two contributing factors, σ- and π-electrons. The dependence of the vicinal coupling constant on the electronegativities of substituents has been studied in some ethane[18] and ethylene derivatives.[19] For ethane and ethylene derivatives, the vicinal coupling constants are expressed as:[20]

$$J(\mathrm{CH_3CH_2X})=7.9(1-0.09\Delta E)$$
$$J_{trans}=19(1-0.17\Delta E);$$
$$J_{cis}=11.7(1-0.34\Delta E)$$

where ΔE is the difference in electronegativity

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[13] G. V. D. Tiers "Tables of τ-Values for a Variety of Organic Compounds," Central Research Lab., Minnesota Mining and Manufacturing Company, Minnesota (1958), p. 5.

[14] L. W. Reeves, W. A. Allan and K. O. Strømme, *Can. J. Chem.*, **38**, 1249 (1960).

[*] Whereas two OH stretching vibrations, at 3600 and 3526 cm^{-1}, were found for 4, 6-dibromo-*o*-cresol, a single band was observed, at 3520 cm^{-1}, for α, 4, 6-tribromo-*o*-cresol in the OH-stretching region. Baker[12] observed two peaks, at 3598 and 3524 cm^{-1}, for *o*-bromophenol and assigned them to the trans (free) and cis (hydrogen bonded) forms respectively.

[15] I. Yamaguchi, *Mol. Phys.*, **6**, 105 (1963).

[16] J. Martin and B. P. Dailey, *J. Chem. Phys.*, 37, 2594 (1962).

[17] P. F. Cox, *J. Am. Chem. Soc.*, **85**, 380 (1963).

[18] R. E. Glick and A. A. Bothner-By, *J. Chem. Phys.*, **25**, 362 (1956).

[19] J. S. Waugh and S. Castellano, ibid., 35, 1900 (1961); S. Castellano and J. S. Waugh, ibid., **34**, 295 (1961); T. Schaefer, *Can. J. Chem.*, **40**, 1 (1962).

[20] C. N. Banwell and N. Sheppard, *Discussions Faraday Soc.*, **34**, 115 (1962).

between X and the hydrogen atom. In ethylene derivatives, the variation in coupling constants with the electronegativity is much greater than that in substituted ethanes. From this fact, it may be concluded that the contributions of both σ- and π-electrons are reduced by the introduction of an electronegative group. In other words, a decrease in the charge density in the double bond caused by the introduction of an electronegative groups is reflected in a decrease in the coupling constant of vicinal protons.

In the case of 4, 6-disubstituted *o*-cresols, however, the meta coupling intensifies the proportionality with an increase in the electronegativity of substituents. This discrepancy indicates the participation of another mechanism, which probably arises from the presence of a benzene ring contributing to the coupling. Since the angle between two C–H bonds can be assumed to be fixed, the change in the meta coupling is attributable to that in electron distribution, but it is not possible to give a clear interpretation immediately, because it is not clear whether the changes in the proton-coupling constants in these compounds are due to changes in the σ-electronic system or to changes in the π-orbitals.

Long-range Coupling. — The coupling constants, $J(3\text{–}CH_3)$ and $J(5\text{–}CH_3)$, are less than 1 c. p. s. It is reasonable that $J(3\text{–}CH_3)$ is slightly larger than $J(5\text{–}CH_3)$. However, it is noteworthy that an unexpectedly large value was observed for the spin-spin coupling constant between the methyl group and the ring proton at the para position across six bonds. Whereas the value of $J(5\text{–}CH_3)$ is quite similar within the range of the accuracy of this experiment, the value of $J(3\text{–}CH_3)$ seems proportional to the electronegativity of the substituents 4 and 6.

It is to be expected that a larger contribution from the methyl-hyperconjugation and the resulting shift of the NMR signal of methyl protons to a lower field will be observed for compounds with more powerful electron-withdrawing substituents. Therefore, there should be a proportional relationship between the chemical shift of the methyl protons and the benzylic coupling constant, $J(3\text{–}CH_3)$, provided that the hyperconjugation of the methyl group contributes considerably to the benzylic coupling. In Fig. 4, the plots for compounds I, II, III, and IV fall well on a straight line, but the plot for compound V deviates from the line, probably because of the effect of the large volume of iodine atoms at the ortho position.

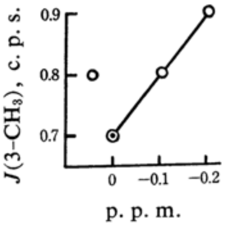

Fig. 4. Difference between methyl proton chemical shifts of 4, 6-disubstituted *o*-cresols and that of 4, 6-dichloro-*o*-cresol vs. $J(3\text{–}CH_3)$.

It can also be expected that the replacement of a methyl group with a bromomethyl group decreases the extent of hyperconjugation because of the fixation of the bromomethyl group in a conformation inadequate for hyperconjugation by an intramolecular hydrogen bond. As expected, no benzylic coupling was observed in the case of α, 4, 6-tribromo-*o*-cresol. This fact indicates a significant contribution by the hyperconjugation to the benzylic coupling. In other words, the hyperconjugation of a methyl group with the benzene ring is due to the partial transfer of charges from the methyl group to the ring system. The introduction of bromine into the methyl group reduces the charge transfer from the substituent to the ring system and makes the benzylic coupling very weak. In short, a resolvable benzylic coupling indicates an appreciable migration of charges from the methyl group to the ring system. From this point of view, it seems possible to give an interpretation of the facts described in the introduction.

Although there are two kinds of methyl groups in 4, 6-dimethyl-*o*-cresol, only a single signal was observed for the methyl protons. It is not possible to estimate the benzylic coupling constants directly from the spectrum, but a considerable magnitude of benzylic coupling may be inferred from the appreciable broadening of the signals of both the methyl and ring protons.

Freeman et al.[21] have reported the presence of a weak long-range coupling between the OH proton and the ring proton 4 at the meta position in methyl salicylate. In the present case, however, it may be concluded that the OH proton couples with neither of the two ring protons at the meta positions since no changes in the fine structure of signals were observed in methanol, acetone, or NaOD-D_2O.

Summary

The nuclear magnetic resonance spectra of seven 4, 6-disubstituted *o*-cresols (4, 6-dinitro-, 4-nitro-6-bromo-, 4, 6-dichloro-, 4, 6-dibromo-, 4, 6-diiodo-, 4, 6-dimethyl-, and α, 4, 6-tribromo-*o*-cresol) have been examined in dilute

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[21] R. F. Freeman, N. S. Bhacca and C. A. Reilly, *J. Chem. Phys.*, **38**, 293 (1963).

deuterochloroform solutions at 60 Mc./sec.

The observed chemical shifts of the ring protons 3 and 5 of 4, 6-disubstituted *o*-cresols are in good agreement with the values calculated from the shielding parameters of substituents by assuming the additivity rule.

The spin-spin coupling constant between two ring protons is proportional to the sum of the electronegativities of the substituents 4 and 6.

There are weak long-range couplings between the methyl and ring protons. It has been suggested that hyperconjugation contributes to these couplings.

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