Correlations of Polar Effects of Substituents with Nuclear Magnetic Resonance Spectra of Phenols[1]

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The chemical shifts of the hydroxyl proton signal from substituted phenols in dimethyl sulfoxide solutions are strongly dependent on the nature of the substituent. When substituted phenols are compared with phenol itself, the change in chemical shift ($\Delta\delta$) ranges from +49 to −100 cps. A plot of $\Delta\delta$ *vs.* Hammett σ is linear with slope (ρ) equal to +1.536; the "normal" regression line is described by the equation $\sigma = 0.651(\Delta\delta) + 0.031$. New σ constants may be determined with unusual ease by this approach; σ for m-$OCOC_6H_5$ is found to be 0.33 and σ for p-$OSO_2C_6H_4CH_3$-p is found to be 0.20. Data for *ortho*-substituted phenols are correlated in an orderly fashion also.

The well-known and widely used Hammet σ–ρ relationship correlates a vast body of rate and equilibrium data.[3] Although the relationship must be modified in some cases, the Hammett σ constant is probably the best quantitative measure of the electron-displacing effect of a substituent group, and a linear correlation between some function of a reaction series and the σ constants is usually regarded as significant. Varying degrees of success have been reported in correlating chemical-shift data for substituted benzenes with σ constants.[4] Of particular interest for the present study is the report that hydroxylic proton chemical shifts (extrapolated to infinite dilution) for phenols in carbon tetrachloride solution are independent of the nature of the *para* substituent.[5]

During the course of another study,[6] we noticed a fair qualitative relationship between the nmr chemical shift of hydroxylic protons hydrogen bonded to DMSO (dimethyl sulfoxide) solvent and the expected electron-withdrawing effect of nearby substituents in aliphatic alcohols. We have now investigated the nmr data of of a series of substituted phenols in DMSO solvent and have found an unusually good linear correlation between the chemical shifts of the phenolic protons and the σ constants of *metal* and *para* substituents.[7] This approach is perhaps the most convenient one presently in use for determining the σ constant for a new substituent. In contrast to the results obtained with more traditional approaches,[3] even *ortho*-substituted phenols give data which are well correlated with the data from *meta*- and *para*-substituted phenols.

DMSO solvent minimizes dependence of chemical shift on concentration of the hydroxylic solute.[8] Although the chemical shift for phenolic proton in carbon tetrachloride solution varies from −5.95 to −6.75 ppm[9] in the concentration range 5–20%, there is no change in chemical shift in DMSO solution in the same concentration range. On the other hand, the chemical-shift differences among a series of substituted phenols are, we find, appreciably magnified in DMSO solvent compared with carbon tetrachloride solvent. For the series of 29 substituted phenols which we have studied, the phenolic proton chemical shift varies from −8.50 ppm (p-OH) to −10.98 ppm (p-NO_2); the signal for unsubstituted phenol appears at −9.32 ppm. The data for *meta*- and *para*-substituted phenols are summarized in Table I, and a plot of chemical shift relative to unsubstituted phenol ($\Delta\delta$) *vs.* Hammett σ constants for the substituents is shown in Figure 1. Except for the three substituents p-NO_2, p-CHO, and OH (p-, m-, and 3,5-di-OH), the data points fall very close along a straight line with slope equal to 1.536 and intercept equal to −0.048. The equation for the normal regression line is $\sigma = 0.651(\Delta\delta) + 0.031$.[10]

The deviations are associated with strong resonance contributions of the p-NO_2 and p-CHO substituents or with enhanced electron release by the OH substituents due to specific solvation effects. The correlating line falls in between data points for the two electron-withdrawing substituents based on σ and those based on σ^-; points based on σ and σ^- for p-phenyl appear about equally spaced on each side of the line. The requirement of a special σ^- for *para* substituents strongly involved in resonance with a phenol nucleus has long been recognized.[3] The sensitivity of the highly stretched phenolic O–H bond in DMSO solvent to influence of resonance contributions from a *para* substituent must lie in between that of a carboxylate ion (from benzoic acid) and a phenoxide ion.

The substituent OH, whether in *meta* or *para* position, apparently is much more electron releasing than the ordinary σ constant predicts. We believe that this effect is a reflection of alteration of the substituent

(1) (a) Presented at the Southeast–Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn, Dec 5, 1965, Abstracts, p 78; (b) abstracted from the Ph.D. dissertation of G. A. K., submitted to Louisiana State University, Jan 1966.

(2) NASA trainee, 1963–1965.

(3) For reviews of the Hammett equation, see (a) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953); (b) P. R. Wells, *ibid.*, **63**, 171 (1963); (c) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

(4) (a) Chemical shifts of side-chain H in ethylbenzenes: K. L. Williamson, N. C. Jacobus, and K. T. Soucy, *J. Am. Chem. Soc.*, **86**, 4021 (1964) [this article includes a good, brief review of Hammett σ constants and chemical-shift data]; (b) ^{19}F in fluorobenzenes: H. S. Gutowsky, D. W. McCall, B. R. McGarvey, and L. H. Meyer, *ibid.*, **74**, 4809 (1952); (c) ^{19}F in fluorobenzenes: R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *ibid.*, **81**, 5352 (1959); (d) formyl H in benzaldehydes: R. E. Klinck and J. B. Strothers, *Can. J. Chem.*, **40**, 1071 (1962); (e) methoxy protons in substituted anisoles: C. Heathcock, *ibid.*, **40**, 1865 (1962); (f) acetylenic H in phenylacetylenes: C. D. Cook and S. S. Danyluk, *Tetrahedron*, **19**, 177 (1963); (g) ethyl protons in ethyl 4-substituted 2-nitrobenzenesulfenates: C. Brown and D. R. Hogg, *Chem. Commun.*, 150 (1965); (h) vinyl H in substituted heterocyclic ArCH=CHCOOH: A. R. Katritzky and F. J. Swinbourne, *J. Chem. Soc.*, 6706 (1965).

(5) W. G. Paterson and N. R. Tipman, *Can. J. Chem.*, **40**, 2122 (1962). Only p-Cl, p-Br, p-I, and p-OMe were included as substituents in this study.

(6) J. G. Traynham and G. A. Knesel, *J. Am. Chem. Soc.*, **87**, 4220 (1965).

(7) Data points for *meta*- and *para*-substituted phenols fit the line equally well. For contrast, see ref 4b.

(8) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(9) All chemical shifts cited are relative to internal tetramethylsilane.

(10) A "normal" regression model was adopted for a statistical study of the well-correlated points with the aid of an IBM 1620 computer at the Louisiana State University Computer Center. We acknowledge with appreciation the assistance of Dr. T. M. Couvillon in preparing the program for the computer. The statistical treatment is described in detail in the Ph.D. dissertation of G. A. K.

TABLE I
CHEMICAL-SHIFT DATA FOR O*H* SIGNALS FROM DMSO SOLUTIONS OF PHENOLS

Substituent	Chemical shift, ppm[a]	$\Delta\delta$[b]	σ[c]
1, *p*-NO_2	−10.98	1.66	0.778 (1.270)
2, *p*-CHO	−10.54	1.32	0.216 (1.126)
3, *m*-NO_2	−10.34	1.02	0.710
4, *m*-Cl	−9.84	0.52	0.373
5, *m*-F	−9.84	0.52	0.337
6, *p*-I	−9.66	0.34	0.276
7, *p*-Br	−9.66	0.34	0.232
8, *p*-Cl	−9.62	0.30	0.227
9, 4-Cl, 3-Me	−9.50	0.18	0.174
10, *p*-C_6H_5	−9.44	0.12	0.009 (0.16)
11, *p*-F	−9.36	0.04	0.062
12, H	−9.32	0.00	0.00
13, *m*-Me	−9.16	−0.14	−0.069
14, *p*-Me	−9.04	−0.28	−0.170
15, *m*-OH	−9.02	−0.30	−0.002
16, 3,5-Di-OH	−9.00	−0.32	0.162
17, 3,4-Di-Me	−8.98	−0.34	−0.229
18, *p*-*t*-Pentyl	−8.96	−0.36	−0.190
19, *p*-OMe	−8.76	−0.56	−0.268
20, *p*-OH	−8.50	−0.82	−0.357
21, *m*-$OCOC_6H_5$	−9.78	0.46	0.330[d]
22, *p*-OTs	−9.58	0.26	0.200[d]
23, *o*-Br	−10.14	0.82	0.21 (0.568)[e]
24, *o*-Cl	−9.96	0.64	0.20 (0.448)[e]
25, *o*-C_6H_5	−9.38	0.06	(0.61)[e]
26, *o*-Me	−9.14	−0.18	−0.17 (−0.10)[e]

[a] Relative to internal tetramethylsilane standard. [b] Chemical shift relative to unsubstituted phenol, in ppm. [c] See ref 3a; except where otherwise noted, first number is σ, number in parentheses is σ^-. [d] New substituent constants calculated from this work. [e] First number is σ_0^*, relative to H, from ref 3c; number in parentheses is value which fits $\Delta\delta$ to linear plot in this work.

by specific solvation. All of the OH groups in the OH-substituted phenols are solvated, and the actual substituent is not OH but is O–H····DMSO. Just as solvation by DMSO caused a strong downfield change in the chemial shift of the phenolic proton signal, so does it enhance the electron-releasing power of the OH substituent.[11] Because the substituent is substantially altered by solvation, use of σ for the unaltered OH substituent is of course inappropriate. The σ value which would place the chemical-shift data points for OH substituents directly on the line in Figure 1 may be taken as σ for O–H····DMSO substituent.

The average deviation of σ from the line of slope 1.54 for all 20 *meta*- and *para*-substituted phenols is ±0.102; if σ^- values are used in place of σ for *p*-NO_2, *p*-CHO, and *p*-C_6H_5, the average deviation is reduced to ±0.069. The average deviation for the substituents for which one would not expect some resonance or special solvation effects is only ±0.022, and the correlation coefficient for these latter 14 data points is 0.995.[12]

This unusually excellent correlation prompted us to evaluate σ for some readily available substituents for which σ values have not been previously reported.

(11) The effect with additional OH substituents is approximately additive. The deviation of data point 16 (3,5-di-OH) from the line is about twice that of data point 15 (*m*-OH).

(12) If the plot is based on σ values from the (less inclusive) tabulation of Wells,[3b] the line has slope ρ = 1.506 and intercept = −0.049. The equation for the line is σ = 0.664($\Delta\delta$) + 0.023, the average deviation of σ for data points 3–8, 11–14 is ±0.015, and the correlation coefficient is 0.995. The calculated value of σ for *m*-$OCOC_6H_5$ is 0.328 and that for *p*-OTs is 0.195.

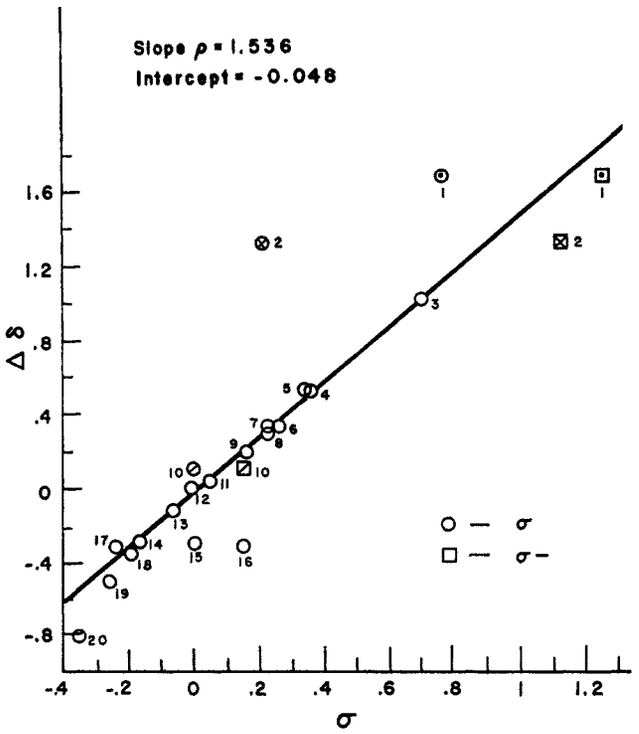

Figure 1.—Relative chemical shifts of OH of *meta*- and *para*-substituted phenols ($\Delta\delta$) *vs.* Hammett σ constants. Numbered points correspond to entries in Table I.

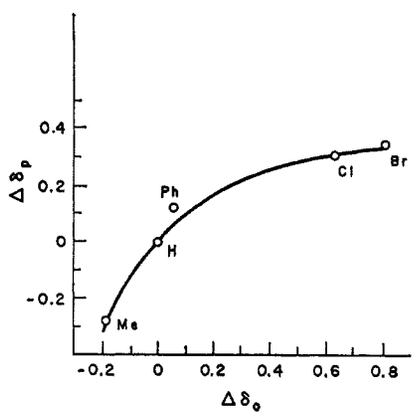

Figure 2.—Relative chemical shifts of OH of *para*-substituted phenols *vs.* those of corresponding *ortho*-substituted phenols.

The chemical shifts for the O*H* signal obtained with DMSO solutions of *m*-benzoyloxyphenol ($\Delta\delta$ = 0.46) and *p*-(*p*-toluenesulfonyloxy)phenol ($\Delta\delta$ = 0.26) correspond, respectively, to σ for *m*-$OCOC_6H_5$ = 0.330 and σ for *p*-$OSO_2C_6H_4CH_3$-*p* = 0.200.[12] These σ values should be quite reliable, because neither significant resonance nor solvation effects are expected for these substituents.

ortho **Substituents.**—Because of the considerable importance of steric factors with *ortho* substituents, an orderly array of points is never obtained when log $(k/k_0)_p$ is plotted against log $(k/k_0)_o$,[3] where k and k_0 refer to rate or equilibrium constants of substituted and unsubstituted parent compounds, respectively, and subscripts p and o refer to *para*- and *ortho*-substituted series, respectively. It is perhaps surprising, then, that a plot of $\Delta(\delta)_p$ *vs.* $\Delta(\delta)_o$ for the few *ortho*-substituted phenols which we included in our study is a smooth (nonlinear) curve (Figure 2).[13] For *ortho* substituents

(13) A definite trend between the magnitudes of δ_p and δ_o for substituted fluorobenzenes has been reported.[4b]

of comparable size (E_s values for Me and Br are identical[3c]), the deviation from linearity is in the direction of *larger* $\Delta(\delta)_o$ values with increasing electron-displacing ability than a linear correlation would require. That is, the deviations are not in the direction which would be expected if the usual steric effects of *ortho* substituents were being manifested (diminished interaction between phenol and solvent DMSO). We believe that an *ortho* substituent interferes far less (perhaps not at all) with the solvation of the phenol OH by a *single* molecule of DMSO than it does with the multimolecular solvation usually encountered in situations from which σ constants are evaluated (for example, dissociation of benzoic acid to heavily solvated benzoate ions).

ortho-Substituent σ constants which would be evaluated from our chemical-shift data are a little higher than those reported by Taft,[3c] with larger differences occurring between σ for the stronger electron-displacing halogen substituent than for the weaker electron-displacing methyl one. The magnitudes of σ_p and σ_o^* are nearly the same except for substituents, such as OMe and F, which have steric substituent constants (E_s) substantially larger than zero, in which cases σ_o^* is larger than σ_p.[3c] The minimal steric effects of *ortho* substituents in our study seem to result in a similar apparent enhancement of the polar substituent effect of the *ortho* substituent over the *para* one.

We expect to investigate further the validity of this simple procedure for estimating polar substituent constants of *ortho* substituents.

Experimental Section[14]

Nmr data were obtained with a Varian Associates HA-60 spectrometer for DMSO solutions approximately 5–20% in phenol. Solutions of phenol and *m*-fluorophenol were examined over a range of concentrations to demonstrate the lack of dependence of chemical shift on concentration. Purities of commercially available phenols were checked by melting point and/or gas chromatographic analysis, and only samples which passed the usual criteria of purity were used. Freshly prepared solutions were used, for, although the age of the solutions did not affect the chemical shift observed, phenols substituted with strongly electron-attracting groups (p-NO_2 and p-CHO) gave diffuse signals when old solutions were used.

(14) We acknowledge with appreciation the assistance provided by Mr. R. Seab and Mr. W. Wegner in the operation of the nmr spectrometer.

Isomerization of 1-Thioacylazetidines and Related Compounds

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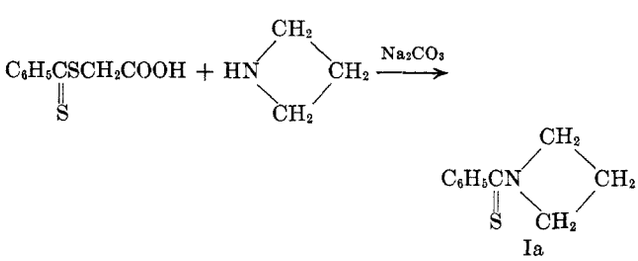
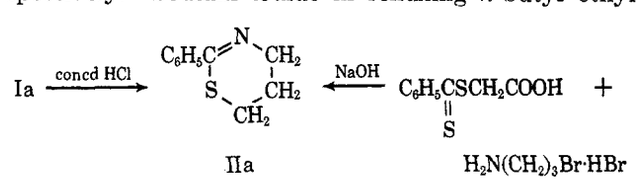
1-Thiobenzoyl-, 1-(aryloxythiocarbonyl)-, and 1-(dithio-*p*-chlorophenyloxycarbonyl)azetidines, 1-(N-phenylthiocarbamyl)-2-methylazetidine, and 1-(N-phenylcarbamyl-)-2-methylazetidine were prepared and isomerized. The 1-thioacylazetidines displayed greater tendency to isomerize than the corresponding 1-acylazetidines. Such a tendency was quite pronounced in the case with urethans and thionurethans; in the former, no isomerization reaction has been observed, while the latter were isomerized with concentrated hydrochloric acid. The isomerization reaction of 1-(N-phenylthiocarbamyl)-2-methylazetidine with acids in refluxing toluene showed more SN2-like character than of 1-(N-phenylcarbamyl)-2-methylazetidine.

In an earlier paper,[1] the isomerization of 1-(N-phenylcarbamyl)-, 1-(N,N-diphenylcarbamyl)-, 1-(N-phenylthiocarbamyl)-, and 1-benzoylazetidine was reported. With acids, the 1-acyl- or thioacylazetidines were isomerized to 2-substituted dihydro- (or tetrahydro-) oxazines or thiazines quite analogously to the conversion of 1-acyl- or thioacylaziridines to 2-substituted oxazolines or thiazolines. However, in contrast to the aziridine derivatives, the azetidine derivatives were found to be stable to heat and nucleophilic reagents, and especially lacking in self-polymerization property under moderate conditions. The fact prompted us to prepare several 1-thioacylazetidines in order to elucidate the isomerization reaction especially in relation to the effect of the structural change on ease of the rearrangement.

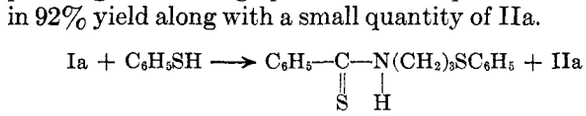
1-Thiobenzoylazetidine (Ia) was prepared by the reaction of azetidine with thiobenzoylthioglycolic acid.[2] Ia was converted to 2-phenyl-4,5-dihydro-6H-1,3-thiazine (IIa) in 24% yield (based on the quantity of IIa picrate) on standing in concentrated hydrochloric acid at room temperature for 10 days. Reaction with dichloroacetic acid or boron trifluoride etherate in



refluxing toluene also gave IIa in 28 or 75% yield, respectively. Sodium iodide in refluxing *n*-butyl ethyl



ketone was also effective for the isomerization. Thiophenol gave the ring-opened addition product with Ia in 92% yield along with a small quantity of IIa.



1-(Aryloxythiocarbonyl)azetidines were prepared from chlorothionformic acid aryl esters and azetidine.

(1) Y. Iwakura, A. Nabeya, T. Nishiguchi, and Y. Ichikawa, *J. Org. Chem.*, **30**, 3410 (1965).

(2) J. C. Crawhall, and D. F. Elliott, *J. Chem. Soc.*, 2071 (1951).