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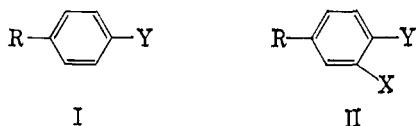
A Study of Free Energy Relationships in Hindered Phenols. Linear Dependence for Solvation Effects in Ionization¹

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RECEIVED JANUARY 26, 1963

Dissociation constants in water and in 50% ethanol have been determined spectrophotometrically for a series of 4-substituted phenols and for the corresponding 2,6-di-*t*-butyl-4-substituted phenols. Although the pK values for hindered phenols show a linear dependence on the σ -constant, there is a marked deviation from additivity, ρ being 57% greater than for the unhindered phenols in water and 73% greater in 50% ethanol. The results suggest that ionization and solvation at the hindered site are interrelated and that the degree of solvation at the phenolate ion may be correlated with σ in the same way as electron density distribution. The anomalously high pK value for 2,6-di-*t*-butyl-4-nitrosophenol is ascribed to the less acidic, but thermodynamically more stable, quinone monooxime tautomer. The anomalously low pK value for the di-*t*-butyl-4-nitrophenol is discussed in terms of alternative explanations. Facile tautomerism is demonstrated by the quantitative methylation of the hindered nitrophenol to the stable *aci*-nitro methyl ether XIII with diazomethane.

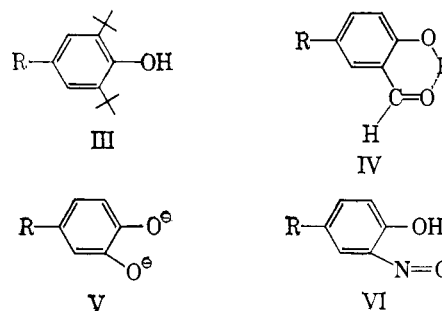
If an aromatic ring is substituted as in I, the effect of variations in R on equilibria or reaction rates at Y may be correlated by the familiar Hammett linear free energy relationship, $\log k = \sigma\rho + \log k_0$.² If a fixed



substituent, X, is now added *ortho* to Y, as in II, we may expect, according to the additivity principle,² that the Hammett relationship will still be obeyed, since interaction between X and Y, regardless of its nature, should remain essentially constant as R is varied.

Such an argument may be tested by comparing the Hammett plots for I and II under equivalent conditions. The slopes of the two lines should be identical (within experimental error) and ρ_{II} should be displaced from ρ_I by an amount related to the total contribution of X to the aromatic system (the sum of inductive, resonant, and steric effects, etc.). The validity of the principle has been demonstrated experimentally in the effect of a 2-amino group on the carbonyl stretching frequencies of 4-substituted benzoic acids,³ in the effect of a 2-methyl group on the rates of esterification of 4- and 5-substituted benzoic acids with diphenyldiazomethane,⁴ in the effect of a 2-nitro group on the dissociation constants of 4-substituted phenols,^{5a} and in the effect of 2-halo and 2-methoxy substituents on the first dissociation constants of 4- and 5-substituted benzenephosphonic acids.^{5b} However, a slight variation in ρ was observed in the effect of 2-methyl on the ionization constants of 4- and 5-substituted benzoic acids⁴ and in the effect of 2-halo and 2-methoxy groups on the *second* ionization constants of 4- and 5-substituted benzenephosphonic acids.^{5b} It is evident that a small variation in ρ may occur when the solvation of Y is implicated in the property being measured (such as degree of ionization) and that the requirements for solvation of Y may vary with the nature of R.

One may, in fact, predict that some variation in ρ should occur whenever there exists a significant interaction between X and Y. Such interaction may take several forms, *e.g.*, steric hindrance to solvation of the anion of a phenol (III), strong hydrogen bonding (IV), electrostatic repulsion (V), and potential tautomeric coupling (VI). In the present communication, we deal



with the first of these systems, that of type III. The value of ρ for ionization of III should exhibit a substantial deviation from that for simple 4-substituted phenols for the following reasons: (1) among common substituents, the *t*-butyl group has one of the largest *ortho* steric effects^{2d}; (2) resonance coupling between R and Y is maximal when Y is O⁻²; (3) the size of the solvation sphere for a phenolate ion is probably greater than that for a carboxylate ion or any other negatively charged substituent⁶; (4) the nonbonded distance between hydroxyl and *t*-butyl in III is very small; (5) the possibility for relief of steric interference in such a system by conformational flexibility or distortion is very small.

In view of the fact that values of σ for a given substituent are markedly dependent upon the type of reaction studied,^{7a} all values of σ_p used in the present work were calculated solely from the thermodynamic dissociation constants of 4-substituted phenols in water at 25° (Table I, column 2).^{7b} With the exception of two cases (4-*t*-butylphenol and 4-carboxamidophenol), pK_a values were drawn from the literature; in some instances the values were confirmed by spectrophotometric measurement. Substituent constants (σ_p^-) were calculated from the equation $pK_a = 9.919 - 2.229\sigma$ derived by Biggs and Robinson⁸ and are recorded

(6) Based on hydration numbers of hydroxyl and acetate ions, see E. Glueckauf, *Trans. Faraday Soc.*, **51**, 1235 (1955); C. B. Monk, "Electrolytic Dissociation," Academic Press, Inc., New York, N. Y., 1961, p. 267.

(7) (a) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. trav. chim.*, **78**, 815 (1959). (b) For the sake of consistency in symbolism, all σ_p values are reported as σ_p^- since they are based on the ionization of phenols. It should be realized, however, that $\sigma_p^- \cong \sigma_p$ for saturated 4-substituents.

(8) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).

(1) Paper V of a series on phenol-dienone tautomerism. For paper IV: see L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **84**, 1629 (1962).

(2) (a) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter 7; (b) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (c) V. A. Palm, *Russ. Chem. Rev.*, 471 (1961); (d) 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.

(3) A. E. Kellie, D. G. O'Sullivan and P. W. Sadler, *J. Org. Chem.*, **22**, 29 (1957).

(4) J. D. Roberts and J. A. Yancey, *J. Am. Chem. Soc.*, **73**, 1011 (1951); see also J. D. Roberts and C. M. Regan, *ibid.*, **76**, 939 (1954); H. L. Goering, T. Rubin, and M. S. Newman, *ibid.*, **76**, 787 (1954).

(5) (a) M. Rapaport, C. K. Hancock, and E. A. Meyers, *ibid.*, **83**, 3489 (1961); (b) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *ibid.*, **76**, 1548 (1954).

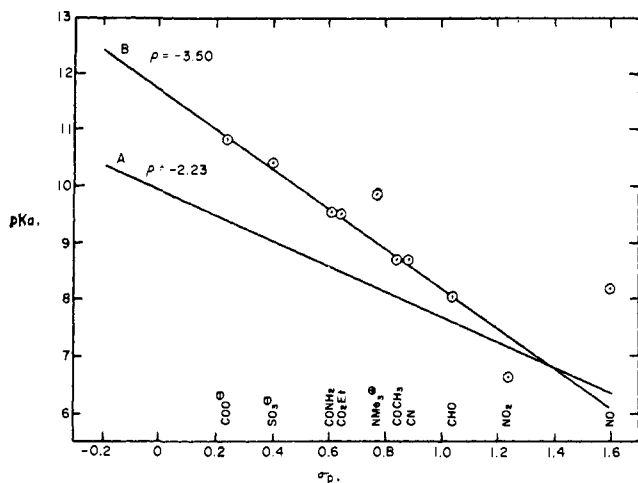


Fig. 1.—Correlation of pK_a with σ_p (H_2O , 25°): A, 4-substituted phenols (ref. 8); B, 2,6-di-*t*-butyl-4-substituted phenols.

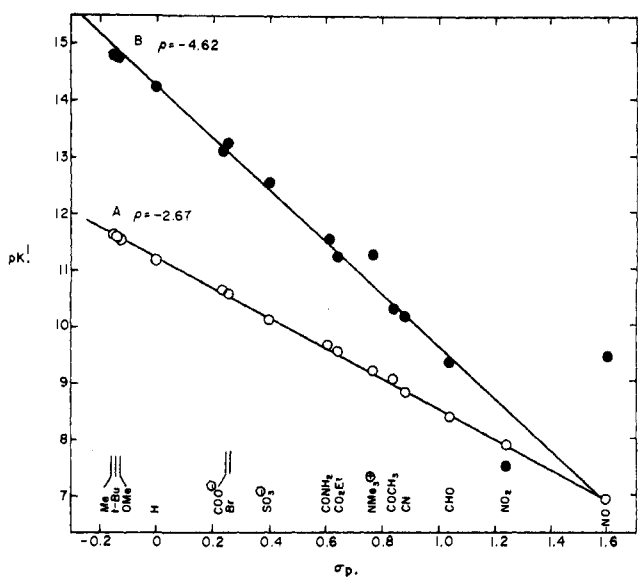


Fig. 2.—Correlation of pK' with σ_p (50% ethanol, 25°): A, 4-substituted phenols; B, 2,6-di-*t*-butyl-4-substituted phenols.

in Table I, column 4, and for 4-substituted 2,6-di-*t*-butylphenols in column 5. Because the acidities of several members of the latter series are similar to that of the solvent itself, their pK' values could not be determined by direct spectrophotometry or by titration.

However, use of the spectrophotometric extrapolation technique¹¹ (see Experimental and Fig. 3) furnished the data necessary to complete the series.¹²

Only those di-*t*-butylphenols which carry charged *p*-substituents (III, $R = -COO^-$, $-SO_3^-$, $-N(CH_3)_3^+$) are readily soluble in water. A greater number are soluble in aqueous alkali but precipitate upon addition of acid; however, at the low concentrations necessary for spectrophotometric pK measurements, optical densities for the undissociated phenols could be determined by acidification of alkaline solutions and immediate recording of the spectra. Precipitation of the phenol began, in most cases, 15–30 min. following acidification. By this method pK_a values were determined for a number of di-*t*-butylphenols and the results are recorded in Table I, column 3. Since the five remaining members of the series are insoluble in aqueous alkali, their pK_a values could not be determined.⁹

The entire series of measurements was, therefore, repeated using 50% (v:v) aqueous ethanol as solvent. The pH values of buffers in the mixed solvent system were determined using a glass electrode and no effort was made to obtain thermodynamic pK values by correcting for activities. The apparent pK values (pK') thus obtained for 4-substituted phenols¹⁰ are recorded

(9) Hypothetical pK_a values for these compounds may be obtained by extrapolation of curve B, Fig. 1, assuming a complete linear dependence of pK on substituent constant.

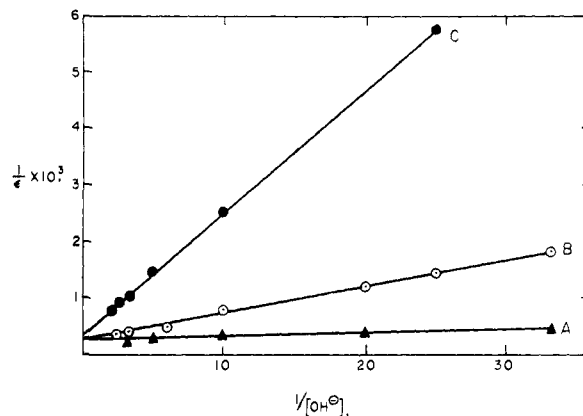


Fig. 3.—Determination of ϵ for 2,6-di-*t*-butyl-4-substituted phenols by spectrophotometric extrapolation: A, $R = Br$; B, $R = H$; C, $R = CH_3$.

in Table I, column 4, and for 4-substituted 2,6-di-*t*-butylphenols in column 5. Because the acidities of several members of the latter series are similar to that of the solvent itself, their pK' values could not be determined by direct spectrophotometry or by titration. However, use of the spectrophotometric extrapolation technique¹¹ (see Experimental and Fig. 3) furnished the data necessary to complete the series.¹²

TABLE I
VALUES OF pK AND σ FOR 4-SUBSTITUTED PHENOLS AT 25°

R	pK_a (H_2O)		pK' (50% EtOH)		σ_p ^a	σ_p ^b
	X = H	X = <i>t</i> -Bu	X = H	X = <i>t</i> -Bu		
CH ₃	10.26 ^c	(12.23) ^c	11.60	14.77	-0.15	-0.17
<i>t</i> -Bu	10.23	(12.19)	11.55	14.75	-0.14	-0.20
CH ₃ O	10.21 ^c	(12.15)	11.50	(14.82) ^d	-0.13 ⁱ	-0.27
H	9.99 ^c	(11.70)	11.16	14.22	0	0
COO ⁻	9.39	10.80	10.61	13.10	0.24	0.13
Br	9.36 ^c	(10.83)	10.57	13.23	.25	.23
SO ₃ ⁻	9.03 ^f	10.40	10.10	12.53	.40	.38
CONH ₂	8.56	9.53	9.65	11.52	.61	.63
CO ₂ Et	8.50	9.50	9.56	11.20	.64	.68
Me ₃ N ⁺	8.21 ^g	9.84	9.20	11.24	.77	.86
COCH ₃	8.05 ^h	8.68	9.06	10.27	.84	.87
CN	7.97 ⁱ	8.70	8.80	10.15	.88	1.00
CHO	7.60	8.05	8.40	9.33	1.04	1.13
NO ₂	7.15 ^c	6.65	7.89	7.49	1.24	1.27
NO	6.36 ^j	8.18	6.90	9.41	1.60	1.63 ⁱ

^a Values calculated for use in this investigation. ^b Values given by Jaffé (ref. 2b). ^c Ref. 8. The remaining pK values of column 2 were redetermined spectrophotometrically, confirming the literature values cited. ^d An experimental value could not be determined owing to the extreme sensitivity of an alkaline solution to oxygen. The value given is derived from infrared spectral data (see following paper). ^e Values in parentheses in column 3 are hypothetical and were obtained by extrapolation of curve B, Fig. 1. ^f E. E. Sager, M. R. Schooley, A. S. Carr, and S. F. Acree, *J. Research Natl. Bureau Standards*, **35**, 521 (1945). ^g S. Oae and C. C. Price, *J. Am. Chem. Soc.*, **80**, 3425 (1958). ^h F. G. Bordwell and G. D. Cooper, *ibid.*, **74**, 1058 (1952). ⁱ M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *ibid.*, **81**, 4226 (1959). ^j See ref. 7 for other instances in which *p*-CH₃O shows a low σ -constant.

Plots of σ_p vs. pK_a and pK' are shown in Fig. 1 and 2, respectively. Values of ρ were calculated by the method of least squares and are collected in Table II.

(10) Cf. G. Schwarzenbach and E. Rudin, *Helv. Chim. Acta*, **22**, 360 (1939). These workers have determined pK' values by titration for a number of substituted phenols in 48.9% ethanol. While several of our results agree well with the earlier values, significant differences appear in others.

(11) R. S. Stearns and G. W. Wheland, *J. Am. Chem. Soc.*, **69**, 2025 (1947); J. Hine and M. Hine, *ibid.*, **74**, 5266 (1952).

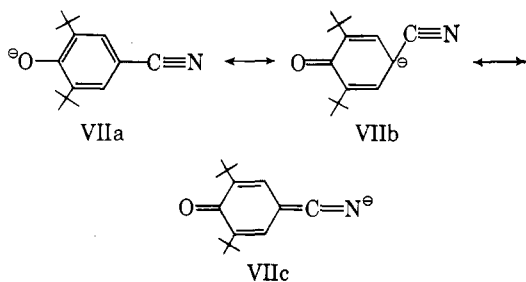
(12) The validity of the pK values obtained from extrapolation is amply confirmed by infrared spectral correlation (cf. following paper).

The ratio, $\rho pK'/\rho pK_a$, for the unhindered series is 1.20 and for the di-*t*-butyl series, 1.32. Therefore, the sensitivity to solvent change is of moderate size for both series. The value of ρ for ionization of 2,6-di-*t*-butylphenols shows a 57% deviation from additivity (where $B/A = 1.00$) in water and a 73% deviation in aqueous ethanol. Since ρ for the di-*t*-butyl series deviates so markedly from that for the unhindered series, it is apparent that any substituent constant derived for the 2-*t*-butyl group from pK data based on III ($R = H$) will not be valid for a 2,6-di-*t*-butylphenol with any other 4-substituent.^{13,14}

TABLE II
VALUES OF ρ FOR IONIZATION OF PHENOLS

	ρpK_a	$\rho pK'$
A. 4-R-phenol	-2.23	-2.67
B. 2,6-Di- <i>t</i> -Bu-4-R-phenol	-3.50	-4.62
B/A	1.57	1.73

As the σ value for R becomes more positive, an increasing fraction of the negative charge of the phenolate anion is diverted to the *p*-position (e.g., VIIa-c).² If it is assumed that the total number of solvent molecules necessary to solvate the negative charge is approximately constant with changing pK values,¹⁵ it is clear that the size of the solvent sphere at the phenolate oxygen should decrease as σ_p^- becomes more positive, i.e., as dispersion of charge increases, and that the deviation from additivity should diminish. Therefore, the extremely weak acidity of hindered phenols with $-\sigma_p$ substituents may be attributed to the inability of the R group to disperse the negative charge and solvent sphere and virtually the entire burden of solvation is placed on the phenolate oxygen.¹⁶ The data in Fig. 1 and 2 are in full accord with the above argument. A surprising result is seen, however, in the close correlation between σ_p^- and the pK values of the hindered phenols, indicating the extent of deviation from additivity, or the distribution of solvent density, to be itself linearly dependent on σ_p^- . When sufficient data are available, it should be possible to add a substituent-dependent solvation term to the Hammett equation.



An unusual feature of Fig. 1 and 2 may be seen in the fact that the Hammett plots intersect within the range of real σ values. It would, appear that, depending only on the identity of the 4-substituent, two bulky *o*-*t*-butyl groups may provide either steric hindrance or steric enhancement for ionization. Indeed, 2,6-di-*t*-butyl-4-nitrophenol is a *stronger* acid than 4-nitrophenol itself.¹⁷ A better understanding of

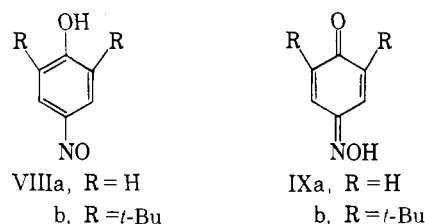
(13) K. U. Ingold (*Can. J. Chem.*, **38**, 1092 (1960)) has recently examined the correlation of phenolic hydroxyl stretching frequencies with σ . Since both di-*t*-butyl and unhindered phenols were found to have the same ρ values, it is evident that the anomalous behavior of hindered phenols described herein is probably limited to properties associated with ionization and solvation.

(14) Using an approximate σ value for *o*-*t*-butyl equivalent to σ_p (-0.14), III ($R = COCH_3$) shows a zero deviation from additivity in its pK_a value.

(15) Such an assumption is based on the concept that solvation number depends primarily on over-all dimensions of the species and total charge (see ref. 6).

(16) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

such paradoxical behavior on the part of an *o*-substituent is obtained from further study of two compounds which deviate markedly from the Hammett plots of Fig. 1 and 2, viz. III ($R = NO$ and $R = NO_2$).¹⁸ It has already been concluded from spectral data,¹⁹ and confirmed in the present work, that the tautomeric equilibrium between the nitrosophenol VIIIb and the quinone monoxime IXb lies almost entirely on the side of the latter. Although *p*-nitrosophenol VIIa is correspondingly tautomeric with quinone monoxime IXa,



the equilibrium is not as heavily one-sided and is solvent-dependent.^{19,20}

It is reasonable to assume, from its low pK value, that VIIIa dissociates normally, as a phenol. The unusually high pK value of VIIIb, however, suggests that its tautomer IXb is the species whose dissociation constant is being measured.²¹ Such behavior is to be expected, since the dissociation constant must represent the thermodynamically stable isomer.²²

The anomalous pK value for the nitro compound X cannot, however, be explained in the same way. Vaughan and Finch¹⁷ suggest that the negatively charged oxygen in the anion of X achieves special stabilization by hydrogen bonding with the adjacent *t*-butyl groups. Were this to be the case, smaller, but observable, pK deviations would be expected for other members of the series (III, $R = CHO, CN, COCH_3$, etc.); Fig. 1 and 2 demonstrate the absence of such deviations. The latter argument also excludes from consideration distortion from coplanarity of the phenolic O-H bond. Again, such an effect should not be limited to the nitro compound and, as is shown in the following paper,²³ spectral correlations indicate the achievement of maximal resonance by *all* members of the series. Any hypothesis based on a tautomeric equilibrium between X and XI is rendered difficult for several reasons: (a) infrared and n.m.r. spectral data in a variety of solvents indicate the equilibrium between X and XI to lie overwhelmingly on the side of the phenolic tautomer; (b) the pK values of aliphatic *aci*-nitronic acids are considerably lower than that found for X^{22c}; (c) the observed pK values were measured at equilibrium, which is established immediately, either from X or from its anion.^{22c}

(17) The unusually high acidity of III ($R = NO_2$) has been observed previously by W. R. Vaughan and G. K. Finch, *ibid.*, **21**, 1201 (1956).

(18) The deviation of the pK value of III ($R = NMe_3^+$) from correlation with σ_p^- and its other anomalous properties are considered in a later paper in this series.

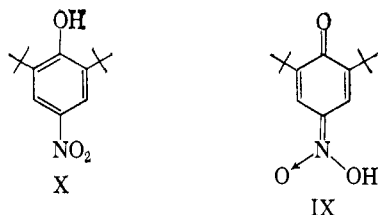
(19) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **27**, 651 (1962). In 50% ethanol, IXb had λ_{max} 305 m μ (ϵ 13,250), 420 m μ (ϵ 3500); $\nu_{max}^{C=O}$ 3570 cm.⁻¹ (2.80 μ) (hydroxyl) and 1640 cm.⁻¹ (6.10 μ) (carbonyl); n.m.r. (CCl₄): vinyl H quartet 6.98-7.65 p.p.m., $J = 3$ c.p.s.

(20) Infrared spectral data indicate the quinone monoxime form IXa to be highly favored in dilute CCl₄ solution. Cf. A. W. Baker, *J. Phys. Chem.*, **62**, 744 (1958); D. Hadzi, *J. Chem. Soc.*, 2725 (1956).

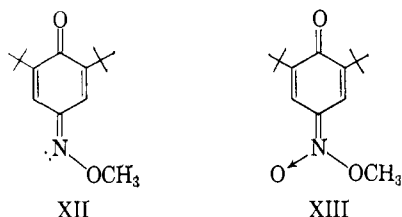
(21) pK values for authentic oximes, of comparable structure, are not available. Simple oximes, such as that of acetone, have pK values in the range of 12.0-12.5 (C. V. King and A. P. Marion, *J. Am. Chem. Soc.*, **66**, 977 (1944)).

(22) (a) G. Wheland, "Advanced Organic Chemistry," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, pp. 713-720; (b) L. K. Creamer, A. Fischer, B. R. Mann, J. Packer, R. B. Richards, and J. Vaughan, *J. Org. Chem.*, **26**, 3148 (1961); (c) S. Turnbull and S. H. Maron, *J. Am. Chem. Soc.*, **65**, 212 (1943).

(23) L. A. Cohen and W. M. Jones, *ibid.*, **85**, 3402 (1963).

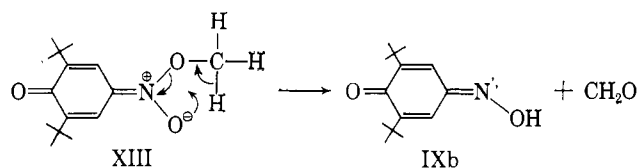


The action of diazomethane on *p*-cyanophenol, *p*-nitrosophenol, and *p*-nitrophenol leads exclusively to the corresponding anisoles. Since 2,6-di-*t*-butyl-4-cyanophenol also forms the corresponding anisole,²⁴ it is evident that diazomethane is not sterically prevented from reacting with a hindered phenol of sufficient acidity. Nevertheless, both the hindered nitrosophenol IXb and the hindered nitrophenol X react with diazomethane to form the respective iminoethers XII and XIII exclusively. Support for the quinonoid structures is derived from ultraviolet, infrared, and n.m.r. spectral data.



The latter data are of particular interest owing to the nonequivalent fields in the vicinity of the two ring-vinyl protons.²⁵ Not only do the protons exhibit distinct chemical shifts (see Experimental and ref. 19), but also show a significant coupling constant (3 c.p.s.), despite their separation by a cross-conjugated system.

Although XIII is a stable, orange compound, even in solution,²⁶ it decomposes at its melting point, or in hot solvents, to the quinone monoxime IXb and formaldehyde,²⁷ possibly *via* a cyclic process



The preparation of XII and XIII permits a comparison of ultraviolet spectral data for the quinonemethine ethers and for the phenolate anions of IXb and X, in which the quinonoid forms are probably dominant in the resonance hybrids. As shown in Table III, the anions absorb at considerably longer wave lengths than the quinonemethine ethers, demonstrating the fact that the energy needed for electron excitation is markedly decreased by the presence of the negative charge in the anionic species.²⁸

(24) E. Müller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Chem. Ber.*, **92**, 2278 (1959).

(25) Chemical shift differences arising from *syn-anti* isomerism in ketoximes may be observed in aromatic solvents, or if an aromatic ring is present in the molecule. See E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961).

(26) The *aci*-nitro methyl ether of 2-nitrophenol has been reported and found to be quite unstable (A. Hantzsch and H. Gorki, *Ber.*, **39**, 1073 (1906)). The corresponding *aci*-nitro ether of 4-nitrophenol could not be obtained by these workers. The stability of XIII should not be surprising, in view of the general tendency of 2,6-disubstitution to stabilize quinonoid and quinonemethine structures. Cf. L. J. Filar and S. Winstein, *Tetrahedron Letters*, No. **25**, 9 (1960); C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956); **81**, 1176 (1959).

(27) A similar decomposition of aliphatic *aci*-nitro methyl ethers has been described by F. Arndt and J. D. Rose, *J. Chem. Soc.*, 1 (1935). Such decomposition may be taken as additional proof for the assigned structure XIII.

(28) Strained 2,6-polymethylene-4-nitrophenolate anions also absorb in the range 450–458 m μ . See V. Prelog, K. Wiesner, W. Ingold, and O. Häfziger, *Helv. Chim. Acta*, **31**, 1325 (1948).

TABLE III
ULTRAVIOLET SPECTRAL DATA (50% EtOH)

	Neutral		Alkaline	
	λ , m μ	(ϵ)	λ , m μ	(ϵ)
IXb	305	(13,250)	382	(18,500)
XII	315	(19,500)		
X	325	(10,000)	450	(30,500)
XIII	355	(13,600)		

It is our opinion that the anomalously high acidity of the hindered nitrophenol X is related to a facile tautomerism between X and XI, but in a manner which is neither obvious nor explicable by the usual mathematical analysis of tautomeric systems.²²

Experimental²⁹

Materials.—Commercial phenols were purified as necessary. 4-Hydroxybenzamide^{30a} and 4-hydroxyphenyltrimethylammonium chloride^{30b} were prepared according to published procedures.

2,6-Di-*t*-butylphenol is commercially available, as are its 4-methyl and 4-*t*-butyl homologs. The 4-methoxy and 4-acetyl³¹ derivatives were the gift of Dr. H. Cahnmann of this Institute; the 4-nitrophenol was provided by the Ethyl Corporation, Detroit, Mich. The preparation of several hindered phenols has been described in earlier papers of this series: 4-formyl-,¹⁵ 4-cyano-,¹⁵ 4-carboxy-,¹⁵ 4-carbomethoxy-,¹⁵ 4-bromo-,¹⁵ and 4-carboxamido-2,6-di-*t*-butylphenol.²⁹ The 4-nitrosophenol was prepared by nitrosation of 2,6-di-*t*-butylphenol using sodium nitrite in acetic acid.³²

3,5-Di-*t*-butyl-4-hydroxybenzenesulfonic Acid.—To a solution of 0.25 g. of 2,6-di-*t*-butyl-4-mercaptophenol³³ in 10 ml. of 97% formic acid was slowly added 1 ml. of 30% hydrogen peroxide, with ice cooling. The mixture was stored at room temperature overnight, excess performic acid reduced by saturation with sulfur dioxide, and the mixture concentrated *in vacuo* to a colorless oil. The sulfonic acid was extracted from the oil with warm chloroform and crystallized from chloroform-ligroin as hydrated prisms or as plates, m.p. 100–105°.

Anal. Calcd. for C₁₄H₂₀SO₄·H₂O: C, 55.24; H, 7.95; S, 10.53. Found: C, 55.25; H, 7.88; S, 11.13.

Water of hydration could not be removed without decomposition of the acid. The compound is readily soluble in water, giving a strong acid reaction.

3,5-Di-*t*-butyl-4-hydroxyphenyltrimethylammonium Chloride.—In early experiments, 2,6-di-*t*-butyl-4-nitrophenol was hydrogenated in the usual manner and the mixture worked up to obtain the aminophenol. The latter compound, however, was found to be extremely sensitive to oxidation³⁴ and, in subsequent runs, the amine was methylated *in situ*. Hydrogenation was performed in a round-bottom flask suitable for subsequent reflux operations without transfer of the contents as follows:

To a solution of 7.5 g. of 2,6-di-*t*-butyl-4-nitrophenol in 150 ml. of purified dioxane was added 2 g. of 10% palladium-charcoal and 10 ml. of 6 *N* hydrochloric acid. The calculated amount of hydrogen was absorbed in ca. 48 hr. and the flask was then flushed with a stream of purified nitrogen while 20 g. of powdered, anhydrous sodium carbonate and 25 ml. of methyl iodide were added. The mixture was refluxed with magnetic stirring and protection from air for 16 hr. Following filtration, the hot dioxane solution was concentrated to a red solid. Despite repeated purifications, the quaternary ammonium iodide could not be freed of color (probably due to free iodine); it was converted to the chloride by shaking a methanolic solution with wet, freshly prepared silver chloride. The colorless filtrate was concentrated to dryness and the quaternary ammonium chloride crystallized from dichloromethane-ligroin as fine needles (75% yield), m.p. 212–214°. Analysis and infrared spectra indicated the material to be hydrated. Several attempts to dehydrate the compound at elevated temperatures resulted only in decomposition with partial loss of halogen.

Anal. Calcd. for C₁₇H₃₀NOCl·H₂O: C, 64.23; H, 10.15; N, 4.41; Cl, 11.15. Found: C, 64.08; H, 10.36; N, 4.51; Cl, 11.15.

(29) Melting points were determined on a Kofler block and are uncorrected. Ultraviolet spectra were determined on a Cary recording spectrophotometer, Model 14. Infrared spectra were measured on a Perkin-Elmer Infracord; n.m.r. spectra were obtained on a Varian A-60 spectrometer.

(30) (a) L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **84**, 1625 (1962); (b) H. v. Pechmann, *Ber.*, **32**, 3682 (1899).

(31) T. Matsuura, A. Nishinaga, and H. J. Cahnmann, *J. Org. Chem.*, **27**, 3620 (1962).

(32) Preparation of this compound by nitrosation in ethanol has recently been described (ref. 19).

(33) Gift of the Consolidated Coal Co., Library, Pa.

(34) T. J. Barnes and W. J. Hickinbottom, *J. Chem. Soc.*, 953 (1961), have observed a similar sensitivity of the aminophenol to oxygen.

TABLE IV
 ULTRAVIOLET SPECTRAL BANDS FOR 4-SUBSTITUTED PHENOLS (50% EtOH)

R	First primary band				Secondary band			
	$\lambda_{\max}^{\text{HCl}}$, m μ	ϵ	$\lambda_{\max}^{\text{NaOH}}$, m μ	ϵ	$\lambda_{\max}^{\text{HCl}}$, m μ	ϵ	$\lambda_{\max}^{\text{NaOH}}$, m μ	ϵ
H	211	6,400	232	10,300	271	1650	288	2625
CH ₃	219	6,550	239	9,350	278	1800	296	2550
<i>t</i> -Bu	219	8,000	238	12,000	275	1800	292	2600
OCH ₃	226	7,500	242	9,700	288	2770	306	3200
Me ₂ N [⊕]	220	7,700	243	11,100	272	1380	288	2250
Br	223	10,300	244	13,700	281	1500	300	2350
SO ₃ [⊖]	228	11,600 ^a	253	16,500	272	925	282	2520
CO ₂ [⊖]	244	12,500 ^b	278	16,350				
COOH	255	13,900						
CONH ₂	252	14,500	292	20,400				
CO ₂ Et	255	18,350	296	25,400				
CN	247	19,000	282	22,600				
COCH ₃	277	15,800	327	25,800				
CHO	285	16,700	336	24,800				
NO ₂	316	10,600	401	20,500				
NO	303	18,100	403	32,500				

^a At pH 3. ^b At pH 7.

 TABLE V
 ULTRAVIOLET SPECTRAL BANDS FOR 2,6-DI-*t*-BUTYL-4-SUBSTITUTED PHENOLS (50% EtOH)

R	First primary band				Secondary band			
	$\lambda_{\max}^{\text{HCl}}$, m μ	ϵ	$\lambda_{\max}^{\text{NaOH}}$, m μ	ϵ	$\lambda_{\max}^{\text{HCl}}$, m μ	ϵ	$\lambda_{\max}^{\text{NaOH}}$, m μ	ϵ
H	214	6,250	244	11,000 ^e	271	1600	295	3630 ^e
CH ₃	222	6,900	250	10,600 ^e	278	1800	303	3780 ^e
<i>t</i> -Bu	223	9,500	251	10,200 ^e	272	1700	300	3450 ^e
OCH ₃	229	8,200			285	3400		
Me ₂ N [⊕]	224	6,350	261	8,800	270	1025	298	4200
Br	226	11,500	257	16,000	280	1275	305	3580
SO ₃ [⊖]	233	12,300 ^a	270	18,400	272	1150	300 ^d	3000
CO ₂ [⊖]	250	13,700 ^b	302	20,400				
COOH	260	13,300						
CONH ₂	258	12,000	321	22,200				
CO ₂ Et	261	14,800	324	29,600				
CN	252	16,900	307	31,200				
COCH ₃	284	13,300	363	32,500				
CHO	293	15,000	370	38,400				
NO ₂	325	10,000	450	30,500				
NO	305	13,250	382	18,500				

^a At pH 3. ^b At pH 7. ^c Spectra could not be measured for the anion because of rapid oxidation to quinone. ^d λ_{\max} and ϵ are estimated values, the band at 300 m μ appearing as a shoulder on the 270 m μ first primary band. ^e Values of ϵ for the anions were determined by spectral extrapolation (ref. 11).

2,6-Di-*t*-butylbenzoquinone-4-oxime Methyl Ether (XII).—To a solution of 2,6-di-*t*-butyl-4-nitrosophenol (VIIb) in ether was added an excess of ethereal diazomethane and the mixture was stored for several days in the dark. The reaction mixture was taken to dryness, the residue extracted with petroleum ether (30–40°) and the extract absorbed on a column of neutral alumina. Following elution of the column with ligroin (60–70°), the product was obtained as a pale yellow solid which was recrystallized from acetonitrile-water as needles, m.p. 81–81.5°; $\lambda_{\max}^{\text{EtOH}}$ 315 m μ (ϵ 19,500); $\nu_{\max}^{\text{CCl}_4}$ 1634 cm.⁻¹ (6.12 μ) (s), 1585 cm.⁻¹ (6.31 μ) (m); n.m.r. (CCl₄): CH₃O 4.10 p.p.m.; vinyl H quartet 6.81–7.35 p.p.m., $J = 3$ c.p.s.

Anal. Calcd. for C₁₆H₂₃NO₂: C, 72.25; H, 9.30. Found: C, 72.09; H, 9.23.

When methylation of VIIb was attempted with dimethyl sulfate and alkali, 3,5,3',5'-tetra-*t*-butyldiphenoquinone was the only product isolated.

2,6-Di-*t*-butyl-4-nitrophenol-*aci*-methyl Ether (XIII).—A solution of 2,6-di-*t*-butyl-4-nitrophenol in ether was treated with ethereal diazomethane. A brisk evolution of nitrogen was accompanied by the development of a deep red color. After several hours, the solvent was removed and a solution of the residue adsorbed from ligroin onto neutral alumina. The column was eluted with ligroin (60–70°) and the orange, crystalline product recrystallized from petroleum ether (30–40°). The methyl ether melted at 105–106° in a bath preheated to 90°. When the temperature of the bath was raised slowly, the compound underwent a transition in form and color at 105° and finally melted at 210–215°. The higher melting material was identified as VIIb. When a sample of XIII was heated to 110° in a test tube, a white solid sublimed onto the walls of the tube, identified as a polymer of formaldehyde by conversion to the

2,4-dinitrophenylhydrazone of formaldehyde. The residual material was identified as the oxime VIIb by mixture melting point and ultraviolet and infrared spectra. The same transformation was observed by heating XIII in solution in toluene or dioxane; $\lambda_{\max}^{\text{EtOH}}$ 355 m μ (ϵ 13,600); $\nu_{\max}^{\text{CCl}_4}$ 1653 cm.⁻¹ (6.05 μ) (m), 1625 cm.⁻¹ (6.15 μ) (s); n.m.r. (CCl₄): CH₃O, 3.95 p.p.m., vinyl H quartet 7.28–7.55 p.p.m., $J = 3$ c.p.s.

Anal. Calcd. for C₁₅H₂₃NO₄: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.02; H, 8.63; N, 5.24.

Determination of Dissociation Constants in Water.—Spectral measurements and calculations were performed according to the standard procedure³⁵ using buffer salts supplied by the National Bureau of Standards. Values of λ_{\max} and ϵ for the various phenols and phenolate ions are summarized in Tables IV and V. Calculations were based on optical density values taken from the long wave length slope of the spectral curve.³⁶ All operations were performed in a constant temperature room at 25°. A dilute, aqueous solution of the phenol (0.5 ml.) was added to 2.5 ml. of acid, alkali, or buffer in a 3-ml. silica cell and the stoppered cell allowed to reach temperature equilibrium.³⁷ Following spectral measurements, pH values of the solutions were determined using a Beckman Model G pH meter; no significant changes from the

(35) R. A. Robinson in "Structure of Electrolytic Solutions," W. J. Hamer, Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, Chapter 16.

(36) In the case of III (R = SO₃⁻), spectral peaks in acid occurred at 234 and at 272 m μ . In alkali, the 234 m μ shifted to 270 m μ , completely masking the longer wave length band by its higher extinction coefficient. Accordingly, the short wave length slope was used in pK calculations.

(37) The high sensitivity to oxygen of the di-*t*-butylphenols, particularly in alkaline media, necessitates the use of a cell containing minimal air space.

pH values of the original, undiluted buffers were observed; pK values were calculated according to eq. 1 where a is the optical density of a solution of the phenol in acid at a given wave length,

$$pK = pH + \log(b - \epsilon/\epsilon - a) - \log \gamma \quad (1)$$

b the optical density of the phenolate anion at the same wave length, and ϵ the optical density in a buffer medium of known pH; $\log \gamma$ is a small correction (0.05-0.10 pK unit) for the activity coefficient of the buffer.³⁸

For those di-*t*-butylphenols which were insoluble in water, solutions were prepared in 0.01 *N* sodium hydroxide. When such solutions were diluted to concentrations appropriate to spectral measurement, the additional ions made a negligible change in the ionic strength of the buffer. However, pH values of the buffers were altered slightly, and the values of pH used in pK_a calculations were those obtained by direct measurement of the spectral sample.

Determination of Dissociation Constants in 50% Ethanol.—Acid, alkaline, and buffer media were prepared as above, at twice the ionic strength, and each diluted with ethanol in the volume ratio 3:2. Volume changes accompanying such a procedure were disregarded. When 2.5 ml. of each solution was mixed with 0.5 ml. of ethanol containing a low concentration of the phenol, the final solution (3.0 ml.) was 50% in ethanol and at the same ionic strength as the aqueous buffer mixture. Immediately following spectral measurements, pH values of the spectral samples were determined, using a blue tip electrode (Beckman Type E-2) for such highly alkaline media. Microbeakers containing the buffer solution were fitted with polyethylene caps and a stream of purified nitrogen passed through during the measurement to exclude both oxygen and carbon dioxide. Since meter readings drifted gradually in the mixed solvent system, the average of three readings, taken at 2-min. intervals immediately following immersion of the electrodes, was used. Calculations were based on apparent pH values determined in this way as far as a meter reading of pH 12. For those phenols which were too weakly acidic to ionize sufficiently at pH 12, the following extrapolation procedure was used.

(38) A number of values for $\log \gamma$ were taken from the literature: see D. T. Y. Chen and K. J. Laidler, *Trans. Faraday Soc.*, **58**, 480 (1962); A. I. Biggs, *ibid.*, **52**, 35 (1956).

Determination of pK Values by Spectral Extrapolation.¹¹—Carbonate-free *M* sodium hydroxide and *M* potassium chloride were mixed in appropriate ratios to yield solutions varying in alkali content from *M* to 0.001 *M* and of constant ionic strength. Each solution (50 ml.) was diluted with 33.3 ml. of ethanol and stored in a polyethylene bottle under nitrogen. Titration of the solutions at 3-day intervals demonstrated that their alkali content did not drop appreciably over several weeks at 0°. Ethanolic solutions of di-*t*-butylphenols (0.5 ml.) were added to 2.5 ml. of aqueous, ethanolic alkali and optical density determined at a wave length at which the contribution to spectral absorption of the undissociated phenol was small. When values of D/c ($=1/\epsilon'$, where ϵ' = apparent extinction coefficient) were plotted against $1/[\text{OH}^-]$, straight line plots were obtained (Fig. 3) whose slopes and intercepts were calculated by the method of least squares. Since the intercept on the ordinate corresponds to $1/\epsilon$, the true extinction coefficient for the phenolate ion may be calculated, although it is spectrophotometrically inaccessible. The dissociation constant for the weak acid (K_a) may be obtained from the equation¹¹ $K_a = K_s/m\epsilon$, where m is the slope of the line, ϵ the true extinction coefficient, and K_s the ion product for the solvent. Although ion products are known for both water and ethanol,³⁹ no data were available for 50% ethanol. A value for K_s (50% ethanol) was obtained indirectly by applying the extrapolation technique to several phenols whose pK values had been determined by the spectrophotometric procedure described above, but which were sufficiently weak to remain incompletely dissociated in 0.001 *M* to 0.05 *M* alkali (e.g., III, R = Br, COO⁻). From the slopes and intercepts obtained for these phenols, values of K_s were calculated. A mean value of $1.2 \pm 0.2 \times 10^{-15}$ was obtained, which was then used in K_a calculations for less acidic phenols.

Acknowledgments.—The authors are indebted to Mr. H. G. McCann and his associates of this Institute for performing the microanalyses, to Dr. E. D. Becker and Mr. R. B. Bradley for measurement of n.m.r. spectra, and to Dr. H. A. Saroff for valuable discussion.

(39) From estimated data of P. Ballinger and E. A. Long (*J. Am. Chem. Soc.*, **82**, 795 (1960)), a K_s value of 1.7×10^{-15} (6% aqueous ethanol) may be calculated.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MD.]

A Study of Free Energy Relationships in Hindered Phenols. Correlation of Spectral Properties with Substituent Constants¹

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RECEIVED JANUARY 26, 1963

A linear correlation of ultraviolet spectral data with substituent parameters has been achieved for 4-substituted phenols, 2,6-di-*t*-butyl-4-substituted phenols, and for their corresponding anions. The incorporation of both electron-withdrawing and electron-releasing substituents into a single slope was achieved by: (a) the use of $\Delta\nu$, the difference in the ultraviolet frequencies of the 4-substituted phenol and the corresponding monosubstituted benzene, and (b) the use of σ_R' , a new resonance parameter. The latter was calculated as $\sigma_p - (2/3)\sigma_m$ on the basis that the inductive effect of a substituent in the *p*-position is only two-thirds as great as when in the *m*-position. From the fact that ρ (ultraviolet spectral shifts) for the 2,6-di-*t*-butylphenols is only slightly greater than that for the unhindered phenols, it is concluded that the phenolic O-H bond is coplanar with the aromatic ring in the former series. Chemical shifts for the hydroxyls in the n.m.r. spectra of hindered phenols have been shown to vary linearly with σ_p^- . Similarly, a linear dependence on σ_p^- is demonstrated for the infrared stretching frequencies of the phenolic hydroxyl groups.

The demonstration that the pK values of 2,6-di-*t*-butylphenols vary directly with σ -constants for 4-substituents, but with almost twice as great a ρ value as in the unhindered series,¹ prompted us to attempt the correlation of other physical properties of the hindered phenols with substituent parameters. Accordingly, their ultraviolet, nuclear magnetic resonance, and infrared spectra have been examined and are discussed in sequence.

The conformation of the hydroxyl group is a matter of particular interest in the chemistry of 2,6-di-*t*-butylphenols. Space-filling models indicate that the proton of a planar phenolic hydroxyl is barely accommodated between two CH₃'s of an adjacent *t*-butyl group. Al-

ternatively, the O-H bond may be rotated about the C-O axis until it is perpendicular to the aromatic plane. Should coplanarity of the O-H bond with the aromatic ring be altered to any extent, overlap of the *p*-electrons of oxygen with the aromatic π -system would be impaired, as would resonance coupling between the phenol and a 4-substituent.² The infrared stretching frequencies of phenolic hydroxyl groups have been shown to vary linearly with σ_p values for 4-substituents, both in the simple and in the 2,6-di-*t*-butyl series.³ Since ρ was found to be the same for both series, it was con-

(2) L. L. Ingraham, in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 11; R. W. Taft, Jr., and H. D. Evans, *J. Phys. Chem.*, **61**, 1427 (1957); B. M. Wepster, *Rec. trav. chim.*, **76**, 335, 357 (1957).

(3) K. U. Ingold, *Can. J. Chem.*, **38**, 1092 (1960), and references cited therein.

(1) Paper VI of a series on phenol-dienone tautomerism. For paper V, see L. A. Cohen and W. M. Jones, *J. Am. Chem. Soc.*, **85**, 3397 (1963).