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SUBSTITUENT EFFECTS ON THE RATE OF ACID-CATALYZED PROTON EXCHANGE OF PHENOL IN METHANOL*

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Abstract—OH-proton exchange of phenol in methanol containing HCl is catalyzed by methyloxonium ion; the second-order rate constant is $7{\cdot}3 \times 10^5$ sec^{-1} M^{-1} at −80°; $\Delta H^{\ddagger} = 4{\cdot}7$ kcal; $\Delta S^{\ddagger} = -6{\cdot}6$ gibbs. Substituent effects are large, in spite of the high reactivity. The effects of a *para*-substituent are described fairly well by the Bronsted and Hammett relationships. The effects of an *ortho*-substituent can be analyzed into polar and steric contributions. *ortho*-Disubstitution by bulky substituents results in an unexpectedly high rate constant in the case of 2,6-dibromophenol and 2,6-di-t-butylphenol.

Proton transfer from an acid to a base is often found to be a termolecular reaction in which an amphiprotic molecule participates. In most examples the amphiprotic molecule is a molecule of the hydroxylic solvent.[1-3] However, in the case of acid-catalyzed OH-proton exchange between phenol (present as a solute in methanol) and methanol, the reaction that takes place is probably (1) and the amphiprotic molecule is probably a molecule of phenol, the solute.[4]

$$\mathrm{Me{-}\overset{H}{\overset{|}{O}}{}^{\oplus}{-}H + \overset{Ar}{\overset{|}{O}}{-}H + \overset{H}{\overset{|}{O}}{-}Me \rightarrow Me\ \overset{H}{\overset{|}{O}} + H{-}\overset{Ar}{\overset{|}{O}}{}^{\oplus} + H{-}\overset{H}{\overset{|}{O}}{-}Me} \qquad (1)$$

Evidence in favor of this mechanism includes the following: For the analogous acid-catalyzed proton exchange of phenol in *water* it has been shown, on the basis of the known basicity of phenol in water, that reaction is far too fast to permit a mechanism in which $ArOH_2^+$ is a reaction intermediate.[5] For the analogous acid-catalyzed proton exchange between methanol molecules in *methanol* it has been shown, by an analysis of the anamolous conductance of $MeOH_2^+$, that reaction cannot be bimolecular; a termolecular process analogous to (1) can accommodate the facts.[6,†]

In this paper we examine the effect of *ortho*- or *para*-substitution in the Ph group on the rate constant for OH-proton exchange of phenol in anhydrous methanol, catalyzed by methyloxonium ion. Rate measurements were made by the NMR method,[4] mostly at −80°. Anhydrous HCl served as the source of $MeOH_2^+$ and was

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[†] The rate constant, *k*, for termolecular reaction involving $MeOH_2^+$, MeOH and MeOH by the mechanism of Eq. (1) is given by $k_{MeOH_2^+}/[MeOH]$, or 5×10^8 sec^{-1} M^{-1} at −80°; see Eq. 26 and data in the loc cit

assumed to be completely ionized and dissociated. The reaction kinetics was second-order for all substrates, according to Eq. (2), which also defines the rate constant k.

$$\text{Rate of OH-proton exchange} = k[\text{ArOH}][\text{MeOH}_2^+] \tag{2}$$

Kinetic results are summarized in Table 1. It is seen that substituent effects on k are large, in spite of the high reaction rates: At −80°, k varies by almost three orders of magnitude. These results will now be interpreted on the basis of the mechanism shown in Eq. (1). The data to be used in this interpretation are summarized in Table 2. Variables are defined as follows.

$$\delta_R \log k = \log k(\text{ArOH}) - \log k(\text{Phenol}) \tag{3a}$$

$$\delta_R pK_A = pK_A(\text{ArOH}) - pK_A(\text{Phenol}) \tag{3b}$$

σ and σ^- are substituent parameters used in the Hammett equation.[7] Values of $\delta_R pK_A$ are listed for two solvents, "alcohol" (methanol or 95% ethanol–5% water) and water. In spite of certain interesting differences, the dominant impression is one of similarity. In what follows, we shall use the $\delta_R pK_A$ values as determined in "alcohol",[8–11] but our qualitative conclusions would be unchanged if we used the values determined in water.[12, 13]

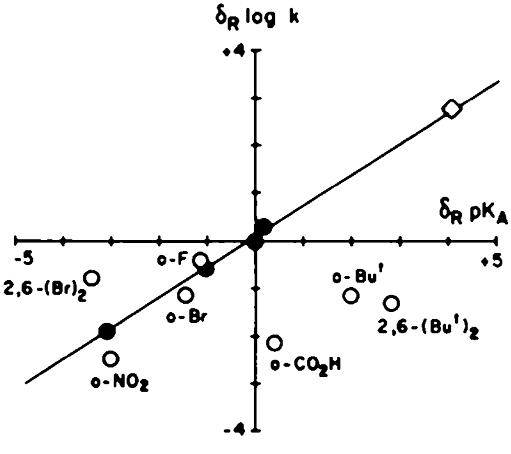


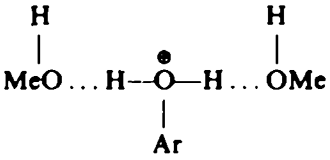
Fig. 1 Relationship of $\delta_R \log k$ (in methanol at −80°) to $\delta_R pK_A$ (in "alcohol" at 25°) for substituted phenols. Data from Table 2. Solid circles, left to right: p-NO$_2$, p-Br, H, p-t-Bu; diamond, methanol.

Figure 1 shows the relationship of $\delta_R \log k$ to $\delta_R pK_A$. Substituent effects may be divided into two groups. (1) The *para*-substituents show a strong trend for log k to increase linearly with pK_A. The line representing this trend also fits the point for methanol,[6][*][†] a much weaker acid. (2) The *ortho*-substituents do not show any simple relationship.

[*] $pK_A(\text{MeOH}) = pK_{\text{autoprotolysis}}/[\text{MeOH}] = 18{\cdot}3$ in methanol at 25°.

[†] It should be noted that the Bronsted relationship for *para*-substituted phenols and methanol in Fig. 1 shows no curvature in spite of the fact that k approaches the magnitude to be expected for diffusion-controlled reaction. Curvature of the Bronsted relationship as reactivity increases is of considerable current interest.[14]

We interpret these results as follows. In the absence of proximity effects caused by *ortho*-substituents, there is a simple linear free energy relationship such that log k increases with the *basicity* of the amphiprotic molecule. We regard basicity as the fundamental variable—the fairly good linear relationship with pK_A results from the tendency of the basicity of the O atom to decrease as the acid strength of ArOH increases. The substantial magnitude of *para*-substituent effects suggests that the valence bond structure (4) makes a substantial contribution to the resonance hybrid in the transition state.



$$\overset{\mathrm{H}\atop |}{\mathrm{MeO}}\ldots\mathrm{H}-\underset{|\atop \mathrm{Ar}}{\overset{\oplus}{\mathrm{O}}}-\mathrm{H}\ldots\overset{\mathrm{H}\atop |}{\mathrm{OMe}} \qquad (4)$$

The scatter of the points for the *ortho* substituents about the straight line in Fig. 1 shows that proximity effects are important and specific. That is to say, the ortho-effects on δ_R log k involve interaction mechanisms that are quite different from those involved in $\delta_R pK_A$. One is reminded, by contrast, of *ortho*-effects in acid- and base-catalyzed ester hydrolysis where the interaction mechanisms seem to be identical.[15] We are puzzled by this contrast, because the transition states in acid- and base-catalyzed ester hydrolysis differ with respect to structure, protonation and charge type in somewhat the same way as do (4) and ArO^-.

We now wish to analyze *ortho*-effects on log k for phenols with one *ortho*-substituent into polar and steric contributions, using the method of Taft.[15] First, we fit the Hammett equation to the data for phenol and *para*-substituted phenols, obtaining the line shown in Fig. 2. For reactions of phenol derivatives one would normally use σ^-, but we found that σ^- would not fit the point for *p*-nitrophenol, presumably because the sort of electron-releasing resonance that is important in *p*-nitrophenoxide ion is unimportant in a transition state that resembles $ArOH_2^+$. To fit the point for *p*-nitrophenol we use an "effective" σ which is a linear combination of σ and σ^-,[16] Eq. (5).

$$\sigma_{eff} = 0{\cdot}66\sigma + 0{\cdot}34\sigma^- \qquad (5)$$

Next, we use *ortho*-sigma values listed by Taft[15]* and the straight line versus σ_{eff} established by the *para*-substituents to estimate the polar contribution to δ_R log k for each *ortho*-substituent. These estimates are then compared with the experimental δ_R log k, and the differences, which we shall call X_S, are calculated. The method is shown in Fig. 2. There are several indications (Table 3) that X_S could result largely from steric interactions: The point for *ortho*-fluoro is virtually on the same line with the *para*-substituents; this fact is consistent with the small size of the F atom—its van der Waals radius is only slightly larger than that of the H atom. For the other substituents, X_S increases roughly in the order of the van der Waals radius and/or of Taft's steric parameter E_S.

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* There is considerable variation in *ortho*-sigma values obtained by different methods.[17]

TABLE 1. KINETIC RESULTS FOR OH-PROTON EXCHANGE OF SUBSTITUTED PHENOLS IN METHANOL

Substituent	Temp(°C)	k(sec^{-1})	ΔH‡(kcal)	ΔS‡(gibbs)
H	−42·5	$6·34 \times 10^6$	4·7	−6·6
	−80·0	$7·3 \times 10^5$	—	
p-Bu^t	−80·0	$1·41 \times 10^6$		—
p-Br^a	−80·0	$2·1 \times 10^5$	—	
p-NO$_2$	−20·0	$4·35 \times 10^5$	5·8	−9·3
	−49·6	$9·18 \times 10^4$		—
	−80·0	$9·2 \times 10^3$	—	
o-Bu^t	−80·0	$5·18 \times 10^4$		—
o-F	−80·0	$2·85 \times 10^5$	—	
o-Br	−80·0	$5·34 \times 10^4$		
o-NO$_2$	−80·0	$2·42 \times 10^3$	—	—
o-CO$_2$H^b	−80·0	$5·4 \times 10^3$	5·5	−11·9
2,6-(Br)$_2$	−41·9	$1·19 \times 10^6$	4·9	−9·0
	−80·0	$1·21 \times 10^5$	—	—
2,6-(Bu^t)$_2$	0·0	$1·13 \times 10^6$	4·1	−15·8
	−29·8	$4·06 \times 10^5$	—	
	−80·0	$3·59 \times 10^4$		—

[a] Ref. 4. [b] Ref. 22.

TABLE 2. DATA USED IN THE ANALYSIS OF SUBSTITUENT EFFECTS IN THE ACID-CATALYZED OH-PROTON EXCHANGE OF PHENOL IN METHANOL

Substituent	$\delta_R \log k$^{a}	$\delta_R pK_A$ at 25°^{a}		
	MeOH, −80°	"alcohol"	water^b	$\sigma(\sigma^-)^c$
p-Bu^t	0·29	0·19^d		−0·197
p-Br	−0·54	−0·98^e	−0·66	0·232
p-NO$_2$	−1·90	−3·04^{e,h}	−2·85	0·778(1·27)
o-Bu^t	−1·15	2·01^d	—	(−0·197)
o-F	−0·41	−1·12^f	−1·29	0·24
o-Br	−1·13	−1·44^e	−1·55	0·21
o-NO$_2$	−2·48	−3·00^e	−2·79	0·80(1·22)
o-CO$_2$H	−2·13	0·42^g		0·45(0·73)
2,6-(Bu^t)$_2$	−1·31	2·84^{d,e}	—	−0·39
2,6-(Br)$_2$	−0·78	—	−3·4	0·42

[a] Eqs 3.
[b] Refs 12, 13.
[c] Refs 7 and 15.
[d] MeOH; Refs 8 and 9.
[e] 95% EtOH-5% HOH; Ref. 10.
[f] 30% EtOH-70% HOH; Ref. 11.
[g] o-CO$_2$CH$_3$.
[h] −3·0 in MeOH, Ref. 8.

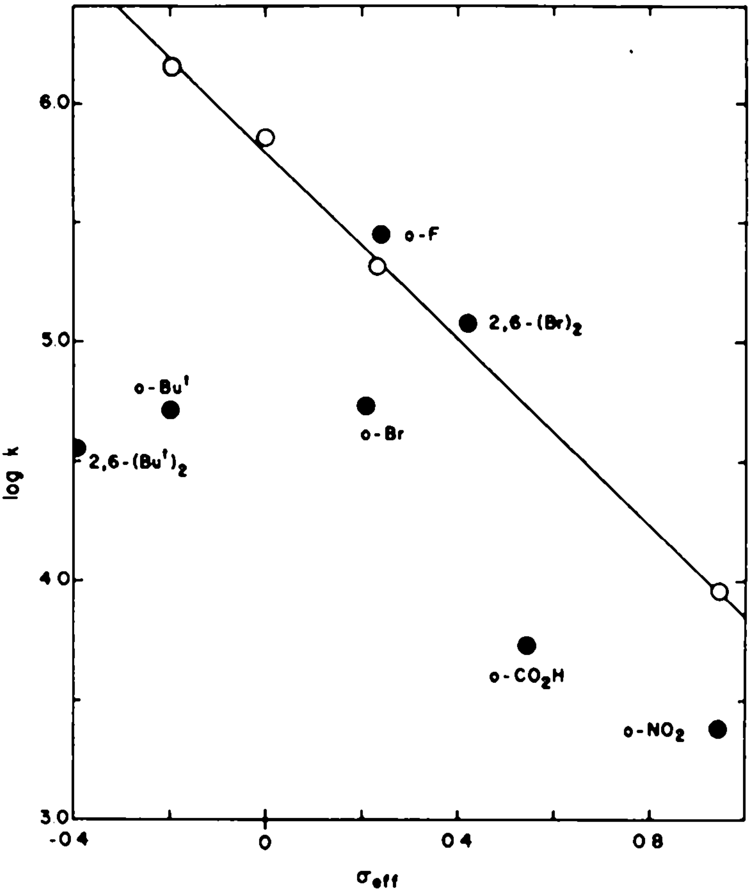

FIG. 2. Analysis of *ortho*-substituent effects on log k (in methanol at $-80°$) by the method of Taft.[15] The straight line represents the equation, $\log k = 5\cdot81 - 1\cdot95\,\sigma_{eff}$; $\sigma_{eff} = 0\cdot66\,\sigma + 0\cdot34\,\sigma^-$. X_s is the vertical displacement from the $\rho\sigma_{eff}$ line.

While the preceding substituent effects conform to well-known patterns, the effect of *ortho*-disubstitution is unusual. We would have expected X_S for a sterically hindered 2,6-disubstituted phenol to be at least twice as large (in absolute value) as that for the corresponding monosubstituted phenol. As a matter of fact, X_S for 2,6-(Bu^t)$_2$ is only slightly more negative than that for *o*-Bu^t, and 2,6-(Br)$_2$ actually reacts *faster* than does *o*-Br, so that X_S is slightly positive. (Table 3). Apparently, symmetrical 2,6-disubstitution by bulky substituents stabilizes the transition state relative to the ground state by a mechanism that is otherwise inactive.

For 2,6-di-t-butylphenol there is consistent evidence of marked steric inhibition of hydrogen bonding. For example, association constants for the formation of hydrogen-bonded complexes between ArOH and pyridines, ketones and ethers in carbon tetrachloride are much greater for *o*-Bu^t than for 2,6-(Bu^t)$_2$.[18,19] Para-substituent effects on pK_A are substantially greater for 2,6-di-t-butylphenol than for

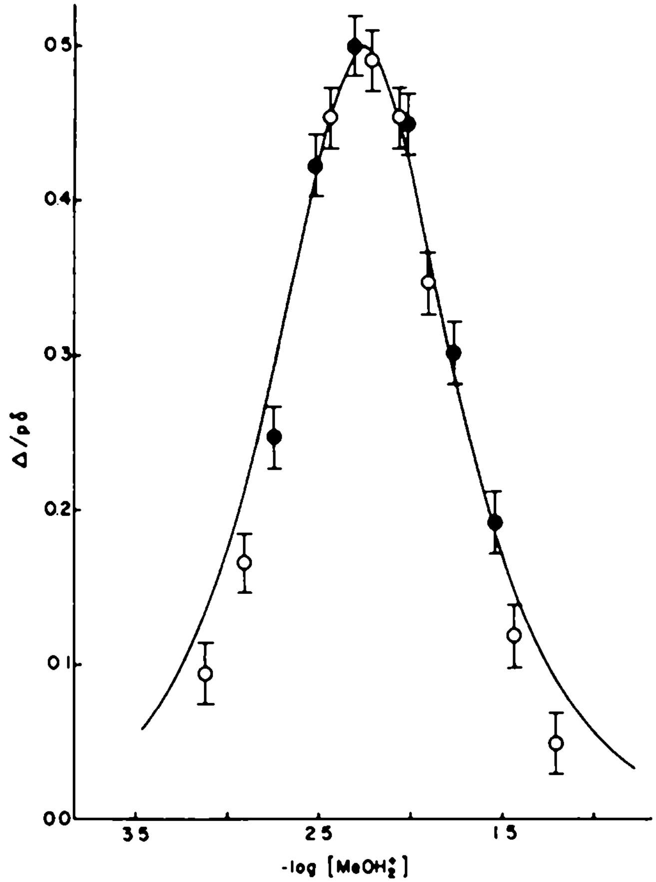

FIG. 3 NMR data for *o*-fluorophenol in methanol at −80°. Solid circles, [ArOH] = 0·27M; open circles, [ArOH] = 0·50M. Δ = exchange broadening of the dominant line in the OH-proton system; p = [ArOH]/([ArOH] + [MeOH]); δ = OH-proton chemical shift between ArOH and MeOH. Smooth curve is calculated on the basis of the rate-law shown in Eq. 2 and $k = 2{\cdot}85 \times 10^5$ sec^{-1} M^{-1}.

TABLE 3. *ortho*-SUBSTITUENT EFFECTS IN THE ACID-CATALYZED OH-PROTON EXCHANGE OF PHENOL IN METHANOL AT −80°

Substituent	van der Waals radius (A°)[a]	E_s[a]	(X_s ± 0·04)[b]
o-H	1·2	—	0·05
o-F	1·35	(0·00)	0·11
o-Br	1·95	−0·49	−0·67
o-NO_2	—	−1·24	−0·59
o-CO_2H	—	—	−1·01
o-Bu^t	ca. 3	—	−1·48
2,6-$(Bu^t)_2$	ca. 3	—	−2·01
2,6-$(Br)_2$	1·95	—	0·09

[a] Ref. 15.

[b] $\log k -5{\cdot}81 + 1{\cdot}95\,\sigma_{eff};\ \sigma_{eff} = 0{\cdot}66\,\sigma + 0{\cdot}34\,\sigma^-$.

phenol.[20] Dielectric relaxation and other properties of phenols in benzene indicate that OH-group rotation is less hindered in 2,6-di-t-butyl-*p*-cresol than in 3,5-dimethylphenol, apparently because the former OH-group is not encumbered by hydrogen-bonding to another molecule.[21] The chemical shift of the OH-protons of 2,6-di-t-butylphenol is distinctly abnormal in methanol. (Experimental).

Returning to the relatively high reactivity of 2,6-di-t-butylphenol in reaction (1), the theory suggests itself that steric inhibition of hydrogen bonding is less severe in the cationic transition state than it is in the ground state. The low value obtained for $\Delta S^{\ddagger}$ for this substrate (Table 1) is consistent with that theory.

EXPERIMENTAL

Materials. MeOH, anhyd HCl in MeOH, and *p*-nitrophenol were prepared or purified as described previously.[4] *ortho*-t-Butylphenol, 2,6-di-t-butylphenol, *o*-bromophenol, *o*-fluorophenol, and phenol were commercial reagents of good quality and were purified by distillation at reduced press. Each substrate was redistilled just before use in a kinetic experiment. *para*-t-Butylphenol, 2,6-dibromophenol, and *o*-nitrophenol were recrystallized to high purity, as indicated by sharp m.ps of the dried compounds. Physical constants of the phenols agreed with lit values. Chemical shifts, δ, of the OH-protons of the phenols relative to the OH-protons of MeOH at −80° were: Substituent, δ(ppm); H, 3·824, *o*-NO_2, 5·102; *o*-Bu^t, 3·484; 2,6-$(\text{Bu}^t)_2$, 1·78; *p*-Bu^t, 3·792; *o*-Br, 4·60; 2,6-$(\text{Br})_2$, 4·18; *o*-F, 4·343.

Solns to be used in kinetic experiments were prepared and analyzed according to standard quantitative techniques.

Kinetic measurements. Rates were measured by NMR techniques, as described previously.[4] Most rate determinations were based on slow-passage measurements of the width of the dominant line in the MeOH-phenol OH-proton system. Rate calculations were based on Eqs 8–11 of Ref. 5. Representative data are shown in Fig. 3. These data span a two-fold variation in [ArOH] and a hundred-fold variation in $[\text{MeOH}_2^+]$. The smooth curve is calculated using the known chemical shift δ (which is measured in the absence of HCl), Eq. 2 for the rate-law, and k as listed in Table 1. The fit is evidently satisfactory.

REFERENCES

[1] C. G. Swain and M. M. Labes, *J. Am. Chem. Soc.* **79**, 1084 (1957).

[2] E. Grunwald, A. Loewenstein and S. Meiboom, *J. Chem. Phys.* **27**, 630 (1957); Z. Luz and S. Meiboom, *Ibid.* **39**, 366 (1963).

[3] E. Grunwald, C. F. Jumper and S. Meiboom, *J. Am. Chem. Soc.* **85**, 522 (1963); M. Cocivera, E. Grunwald and C. F. Jumper, *J. Phys. Chem.* **68**, 3234 (1964).

[4] E. Grunwald, C. F. Jumper and M. S. Puar, *Ibid.* 71, 492 (1967).

[5] E. Grunwald and M. S. Puar, *Ibid.* 71, 1842 (1967).

[6] E. Grunwald, C. F. Jumper and S. Meiboom, *J. Am. Chem. Soc.*, **84**, 4664 (1962).

[7] H. H. Jaffé, *Chem. Revs* 53, 191 (1953).

[8] C. W. Clare, D. Cook, E. F. C. Ko, Y. C. Mac and A. J. Parker, *J. Am. Chem. Soc.* **88**, 1911 (1966).

[9] C. H. Rochester, *J. Chem. Soc.* (B) 121 (1966); *Ibid.* 676 (1965).

[10] G. Schwarzenbach and E. Egli, *Helv. Chimica Acta* 17, 1183 (1934); G. Schwarzenbach and E. Rudin, *Ibid.* **22**, 360 (1939).

[11] G. M. Bennett, G. L. Brooks and S. Glasstone, *J. Chem. Soc.* 1821 (1935).

[12] A. E. Biggs, and R. A. Robinson, *Ibid.* 388 (1961).

[13] M. E. Krahl and G. H. A. Clowes, *J. Cellullar Compar. Physiol.* **11**, 1 (1938).

[14] M. Eigen and G. G. Hammes, *Advances in Enzymology* **25**, 1 (1963).

[15] R. W. Taft, Jr., *Steric Effects in Organic Chemistry* (Edited by M. S. Newman), Ch. 13. Wiley, New York, N.Y. (1956).

[16] J. E. Leffler and E. Grunwald, *Rates and Equilibria of Organic Reactions*, pp. 211–214. Wiley, New York, N.Y. (1963).

[17] I. J. Solomon and R. Filler, *J. Am. Chem. Soc.* **85**, 3492 (1963).

[18] J. Rubin and G. S. Panson, *J. Phys. Chem.* **69**, 3089 (1965).

[19] S. Singh and C. N. R. Rao, *J. Am. Chem. Soc.* **88**, 2142 (1966).

[20] L. A. Cohen and W. M. Jones, *Ibid.* **85**, 3397 (1963).

[21] F. K. Fong, J. P. McTague, S. K. Garg and C. P. Smyth, *J. Phys. Chem.* **70**, 3567 (1966).

[22] M. S. Puar and E. Grunwald, *J. Am. Chem. Soc.* **89**, 4403 (1967).