

Figure 9. Cells used for the reduction of perfluorobiacetyl.

pretation. Reduction with strontium gave two species with very similar hfs by six fluorine atoms. Only one coupling constant, $a^F = 10.87$, could be measured accurately. A value of $a_{CF_3}^C = 5.37$ was observed as was a hfs by ^{87}Sr ($I = 9/2$, 7% abundance) of 0.35 G. Barium reduction gave three similar cis species with a^F for six equivalent fluorine atoms = 10.61, 10.88, 10.93 G. In this case addition of dibenzo-18-crown-6-ether had no effect on the esr spectrum. A value of $a_{CF_3}^C = 5.30$ G was observed as well as an average value of $a^{Ba} = 1.25$ G (^{135}Ba , $I = 3/2$, 6.6%; ^{137}Ba , $I = 3/2$, 11.3%).

Experimental Section

Materials. Perfluorobiacetyl was prepared from 2,3-dichloro-1,1,1,4,4,4-hexafluoro-2-butene (Columbia Organic Co.) according to the literature preparation.⁸ Bulb-to-bulb vacuum transfers gave material that showed no impurities by glpc. Purified material was stored in a vacuum line and vacuum transferred to the reaction cell when needed. Solvents except HMPA were distilled from calcium hydride. Etheral solvents were stored over benzophenone ketyl

in a vacuum line and vacuum transferred to sample cells. Other solvents were degassed in the reaction cells by the freeze-thaw method. Metal *tert*-butoxides prepared by reaction of the metals with *tert*-butyl alcohol were held under high vacuum to remove unreacted alcohol. Inorganic salts were dried under high vacuum in tubes heated by a gas torch to just below the softening temperature of Pyrex glass.

Instrumentation. Esr spectra were recorded using a Varian E-3 spectrometer calibrated with Fremy's salt in 10% aqueous sodium carbonate ($a^N = 13.00$ G). Electrolysis experiments were conducted directly in the spectrometer cavity using a platinum spoon electrode and cell previously described.³ Photolysis experiments involved the use of a focused 800-W Hanovia mercury lamp with quartz optics.

Chemical Reductions. Reductions were conducted in high vacuum Pyrex cells (Figure 9) consisting of mixing chamber A joined to a high volume fused silica esr flat cell B with side-arm chambers adapted to contain a reducing agent (chamber C, C', or C''), perfluorobiacetyl (chamber D), and an additional reagent chamber E. Depending upon the experiment, solvent was added to one or all chambers. Each chamber was separated from the mixing chamber by a high vacuum stopcock. Mixing chamber A when attached to a vacuum line through a ground joint could be rotated so as to place either B or D and E in the down position.

Chamber C was used for standard "metal-mirror" reductions with sodium and potassium. The metals were distilled up tube F under high vacuum to the deposition surface and tube F was then removed. No attempts to purify cesium metal were made. Chamber C' was used to produce finely divided forms of lithium, barium, calcium, and strontium. Bulk metal was sealed in G and the cell assembly attached to the vacuum system with G in the down position. Several milliliters of liquid ammonia (stored over lithium metal on the vacuum line) was condensed in G producing a deep blue solution. After freezing this solution the cell was rotated to place chamber H in the down position and H cooled as chamber G began to warm. Upon thawing the metal ammonia solution (under ammonia pressure) passed through the course fritted disk J joining G and H to remove insoluble oxides. Finally the ammonia was vaporized and the powdered metal deposit warmed under vacuum for several minutes. The course fritted disk K prevented transfer of particulate metal between A and H during reduction. Care was taken to avoid contact of the diketone solution with G.

When iodides or bromides were used as reducing agents the salts were sealed in C'' and heated until dry. Salts placed in the additional reagents chamber (E) received the same treatment. Dibenzo-18-crown-6 ether (Aldrich Chemical Co.) was purified by gently distilling it up a tube to E under vacuum.

Acid-Catalyzed Hydrogen Exchange of Acetophenones. Evidence for the Inapplicability of the Reactivity-Selectivity Principle

T. J. Gilbert and C. D. Johnson*

Contribution from the School of Chemical Sciences, University of East Anglia, Norwich, England. Received February 8, 1974

Abstract: The dependence of rate on acidity for the 3- and 5-hydrogen exchange of some 4-substituted acetophenones in aqueous deuteriosulfuric acid has been determined. Reaction is shown to occur on the keto free base form, the enol form being in such small concentration that if it were sufficiently reactive to undergo observable exchange it would direct the reaction into the 2 and 6 positions. Treatment of the data in terms of standard acidity function theory demonstrates apparent lack of dependence of transition state structure on the rate of hydrogen exchange in aromatic substrates, in contradiction of the widely accepted reactivity-selectivity principle, and thus by implication the Hammond postulate. Related data bearing on the thermodynamic acidity function theory are also discussed.

Decrease in the nuclear hydrogen exchange reactivity of aromatic compounds is commonly connected with increased resemblance of transition state structure

to the Wheland intermediate, considered discernable by isotope effect variation denoting the increased degree of proton transfer, the low C basicity of the aromatic sub-

Table I. Protonation Results (Summary)^a

4-X-acetophenone X	$-H_0$ (half-protonation)	m ($-\text{d log } I/\text{d } H_0$)	$-\text{p}K_a^b$ ($mH_0^{1/2}$)	r^d	ϕ_E^c	$-\text{p}K_a^c$	r^d
OCH ₃	5.12	0.590	3.02	0.994	0.442	3.31	0.987
SCH ₃	6.01	0.574	3.45	0.994	0.454	3.77	0.990
CH ₃	5.64	0.668	3.78	0.992	0.335	4.02	0.971
C ₂ H ₅	5.95	0.620	3.71	0.997	0.407	3.98	0.992
CH(CH ₃) ₂	5.54	0.669	3.69	0.998	0.353	3.94	0.993
C(CH ₃) ₃	5.69	0.700	3.97	0.996	0.322	4.12	0.979
F	6.70	0.612	4.10	1.000	0.411	4.40	0.999
Cl	6.73	0.684	4.60	0.996	0.336	4.85	0.983
NO ₂	8.40	0.630	5.29	0.997	0.387	5.62	0.990

^a Expanded form in the microfilm edition. ^b References 7 and 9. ^c Reference 10. ^d Correlation coefficients of appropriate plots.

strate, and the values of $\text{d log } k/\text{d } H_0$ and of Brønsted coefficients for general acid catalysis close to unity.^{1,2} Such notions have as their theoretical justification the Hammond postulate manifested in reactivity-selectivity and isotope effect correlations concerning the validity of which general doubt has been expressed.³⁻⁵ Kresge has, however, apparently substantiated these concepts with respect to kinetic C protonation of substituted benzenes in aqueous perchloric acid;¹ with regard to these results it may be noted that considerable significance is placed on the result for benzene itself. This has prompted us to report our experimental data and subsequent calculations on the hydrogen-deuterium exchange of the 3,5 position of 4-substituted acetophenones, a necessary preamble to the kinetic measurements and their elucidation being a detailed investigation of the thermodynamic protonation (at carbonyl oxygen) behavior of the substrates under study.

Experimental Section

Materials. The 4-substituted acetophenones were available commercially or prepared by standard procedures.⁶ Sulfuric acid, sulfuric acid-*d*₂, and water-*d*₂ were obtained commercially.

pK_a Determinations. These were carried out by uv spectroscopy as described previously.⁶⁻⁸ In all cases measurements were on a conjugate acid peak. The results are summarized in Table I.

Rate Determinations. These were carried out by means of a Perkin-Elmer R12 60-MHz spectrometer under pseudo-first-order conditions with excess deuterated sulfuric acid in deuterated water. Reaction temperatures were maintained to $\pm 1^\circ$. Reaction vessels, nmr tubes made up in a drybox and sealed, were cooled in ice when not undergoing exchange or being measured. The 2- and 6-ring protons were used as standards, showing no observable exchange under experimental conditions. Peak integrals were scanned ten times each and then averaged. The maintenance of the integrity of the initial aromatic pattern when 4-methoxyacetophenone, the most reactive aromatic substrate, was heated above 60° for 24 hr in various concentrations of aqueous sulfuric acid demonstrated that sulfonation was absent in these reactions. Some blackening of the solutions occurred in the case of the less reactive acetophenones toward the end of the runs, but the nmr pattern showed no ex-

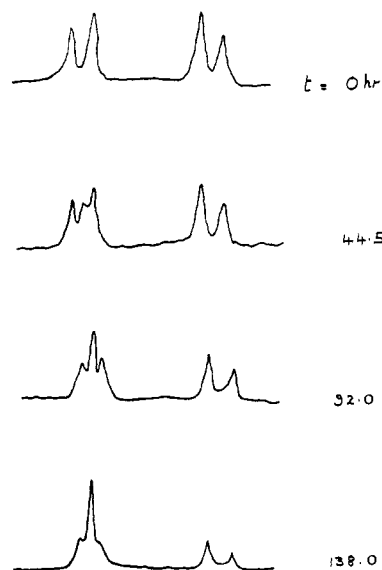


Figure 1. Exchange of 4-methylacetophenone at the 3,5 positions in 86.54% D₂SO₄ at 60°.

Table II. Typical Rate Determination, on 4-Methylacetophenone

(i) Solution Preparation		
Wt of 4-methylacetophenone = 0.1059 g		
Wt of 86.54% w/w D ₂ SO ₄ -D ₂ O = 1.0937 g		
Wt of D ₂ SO ₄ = 0.9465 g and of D ₂ O = 0.1472 g		
Effective wt of D ₂ SO ₄ = 1.0937 - (100/134)(0.1059) = 1.0147 g		
Corrected acid = $\frac{1.0147(100)}{1.0147 + 0.1472} = 85.49\%$		
(ii) Rate Measurement at 60° in 86.54% D ₂ SO ₄ (Effective D ₀ for 25° = -8.32 assuming H ₀ = D ₀ ^a)		
Time, hr	R _t ^b	1 + log R _t /R ₀ ^c
0	0.9275 (R ₀)	
21.00	0.8779	0.9556
44.50	0.8081	0.9196
68.00	0.6738	0.8406
92.00	0.5776	0.7737
115.00	0.5506	0.7529
138.00	0.4693	0.6836

^a J. Sierra, M. Ojeda, and P. A. H. Wyatt, *J. Chem. Soc. B*, 1570 (1970). ^b Ratio of area of the 3,5-proton peak to the standard at time *t*, determined from the average of ten integrals. ^c Slope of (1 + R_t/R₀) vs. time (hr) = -0.002349. Correlation coefficient = 0.992. 10³k_{obsd} = 15.03/sec⁻¹ [k_{obsd} = slope(2.303/3600)].

traneous peaks. Details of a typical run are shown in Table II and Figure 1, while Table III and Figure 2 give the results obtained. The free base rate constants were obtained by use of the equation

$$k_{tB} = k_{\text{obsd}} \left\{ \frac{[\text{BH}^+]}{[\text{B}]} + 1 \right\} \quad (1)$$

extrapolating or interpolating the log [BH⁺]/[B] vs. H₀ graphs for

(1) A. J. Kresge, S. G. Mylonakis, Y. Sato, and V. P. Vitullo, *J. Amer. Chem. Soc.*, **93**, 6181 (1971).

(2) J. R. Adsetts and V. Gold, *J. Chem. Soc. B*, 954 (1969); R. Taylor, *Compr. Chem. Kinet.*, **13**, 1 (1972).

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(5) C. D. Johnson, "The Hammett Equation," Cambridge University Press, New York, N. Y., 1973, Chapter 5.

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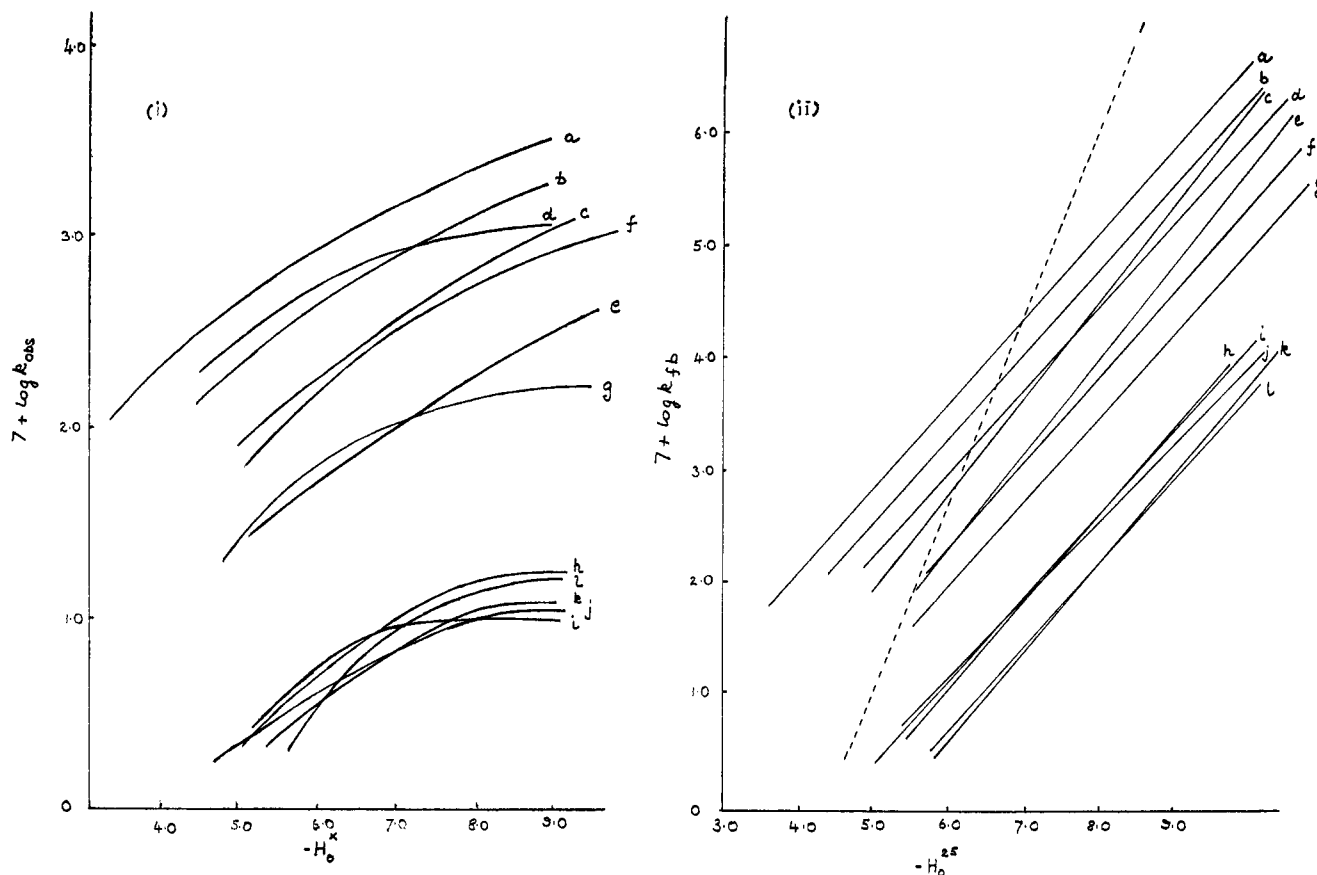


Figure 2. Rate-acidity profiles for 4-X-acetophenones: (a) X = OCH₃, 9%, 60°; (b) X = OCH₃, 18%, 60°; (c) X = OCH₃, 9%, 50°; (d) X = CH₃, 9%, 100°; (e) X = OCH₃, 9%, 40°; (f) X = SCH₃, 9%, 60°; (g) X = CH₃, 9%, 80°; (h) X = CH₃, 9%, 60°; (i) X = C(CH₃)₃, 9%, 60°; (j) X = CH₃, 18%, 60°; (k) X = CH(CH₃)₂, 9%, 60°; (l) X = C₂H₅, 9%, 60°. (i) Observed, (ii) free base (keto form), the dotted line is the result for benzene-*t* exchange; see footnote c, Table VI.

Table III. Slopes of $7 + \log k_{fb}$ against $-H_0$ for Exchange of 4-X-acetophenones^a

X		7 + log k_{fb} vs. $-H_0^{2x}$	$7 + \log k_{fb}$ vs. $-H_0^x$	
			r^b	r^d
CH ₃	9%	60°	0.815	0.995
CH ₃	9%	80°	0.782	0.999
CH ₃	9%	100°	0.756	1.000
CH ₃	18%	60°	0.738	0.998
C ₂ H ₅	9%	60°	0.808	0.997
CH(CH ₃) ₂	9%	60°	0.828	0.999
C(CH ₃) ₃	9%	60°	0.796	1.000
OCH ₃	9%	40°	0.833	0.998
OCH ₃	9%	50°	0.843	0.998
OCH ₃	9%	60°	0.756	0.995
OCH ₃	18%	60°	0.766	0.999
SCH ₃	9%	60°	0.779	0.999

^a Expanded form in the microfilm edition. ^b Correlation coefficient for $7 + \log k_{fb}$ against $-H_0^{2x}$. ^c x is the reaction temperature. ^d Correlation coefficient for $7 + \log k_{fb}$ against $-H_0^x$.

the necessary values assuming a linear dependence of the two quantities (Table I).

The variable temperature experiments on 4-methyl- and 4-methoxyacetophenone enabled calculation of the free base activation parameters shown in Table IV. Table V records the nmr characteristics of the acetophenones.

Exchange reactions were also attempted on 4-chloro-, 4-bromo-, and 4-fluoroacetophenone but they decomposed on heating in acid, depositing dark brown solids.

Discussion

Our chief concern in these studies is the examination of the kinetic acidity dependence for the nuclear ex-

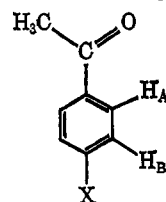
Table IV. Free Base Activation Parameters

$-H_0$	$E_a/4.18$ kJ mol ⁻¹	$\Delta S^\ddagger/4.18$ kJ K ⁻¹ mol ⁻¹	$\Delta G^\ddagger/4.18$ (25°) kJ mol ⁻¹
4-Methoxyacetophenone			
5.00	29.71	10.70	25.89
5.50	29.97	13.43	25.33
6.00	30.70	17.68	24.79
6.50	31.19	21.17	24.23
7.00	30.97	22.33	23.68
7.50	32.16	28.15	23.14
8.00	32.89	32.40	22.60
8.50	33.38	35.89	22.05
9.00	33.87	39.38	21.50
4-Methylacetophenone			
4.50	32.99	7.53	30.06
5.00	33.57	11.20	29.54
5.50	34.00	14.40	29.02
6.00	34.72	18.50	28.51
6.50	35.30	22.13	28.01
7.00	35.73	25.38	27.48
7.50	36.45	29.43	26.99
8.00	36.88	32.68	26.45
8.50	37.47	36.26	25.97
9.00	37.90	39.51	25.44

change of these compounds, but for accurate estimation of the relevant k_{fb} values (eq 1) the thermodynamic protonation constants must be carefully calculated and authenticated, and it is therefore this topic which is initially considered.

Protonation Studies. The ionization values for the acetophenones may be used to calculate pK_a values as

Table V. Chemical Shifts for 4-X-acetophenones



X	Shift τ					
	Free base ^a			Conjugate acid ^b		
	H _A (α)	H _B (α)	CH ₃ (s)	H _A (α)	H _B (α)	CH ₃ (s)
CH ₃	2.23	2.84	7.56	1.37	2.17	6.72
C ₂ H ₅	2.21	2.83	7.58	1.57	2.36	6.74
CH(CH ₃) ₂	2.20	2.78	7.58	1.57	2.32	6.72
C(CH ₃) ₃	2.16	2.59	7.55	1.49	2.12	6.76
OCH ₃	2.17	3.17	7.60	1.48	2.71	6.87
SCH ₃	2.18	2.79	7.52	1.64	2.38	6.74

^a Measured in CCl₄, Me₄Si as internal standard. ^b Measured in D₂SO₄, (Me₄N)₂SO₄ as internal standard.

shown in Table II, using the methods of Yates^{7,9} and Bunnett.¹⁰ As detailed previously, the two methods give similar results, the former affording values systematically some 0.2 to 0.3 pK_a unit more negative than the latter.

A recent criticism¹¹ of Yates' treatment is that it may be invalid since, first, there is no certainty that the acidity function followed by the substrate is identical with H_0 at a common value of zero and, second, that it diverges uniformly therefrom. The coincidence of H_0 and the acidity function at zero is indeed an approximation deduced from practical observations on well established acidity scales. The second is a most important point, but it cannot be considered as applying only to Yates' treatment. Instead it is a general criticism of the experimental validity of the indicator overlap principle. If all plots of $\log I$ vs. H_0 are to be straight lines which in all cases but one they are, and then in perchloric rather than sulfuric acid,¹² any breakdown in this assumption implies a departure from parallelism between overlapping indicators defining the given acidity function of which the substrate under discussion is one. It involves also of course the further assumption which is common to all acidity function determinations, that such plots, parallel over the experimentally accessible region, remain parallel outside this range.¹³ The best indication that this assumption is valid and the calculated pK_a values represent accurate quantities defined on the basis of the standard state of pure water at 25° is to demonstrate that such values correlate in the expected manner, over a wide range preferably extending into the dilute acid region, with other physicochemical properties of the substrates not dependent on acidity function theory for their definition. Such intrinsically important studies include correlation of aniline pK_a's with σ^- ^{14,15}

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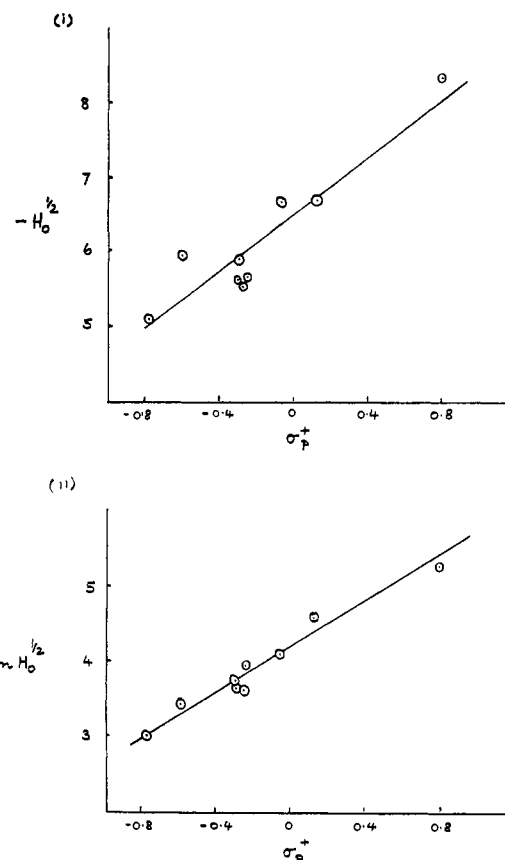


Figure 3. Logarithmic ionization data vs. σ^+ for acetophenones: (i) H_0 (half-protonation) values, (ii) mH_0 (half-protonation) values.

and with enthalpy values,^{16,17} carbinol pK_R⁺'s with σ^+ ,¹⁸ and amide pK_a's with boron trifluoride complex dissociation constants.¹⁹

In the case of acetophenone pK_a values, a suitable correlation should be with σ^+ , and indeed such a correlation using H_0 (half-protonation) values has been demonstrated previously.²⁰ The resultant plots from our work are given in Figure 3, the ρ value for the H_0 (half-protonation) value correlation being 2.02 (to be compared with 2.17²⁰) with a correlation coefficient of 0.931 and for the pK_a values calculated by Yates' method being 1.45 with a correlation coefficient of 0.985. Since in these instances pK_a and H_0 (half-protonation) values are linked by eq 2, the markedly better correlation

$$pK_a = mH_0(\text{half-protonation}) \quad (2)$$

of the pK_a values might be directly attributable to the differing values of m associated with the individual compounds. It is generally assumed that compounds following the same acidity function exhibit the same values of m , but the results obtained above could be interpreted as emphasizing that individual bases generate their own acidity functions, for which the overall acidity function represents only an "averaged" value. We have recourse to this point later, when discussing the acidity

(16) E. M. Arnett and J. J. Burke, *J. Amer. Chem. Soc.*, **88**, 4308 (1966).

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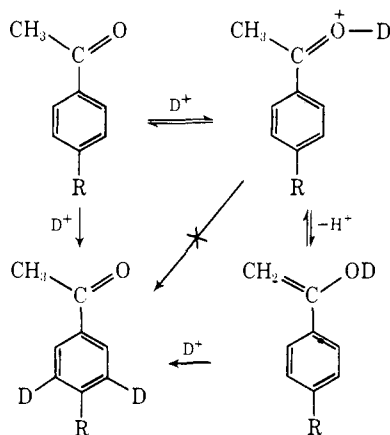
(20) R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, **80**, 6355 (1958).

function applicable to the C protonation of acetophenones.

The free base and conjugate acid ring proton chemical shifts (Table V) also gave approximate correlations with the pK_a values, detailed elsewhere.⁶

Having thus established the authenticity of our experimental m values, *i.e.*, the slopes of the $\log I$ vs. H_0 plots as required for formulation of k_{fb} values in eq 1, we now turn to consideration of the kinetic results.

Kinetic Studies. Rate-Acidity Dependence of Hydrogen Exchange. The observed rate-acidity profiles, Table III and Figure 2, reveal that as expected the exchange reaction proceeds on a species in a minority at least at high acidities, which could be either the free keto base or its enol form.



Of these two reaction candidates, the former must be the favorite, because if the latter was sufficiently more reactive to overcome the effect of its very low concentration, then the enol substituent would be expected to give rise to 2,6 substitution, at least in the 4-alkylacetophenones. It is of interest to put this argument on a more quantitative basis, because it constitutes a specific example of the general case for treatment of competitive reaction between two tautomers in strong acid.

The enol content of acetophenone has been estimated as 0.035% in methanol.²¹ If a similar amount of the enol form of 4-substituted acetophenones is present in aqueous acid solution and it is assumed that reaction occurs on the keto and enol forms in equivalent amounts, *i.e.*,

$$k_E[\text{enol}] = k_K[\text{keto}] \quad (3)$$

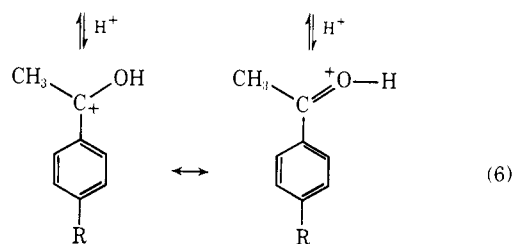
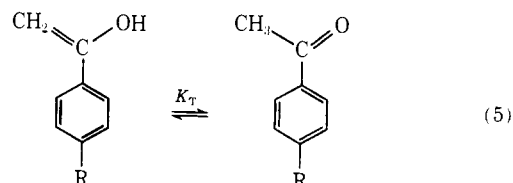
then

$$k_K/k_E = [\text{enol}]/[\text{keto}] = 0.00035 = \Delta k \quad (4)$$

Now $\Delta \log k = \rho \Delta \sigma^+$ and hence $-3.46 = \rho \Delta \sigma^+$. Assuming $\rho = -6$ (see later), $\Delta \sigma^+ = 0.58$, and since $\sigma_m^+ = 0.31$ for the acetyl group, σ_m^+ for the enol function will be -0.27 . Such a value is hard to rationalize, but in any case the σ_o^+ value must be considerably more negative than this since the enol group will have a strong resonance stabilizing effect in conjugation with a positive charge, steric effects being negligible (see later). Thus, a significant proportion of exchange would occur in the 2- and 6-ring positions, being certainly predominant in the case of the 4-alkylacetophenones.

(21) A. Gero, *J. Org. Chem.*, **19**, 1960 (1954).

This argument may also be approached as follows. For the equilibria



$$K_T = [\text{keto}]/[\text{enol}]$$

For C protonation of the enol

$$H_c = (pK_a)_{\text{enol}} + \log [\text{enol}]/[\text{CA}] \quad (7)$$

Kresge having demonstrated that monohydroxy aromatics follow H_c ²² reasonably closely, although di- and trihydroxy compounds show deviations.¹²

For O protonation of the ketone

$$H_{c0} = (pK_a)_{\text{keto}} + \log [\text{keto}]/[\text{CA}] \quad (8)$$

Combining eq 6, 7, and 8

$$\log K_T = H_{c0} - H_c - (pK_a)_{\text{keto}} + (pK_a)_{\text{enol}} \quad (9)$$

Since in eq 9 the term $-(pK_a)_{\text{keto}} + (pK_a)_{\text{enol}}$ is constant and $H_{c0} - H_c$ becomes increasingly more positive as acidity is increased, then the ratio $[\text{keto}]/[\text{enol}]$ must correspondingly increase.

The rate of reaction is given by

$$\text{rate} = k_K[\text{keto}] = k_E[\text{enol}] \quad (10)$$

and since k_K is essentially k_{fb}

$$\log k_{fb} = \log k_E + \log [\text{enol}] - \log [\text{keto}] \quad (11)$$

Combining eq 9 and 11 and differentiating 11 with respect to H_0

$$d \log k_{fb}/dH_0 = d \log k_E/dH_0 + dH_c/dH_0 - dH_{c0}/dH_0 \quad (12)$$

A maximum value of $d \log k_E/dH_0$ assumes that the transition state is the Wheland intermediate, *i.e.*

$$-d \log k_E/dH_0 = dH_c/dH_0 \quad (13)$$

so that eq 12 becomes

$$d \log k_{fb}/dH_0 = -dH_{c0}/dH_0 = -dmH_0/dH_0 = -m \quad (14)$$

Thus for reaction on the enol form, the maximum slope defining the $\log k_{fb}$ vs. H_0 acidity profile would be $-m$. However, in all cases (see Tables I and VI) this slope is greater than $-m$ by an experimentally significant proportion.

Finally, reaction on the keto form may be confirmed by examination of the authenticity of the estimate of the enol content in the first approach by use of eq 9 from

(22) M. T. Reagan, *J. Amer. Chem. Soc.*, **91**, 5506 (1969).

the second. Substituting in this equation the relevant values for 4-methylacetophenone undergoing reaction at $H_0 - 8$, by no means the highest acidity at which reaction was followed, we obtain

$$3.46 = -5.4 + 12.8 + 3.8 + (pK_a)_{\text{enol}}$$

so that $(pK_a)_{\text{enol}}$ is about -8 . Now the pK_a of the 1,1-diphenylethyl cation is -9.4 ,^{22,23} and the presence of the OH group in place of one of the phenyl rings in addition to the presence of a methyl group in the other would certainly result in stabilization of the positive charge by a very considerable amount (σ_p^+ for OH is -0.92 ; cf. -0.17 for C_6H_5 ,²⁴). This is emphasized by the pK_a of the 1-*p*-anisyl-1-phenylethyl cation which is -6.3 ,²² revealing a large response of basicity to substituent effects in such ethylenes. Moreover, there will be no destabilizing steric interaction between the OH group and the aromatic ring, in contrast to the twisting in 1,1-diaryl systems.

The value of -8 therefore would seem to represent very much a lower limit for the basicity of the enol form; almost certainly it would be less negative than this by a considerable margin. There would thus be even less enol form than 0.035%, and reaction *via* this form would presuppose even more emphatically substitution in the 2 and 6 positions, particularly at higher acidities.

Table III shows that the effect of substrate concentration change was also investigated, to ascertain if this was large and irregular and therefore a complicating factor in elucidation of reaction mechanisms. Figure 4 illustrates the variation for 4-methoxyacetophenone, and this and the results for 4-methyl- and 4-methoxyacetophenone in Table III show that the effect is small and displays little variation with acidity, the rate decreasing with increase in concentration. The exchange of 4-aminopyridine has recently been shown²⁵ to give very similar results at a much higher temperature, 147° , over a wide acidity range. Maintaining the concentration of substrates at approximately equivalent equimolecular amounts is clearly sufficient for self-consistent comparable results.

Calculation of the free base rate constants by eq 1 produces logarithmic rate-acidity profiles (Table III and Figure 2) which are very accurately linear. The H_0 values used were those for 25° , as they do not differ greatly from those at 60° ,²⁶ and the ionization ratios were measured at the former temperature. In any case, however, the slopes of the profiles are, within experimental error, apparently insensitive to temperature change. Near constancy of profile slopes with temperature has also been observed for loss of tritium in $HClO-H_2O$ from 1,3-dimethoxybenzene-2-*t* over the range $15-45^\circ$ ²⁷ and for tritium loss from benzene-*t* and naphthalene-1-*t* and -2-*t* in $H_2SO_4-H_2O$ over the range $25-55^\circ$,²⁸ although other results for hydrogen-deuterium exchange in 1- and 2-naphthalenes do display an appreciable variation in slope with temperature.²⁹

(23) N. C. Deno, P. T. Groves, and G. Saines, *J. Amer. Chem. Soc.*, **81**, 5790 (1959).

(24) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(25) A. A. El-Anani, unpublished results.

(26) C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, **91**, 6654 (1969).

(27) A. J. Kresge, Y. Chiang, and Y. Sato, *J. Amer. Chem. Soc.*, **89**, 4418 (1967).

(28) C. D. Johnson, A. R. Katritzky, and B. O'Neill, *J. Chem. Soc., Perkin Trans. 2*, in press.

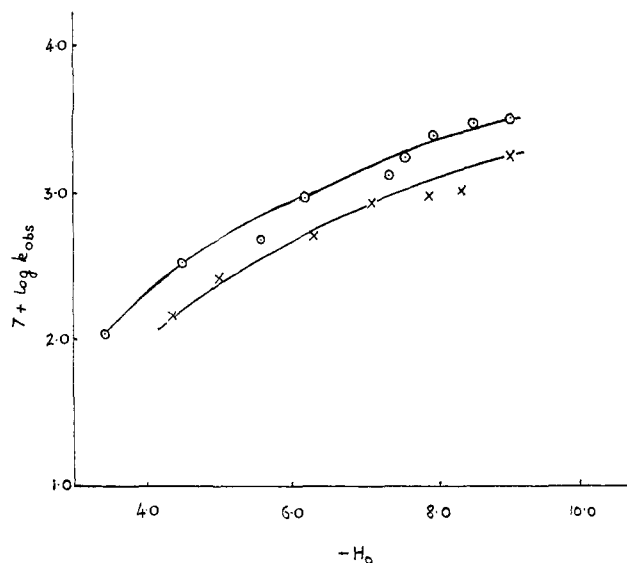


Figure 4. Concentration effects; exchange of 4-methoxyacetophenone at 60° : \circ , 9%; \times , 18%.

The effect of steric hindrance on the rate of exchange was studied by varying the size of the 4 substituent through methyl, ethyl, isopropyl, and *tert*-butyl, which judging from the similarity of their σ_m^+ and σ_p^+ values²⁴ have very similar electronic effects. Figure 2 indicates that the rates for these substituents show only small random variation, so that steric hindrance appears to be negligible for hydrogen exchange in aqueous sulfuric acid. This accords with the conclusion of Ansell, Clegg, and Taylor³⁰ who investigated the detritiation of 1,3,5-triphenylbenzene-2-*t* and found that even in this system steric hindrance was only slight. Taylor has also recently published a series of σ_o^+ constants, calculated from aromatic detritiation reactions,³¹ also in trifluoroacetic acid, from which the correlation for methyl-, *tert*-butyl-, thiomethoxy-, and methoxyacetophenones can be investigated. Given the limited number of points available, correlation is reasonable ($r = 0.982$). The value of ρ is -6.2 , cf. 7.5 for related reactions.³²

Hydrogen Exchange, the Nature of the Transition State, and the Reactivity-Selectivity Principle, with a Note on the Effect of Substituents on Acidity Functions. Kresge has demonstrated^{1,33} the utility of eq 15, where α_A represents a measure of the extent to which the transition state resembles the Wheland intermediate in aromatic hydrogen exchange, being unity when they are the same and zero when the activated complex is the ground state. Equation 15 cannot be used directly

$$\log(k/[H^+]) = \alpha_A \log(I/[H^+]) + \log k^0 K_a^{\alpha_A} \quad (15)$$

here, because $\log I$ values for C protonation of acetophenones are immeasurable due to preferential O protonation. This was inevitable, however, even in the

(29) C. G. Stevens and S. J. Strickler, *J. Amer. Chem. Soc.*, **95**, 3918 (1973).

(30) H. V. Ansell, R. B. Clegg, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 766 (1972).

(31) H. V. Ansell, J. Le Guen, and R. Taylor, *Tetrahedron Lett.*, 13 (1973).

(32) S. Clementi and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1077 (1973).

(33) A. J. Kresge, R. A. More O'Ferrall, L. E. Hakka, and V. P. Vitullo, *Chem. Commun.*, 46 (1965).

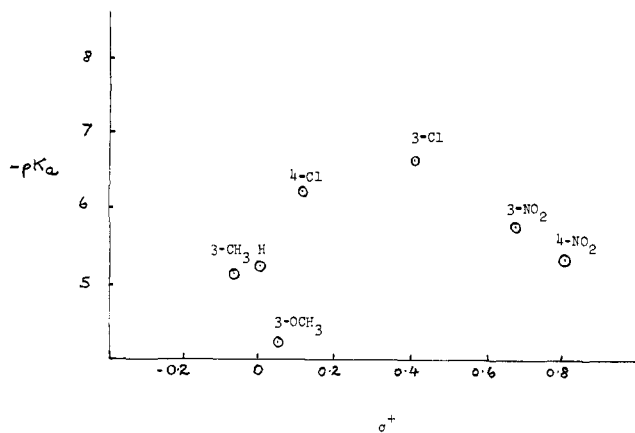


Figure 5. Correlation of pK_a values of acetophenones with σ^+ . pK_a 's obtained from the equation $-\Delta H = 1.78pK_a + 28.1$, where ΔH is the heat of transfer from CCl_4 to FSO_3H in kilocalories per mole.

absence of the latter, because our prime motive in this work, to demonstrate the inapplicability of the reactivity-selectivity principle, demanded that we should consider protonation of C bases weaker than benzene. Equation 15 may be converted to 16, whereupon the problem now resolves itself into a decision as to the acidity function H_x followed by C protonation of acetophenones.

$$\log(k/[H^+]) = \alpha_A(-H_x - \log[H^+]) + \log k^0 \quad (16)$$

The obvious choice is H_c , with the assumption that acidity functions are governed by the site undergoing protonation and are not altered by substituent groups present. We believe that such an assumption is correct, for the reason that the whole basis for the establishment of acidity scales is the systematic alteration of basicity by substituent change sufficiently large to encompass the whole acidity range, involving in the case of H_c methoxy, methyl, chloro, and cyano.²² Since this assumption is basic also to the interpretation of our results, we now consider the question in further detail here, commencing by rephrasing it more exactly, in line with discussion of a previous section; how nearly do the separate acidity functions followed by the individual members of the family of indicators protonating at a common site coincide with the overall acidity function describing their "average" protonation behavior?

The third variable in Hammett's three variable hypothesis³⁴ of acidity functions is given by the term $\log f_B/f_{BH^+}$,³⁵ where f_B is the activity coefficient of a free base and f_{BH^+} that of its conjugate acid. Terms of the

(34) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, p 275.

(35) It may well be that the relationship between one acidity function and another is $\log f_A/f_{AH^+} = C \log f_B/f_{BH^+}$, where A and B are bases defining different acidity functions and C is a constant with variation in acidity. Since logarithmic activity coefficients measure the deviation of the free energy of a system from that in the standard state, such an expression would represent a linear free energy relationship between one acidity function and another. This of course cannot be checked directly because activity coefficients cannot be measured for both a base and its conjugate acid in the same solution, but it seems likely that, even if such log activity coefficient ratios for two bases are different at any given acidity, their responses to a change in that acidity are proportional. This would rule out the disconcerting possibility alluded to earlier which threatens the validity of the Hammett overlap principle, that bases with parallel ionization plots might follow different acidity functions which happen to become parallel over the region of observable protonation.¹³

form $\log f$ are free energy measurements and as such are presumably amenable to dissection into contributing energies from molecular components.³⁶ Protonation of a base B can be represented as



where X represents the protonation site and B' the remainder of the molecule, usually a substituted benzene ring. From the equilibrium in eq 17

$$\log f_B/f_{BH^+} = \log f_X/f_{XH^+} + \log f_{B'}/f_{B'} = \log f_X/f_{XH^+} \quad (18)$$

Thus the acidity function followed by a base depends only on the site of protonation, and is, as observed experimentally, independent of substituents. However large substituent-solvent interactions may be, they will approximately cancel (although second-order differences between such interactions in the free base and its conjugate acid will be one of the main factors accounting for deviations from exact parallelism in log I -percent aqueous acid plots observed in the definition of all acidity functions, they are generally obscured in the final "averaging" process.) Such a cancellation process has recently been demonstrated with respect to the H_0 scale by Yates and Shapiro³⁷ and is emphasized by the fact that protonation of bases bearing even positive substituents follows closest that acidity function dictated by the protonation site.³⁸ It is authenticated by comparison of pK_a values, obtained by the acidity function approach, with the illuminating and extremely interesting measurements of heats of protonation, ΔH , obtained by Arnett and his coworkers, using calorimetric methods.^{39a} Since the latter values involve the difference in heats of solution of bases in inert and polar protonating solvent, substituent-solvent interactions are incorporated in the resultant pK_a values. This is demonstrated in Figure 5 (*cf.* Figure 3), where such interactions produce large deviations from the expected LFER. Such interactions must also lead to errors in direct activity coefficient measurements in varying acid strengths for elucidation of the expression $-\log a_{H^+} + f_B/f_{BH^+}$, because f_B must be measured using a base containing strongly electron-withdrawing groups such as NO_2 , while f_{BH^+} is determined using a strong base member of this series.^{39b}

Now it is clearly important to note however that the hydroxy substituent appears to possess the unique ability to produce breakdown in eq 18, promoting pro-

(36) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 83.

(37) K. Yates and S. A. Shapiro, *Can. J. Chem.*, **50**, 581 (1972).

(38) H_0 *cf.* H_+ : P. Vetešnik, J. Bielařsky, and M. Večeřa, *Collect. Czech. Chem. Commun.*, **33**, 1687 (1968); B. Roth and J. Z. Strelitz, *J. Org. Chem.*, **35**, 2696 (1970); C. F. Reynolds, Ph.D. Thesis, University of Exeter, 1963; P. J. Brignell, C. D. Johnson, A. R. Katritzky, N. Shakir, H. O. Tarhan, and G. Walker, *J. Chem. Soc. B*, 1233 (1967); G. B. Barlin, *J. Chem. Soc., Perkin Trans. 2*, 1459 (1972). H_A *cf.* H_+ : C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc. B*, 1235 (1967); W. I. Congdon and J. T. Edward, *J. Amer. Chem. Soc.*, **94**, 6096 (1972); M. Hashmi, Ph.D. Thesis, University of East Anglia, 1973. H_1 *cf.* H_+ : R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.*, **86**, 3796 (1964). H_0''' *cf.* H_+ : R. D. Frampton, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc. B*, 671 (1972). H_{AZ} *cf.* H_+ : F. A. Long and J. Schulze, *J. Amer. Chem. Soc.*, **86**, 327 (1964). H_R *cf.* H_+ : A. M. Lowen, M. A. Murray, and G. Williams, *J. Chem. Soc., London*, 3318 (1950).

(39) (a) E. M. Arnett, R. P. Quirk, and J. W. Larsen, *J. Amer. Chem. Soc.*, **92**, 3977 (1970); (b) R. H. Boyd, *ibid.*, **85**, 1555 (1963); L. M. Sweeting and K. Yates, *Can. J. Chem.*, **44**, 2395 (1966).

Table VI. Hydrogen Exchange Results in Aqueous Sulfuric Acid

Substrate	Exchange position	$\log k, \text{sec}^{-1}$ (75% acid)	Temp, °C	$-\text{d} \log k / \text{d} H_0^{25}$	r	$-\text{d} \log k / \text{d} H_0$	r	α_A	r
1,2,3-Trimethoxybenzene-4,6- <i>rs</i>	4,6	0.550	25	0.986	1.000	0.615	1.000	0.406	1.000
Anisole-4- <i>d</i> ^b	4	-0.240	25	1.223	1.000	0.723	0.997	0.553	0.999
Benzene- <i>r</i> ^c	1	-4.160	55 ^d	1.462	0.993	1.119	0.990	1.010	0.987
4-Methoxyacetophenone	3,5	-4.150	60	0.756	0.995	0.577	0.996	0.514	0.995
4-Methylthioacetophenone	3,5	-4.830	60	0.779	0.999	0.587	0.999	0.535	0.999
4-Methylacetophenone	3,5	-6.335	60	0.815	0.995	0.584	0.995	0.529	0.995
4-Ethylacetophenone	3,5	-6.520	60	0.808	0.997	0.593	0.995	0.539	0.996
4-Isopropylacetophenone	3,5	-6.465	60	0.828	0.999	0.613	0.998	0.561	0.999
4- <i>tert</i> -Butylacetophenone	3,5	-6.310	60	0.796	1.000	0.587	0.998	0.535	0.999

^a D. P. N. Satchell, *J. Chem. Soc., London*, 463 (1959). ^b D. P. N. Satchell, *ibid.*, 3911 (1956); the results are the same, within experimental error, for anisole-2-*d*, which reacts at a similar rate. ^c Reference 28. ^d $-\text{d} \log k / \text{d} H_0^{55} = 1.64^{28}$

nounced deviation from uniform acidity function behavior, interpreted in terms of differential solvation effects.¹² But this deviation seems only large in the case of di- and trihydroxy compounds; the departure of all other substituted C bases¹² from H_0 including monohydroxy compounds in aqueous sulfuric acid appears from examination of Figure 1 of ref 22 (the relevant data are not provided for a quantitative check) to be matched by or even less than the departure of the individual indicators from the H_0 scale. Indeed, this is made practically certain by the fact that two of the indicators used for the H_0 scale, 1,3,5-trimethoxybenzene and 2,6-dimethoxytoluene, are reported by Kresge¹² to have $-\text{d} \log I / \text{d} H_0$ values of 0.90 and 0.93, respectively. Similar deviations have been noted as present in all such scales; they do not appear to detract from the general validity or usefulness of such scales, but they do underline the caution with which the accuracy and significance of relatively small order effects ascertained by acidity function measurements must be viewed.

Accordingly, we believe that the C protonation of acetophenones will be best represented by H_0 and thus that plots of $\log (k/[H^+])$ vs. $H_0 + \log [H^+]$ give reasonably accurate estimates of α_A . The resultant values are given in Table VI, together with related data on H exchange in methoxybenzenes and benzene itself in the same media, aqueous sulfuric acid. The latter results are for detritiation experiments, but the isotope effect is essentially independent of temperature, acidity, and reactivity^{1,4,40,41} and is anyway negligible compared with the wide differences of reactivity of the compounds being compared. The calculated values of α_A , directly indicative of transition state structure, show that although the acetophenones are of equivalent reactivity to, or less reactive than, benzene, the associated transition states are *not* product like in character. There appears little change in transition state structure over a reactivity range of $>10^7$ for the bases in Table VI, the less reactive members being examined at a temperature 35° in excess of that for the more reactive ones.

This conclusion is given wide support by other data

(40) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **89**, 4411 (1967); B. D. Batts and V. Gold, *J. Chem. Soc., London*, 4284 (1964); S. Olsson, *Ark. Kemi*, **32**, 105 (1971); M. Russell, *ibid.*, **31**, 455 (1970).

(41) A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 1065 (1973).

from these laboratories on hydrogen exchange in benzenoid and heteroaromatic molecules which cover an enormous range of reactivities, temperatures, and substituents in sulfuric acid media.^{32,41,42} These do not represent a series specifically constructed to study transition state structure with reactivity variation but, nevertheless, indicate in all relevant cases logarithmic rate variations with H_0 which have slopes considerably less than unity and thus transition state structures which are approximately constant, and certainly never product like. Of these results, possibly the most significant in the context of the present discussion are those for the conjugate acids of 6-hydroxy- and 6-methoxyquinoline⁴² exchanging in the 5 position at 50°. Despite their relatively slow rate of reaction ($\log k$ at 50° in 75% $H_2SO_4 \sim -4$) their acidity dependence is shallow ($-\text{d} \log k / \text{d} H_0 = 0.7$, $-\text{d} \log k / \text{d} H_0 = 0.44$). Moreover, the close correspondence of results for the two compounds substantiates the conformity of the hydroxy group to general patterns of substituent effects. (Essentially constant α_A values would also arise for the rate-determining protonation of styrenes in their acid-catalyzed hydrolysis,⁴³ judging from the near constancy of their $\text{d} \log k / \text{d} H_0$ values, even though the reactivity range is $>10^6$.)

The α_A value for benzene is thus seen to be anomalous rather than illustrative of a systematic variation, its behavior being indicated by the dotted line in Figure 2; this is found not only for hydrogen exchange in aqueous perchloric and sulfuric acid media but also for nitration in the latter medium,⁴⁴ a most unfortunate circumstance judging from the key role of this substrate in the definition of partial rate factors. Extensive results are available for hydrogen exchange of naphthalene in sulfuric acid, but unfortunately they are contradictory. Detritiation gives α_A values of 0.83 at the 1 position and 0.64 at the 2 position,²⁸ while for dedeuteration both values are about unity,²⁹ indicating a transition state equivalent to the Wheland intermediate.

(42) U. Bressel, A. R. Katritzky, and J. R. Lea, *J. Chem. Soc. B*, 11 (1971).

(43) J.-C. Simandoux, B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 4402, 4410 (1972); W. M. Schubert and J. R. Keeffe, *J. Amer. Chem. Soc.*, **94**, 559 (1972).

(44) R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 800 (1968).

The lack of accurate proportionality between α_A , $-\text{d} \log k/\text{d} H_0$, and $-\text{d} \log k/\text{d} H_c$ (see Table VI) appears to arise from the fact that H_0 and H_c are only approximately of linear relationship. If the selectivity factors $-\text{d} \log k/\text{d} H_0$ are compared directly in Table VI, it seems as though 1,3,5-trimethoxybenzene has a more product like transition state than the acetophenones.

The Kresge equation (eq 15) represents a close approximation to the Brønsted equation applied to the case of specific acid catalysis, α_A being construed without equivocation as indicative of transition state structure. Writing the latter equation using the pseudo-first-order form for the rate constant for slow proton transfer from AH^+ to substrate S we have

$$\log k - \log [\text{AH}^+] = \alpha_B \log \frac{[\text{AH}^+]}{[\text{H}^+][\text{A}]} + \text{constant} \quad (19)$$

with which to compare

$$\log k - \log [\text{H}^+] = \alpha_A \log \frac{[\text{ArH}_2^+]}{[\text{H}^+][\text{ArH}]} + \text{constant} \quad (20)$$

derived by manipulation of eq 15. Correlations arising from the use of eq 15 given here and elsewhere¹ thus constitute examples of the most accurate applications of the Brønsted equation, judging from the fit of points to the line defining α_A , albeit in somewhat specialized cases where the variation in acid strength is derived from change in water concentration. Such a variation is thus expressed by variation in the $\log [\text{ArH}_2^+]/[\text{H}^+][\text{ArH}]$ term rather than by $\text{p}K_a$ differences of general acids added to a medium of constant pH containing the substrate.

In conclusion, it would seem that the results quoted here form a further example of the general inadmissibility of the reactivity-selectivity principle, judging from the constancy of \log rate-acidity profile slopes and thus of α_A values both with respect to acidity and therefore reactivity changes for a given substrate, a factor of 10 rate units in the case of the acetophenones, and to substrate reactivity changes by substituent variation. It may be noted that the plots in Figure 2 ii,

being of essentially constant slope over the entire acidity range studied, give rise to an equivalent conclusion in terms of the Hammett equation, in that ρ will remain approximately constant for whatever acidity is chosen for correlation. These considerations make it hard to believe that for electrophilic substitution reactions⁴⁵ or indeed as a general rule, when other work^{3,4,5} concerning different reaction modes is taken into account, substrate selectivity can be systematically altered by change in reactivity of substrates and reagents. By implication the Hammond postulate would also appear to fail; however, it is hard to contradict the rationality of Hammond's original statement.⁴⁶ Indeed, if the validity of the equation of similar structures and similar energies were denied, the whole status of theoretical chemistry would fall into doubt. It appears important to notice that the two concepts, although often considered synonymous, have each a different status. The reactivity-selectivity principle represents a supposed connection between two experimentally defined quantities, assumed to indicate, *via* a number of approximations, the validity of a theoretical concept, the Hammond postulate. Demonstrating the lack of the experimental connection does not seem necessarily to disprove the theory; it has been suggested that the latter may have a valid experimental manifestation as the principle of least motion.⁴⁷

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Supplementary Material Available. Tables I and II in expanded form will appear following these pages in the microfilm edition of this volume of the Journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$5.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-5846.

(45) G. A. Olah, S. Kobayashi, and J. Nishimura, *J. Amer. Chem. Soc.*, **95**, 564 (1973).

(46) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(47) O. S. Tee and K. Yates, *J. Amer. Chem. Soc.*, **94**, 3074 (1972).