

2 h of X-ray time and fluctuated randomly 2% over the entire data collection. Three orientation monitors were centered after every 200 observations. With $Z = 2$, the calculated density was $1.329 \text{ g}\cdot\text{cm}^{-3}$ and $(\text{Mo K}\alpha) = 0.52 \text{ cm}^{-1}$. No correction for absorption or secondary extinction was made.

The initial carbon atoms were placed on positions resulting from a direct methods calculation.¹⁸ The complete molecule was located through a series of least-squares and Fourier calculations. Hydrogen atoms were placed in calculated positions and held invariant with $U(\text{H})$ approximately equal to 1.5 times the equivalent isotropic thermal parameter of the carbon atom to which it was bound. All non-hydrogen atoms were refined anisotropically. All atoms lie on general positions. Full-matrix least squares on all observed reflections yielded $R = 0.067$ and $R_w = 0.064$.¹⁹ The maximum shift in the last cycle was $<0.02\sigma$, the number of variables was 307, and the number of observations was 2165. In a final difference map, the largest peak represented $<0.20 \text{ e}\cdot\text{\AA}^{-3}$. Neutral atom scattering factors were obtained from ref 20.

Details of the crystallographic experiment are summarized in Table I. The following crystallographic data for **3** are included as supplementary material: (i) atomic positional and thermal parameters for non-hydrogen atoms (Tables H and I, respectively); (ii) bond angles and bond lengths for non-hydrogen atoms (Tables J and K, respectively); (iii) hydrogen atomic parameters (Table L); (iv) least-squares planes (Table M); (v) observed and calculated structure factors (Table N).

Reaction of 7-[(*p*-Methoxybenzoyloxy)norbornadiene (6**) with Iron Pentacarbonyl.** To a solution of **6**⁴ (12.37 g, 51.1 mmol) in freshly distilled di-*n*-butyl ether (60 mL) under nitrogen was added a solution of $\text{Fe}(\text{CO})_5$ (20.42 g, 104.3 mmol) in di-*n*-butyl ether (15 mL). The resulting mixture was refluxed with stirring under nitrogen for 26 h and then cooled to room temperature. Workup of the reaction mixture was performed by using the procedure described above for the corresponding reaction of 7-(benzoyloxy)norbornadiene with $\text{Fe}(\text{CO})_5$. The procedure by which cage dimer **7** was isolated and characterized has been described in an earlier publication along with spectral details and the results of elemental microanalysis of **7**.⁴ After removal of **7**, the crude reaction product was further purified via column chromatography on Florisil (100–200 mesh, 15% ethyl acetate–hexane eluent). The first few chromatographic fractions contained

unreacted **6**; however, continued elution of the column afforded dimer ketone **8** (0.19 g, 4%). Recrystallization of this material from ethyl acetate–hexane mixed solvent afforded pure **8** as a colorless microcrystalline solid: mp 241.3–241.7 °C; IR (KBr) 1718 (vs), 1609 (s), 1280 (br, s), 1170 (s), 1115 (br, s), 1030 (s), 848 (m) cm^{-1} ; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 2.31 (AB, $J_{\text{AB}} = 8.2 \text{ Hz}$, 2 H), 2.70 (AB, $J_{\text{AB}} = 8.2 \text{ Hz}$, 2 H), 3.20 (m, 2 H), 3.32 (m, 2 H), 3.85 (s, 6 H), 4.85 (t, $J = 1.7 \text{ Hz}$, 2 H), 6.18 (m, 2 H), 6.21 (m, 2 H), 6.87 (AB, $J_{\text{AB}} = 8.9 \text{ Hz}$, 4 H), 7.89 (AB, $J_{\text{AB}} = 8.9 \text{ Hz}$, 4 H); $^{13}\text{C NMR}$ (CDCl_3) δ 45.57 (d), 50.53 (d), 52.84 (d), 55.36 (d), 57.87 (d), 84.90 (d), 113.61 (d), 122.39 (s), 131.66 (d), 133.23 (d), 134.29 (d), 163.53 (s), 166.49 (s), 216.84 (s); mass spectrum (70 eV), m/e (relative intensity) 512 (M^+ , 1.0), 136 (9.7), 134 (100.0), 77 (6.1).

Anal. Calcd for $\text{C}_{31}\text{H}_{28}\text{O}_7$: C, 72.64; H, 5.51. Found: C, 72.35; H, 5.44.

Acknowledgment. Financial support of our study by The Air Force Office of Scientific Research (Grant AFOSR-84-0085), The Robert A. Welch Foundation (Grant B-963), The North Texas State University Faculty Research Committee, and the Faculty Research Fund, University of Oklahoma Research Council is gratefully acknowledged. X-ray crystallographic structure determinations were supported in part by a grant from the DHHS, National Cancer Institute [CA17562 (to The University of Oklahoma)]; we also thank the University of Oklahoma Computing Center for providing computing facilities and service in this connection.

Registry No. 1, 89278-39-7; 2, 104351-88-4; 3, 104419-67-2; 4, 104419-68-3; 5, 104351-89-5; 6 (Ar = Ph), 4796-68-3; 6 (Ar = *p*- MeOC_6H_4), 7109-81-1; 7, 89321-10-8; 8, 104351-90-8; $\text{Fe}(\text{CO})_5$, 13463-40-6.

Supplementary Material Available: Molecular drawings of **2** and **3** (Figures 1 and 2, respectively). Tables of (i) atomic positional and thermal parameters for carbon, hydrogen, and oxygen, (ii) bond angles, (iii) bond lengths, (iv) hydrogen parameters, and (v) least-squares planes, for **2** and **3** (18 pages); (vi) observed and calculated structure factors for **2** and **3** (40 pages). Ordering information is given on any current masthead page.

Concerning the Hammett Acidity Function Method for Determination of $\text{p}K_a$ Values

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Physicochemical relationships incorporating $\text{p}K_a$ values derived from the Hammett acidity function method (HAFM), on the one hand, and the Cox–Yates excess acidity function method (EAM), on the other, are compared. To the extent that one accords authenticity to such relationships, the estimates of $\text{p}K_a$ values derived from HAFM may approximate, in some cases, more nearly to the correct thermodynamic quantities than those derived from EAM.

Introduction

Within the relatively narrow range of pH of approximately 2–12, where aqueous solutions may be considered ideal, the procedure for measurement of accurate $\text{p}K_a$ values is straightforward. Outside this range, where activity can no longer be equated to concentration, the theory to be employed becomes more imprecise and ambiguous, and currently presents some confusion. This is a very undesirable situation, however, because the property of acidity of organic molecules is a fundamentally important one. Chemists in general thus require an authenticated,

agreed, and standard procedure for obtaining estimates of $\text{p}K_a$ values on which some reliance can be placed.

Two main procedures may be discerned: the Hammett acidity function and the excess acidity function approaches. It is the purpose of this paper to attempt an objective appraisal of these methods and to discuss which one yields $\text{p}K_a$ estimates most nearly relating to ideal conditions. It may be noted that investigators in this area are particularly well served by reviews, which give good accounts of the state of play in both acid and basic media, at the time of their production. These culminate most

recently with an especially excellent and informative contribution,¹ in which previous surveys are comprehensively referenced.

The Hammett Acidity Function Method. This method could also be referred to as the indicator overlap method. It demonstrates correspondence of activity coefficient ratios as in eq 1. Here, B, B', B'', ... are

$$f_B/f_{BH^+} = f_{B'}/f_{B'H^+} = f_{B''}/f_{B''H^+} = \dots \quad (1)$$

members of a set of basic indicators defining a given acidity function H , arising from the operational eq 2 derived by

$$H = -\log a_{H^+} f_B / f_{BH^+} = pK_a - \log I \quad (2)$$

experimental demonstration of "parallelism" of overlapping plots of $\log I$ ($\log [BH^+]/[B]$) for B, B', B'', ... against some measure of the acidity of the solution. A number of such acidity functions have been defined,¹ each one being applicable to a certain class of conjugate acid-base equilibria.¹ Where a base does not follow a known acidity function, the pK_a may be estimated from eq 3, where m is the slope

$$pK_{BH^+} = mH_0 \quad (\text{half-protonation}) \quad (3)$$

of the plot of $\log I$ vs. H_0 , the acidity function defining the acid dissociation of anilinium ions. The justification for eq 3 is that different acidity functions plot approximately linearly against H_0 , with slopes m . This certainly represents an approximation, however, because many of the original indicator acids defining a given acidity may, due to inexact "parallelism", have values of $\log I$ giving slopes somewhat different from unity when plotted against the acidity function they help to define.² Moreover, the fact that these acidity functions do not merge smoothly into the pH range has also been a matter of legitimate concern and criticism.³ However, it is true to say that $\log I$ values for a given acid-base system of any type plot linearly against H_0 with a very high degree of accuracy, with virtually no exceptions.

Excess Acidity Function Methods. Other methods, aimed to counteract this type of deficiency, incorporate the term $\log [H^+]$ into the equations defining the correlation between $\log I$ and pK_a . They thus assume proportionality between terms as shown in eq 4. This method

$$(f_B f_{H^+} / f_{BH^+}) \propto (f_B f_{H^+} / f_{B'H^+}) \quad (4)$$

was pioneered by Marziano et al. and subsequently refined both by themselves⁴ and Cox and Yates.⁵ The latter use the following equations, deriving X from ionization data of as large a number and variety of acids B^*H^+ as possible.⁵

$$\log (f_B f_{H^+} / f_{BH^+}) = m^*(f_B^* f_{H^+} / f_{B^*H^+}) = m^*X \quad (5)$$

$$\log I - \log [H^+] = m^*X + pK_a \quad (6)$$

These authors clearly demonstrate that this "excess acidity" method incorporates other treatments relying on proportionalities of the form of eq 4^{4,6} and suggest it is the

Table I. pK_a Values for H_0 Indicators

anilinium	HAFM			EAM		
	$pK_a^{a,b}$	$pK_a^{c,d}$	ΔpK_a	$pK_a^{a,e}$	$pK_a^{c,f}$	ΔpK_a
4-NO ₂	1.00	1.00	0.00	1.04	1.01	-0.03
2-NO ₂	-0.30	-0.29	0.01	-0.27	-0.18	0.09
4-Cl-2-NO ₂	-1.06	-1.03	0.03	-1.01	-0.89	0.12
2,5-Cl ₂ -4-NO ₂	-1.75	-1.79	-0.04	-1.72	-1.62	0.10
2-Cl-6-NO ₂	-2.38	-2.43	-0.05	-2.40	-2.45	-0.05
2,6-Cl ₂ -4-NO ₂	-3.27	-3.27	0.00	-3.36	-3.27	0.09
2,4-(NO ₂) ₂	-4.27	-4.26	0.01	-4.53	-4.98	-0.45
2,6-(NO ₂) ₂	-5.39	-5.24	0.15	-5.23	-5.79	-0.56
2-Br-4,6-(NO ₂) ₂	-6.69	-6.68	0.01	-5.88	-7.52	-1.64
3-Me-2,4,6-(NO ₂) ₃	-8.33	-8.22	0.11	-7.64	-11.20	-3.56
3-Br-2,4,6-(NO ₂) ₃	-9.34	-9.46	-0.12	-10.49	-12.55	-2.06

^aH₂O/H₂SO₄, ^bReference 9. ^cH₂O/HClO₄, ^dReference 10. ^eReference 5a. ^fReference 5b.

procedure to choose for determination of pK_a values.¹ Such a claim has much appeal from the point of view of generality, and the method has intrinsic practical and theoretical advantages. Its use comprises a completely systematic algorithm, contrasted with the acidity function method, which requires somewhat arbitrary decisions as to what constitutes "parallelism" within reasonably accurate terms. The excess acidity function method places no direct reliance on H_0 or indeed any other specific acidity function measurement. It represents the closest approach so far to a "universal" acidity function, and it smoothes out the transition from the excess acidity to the pH region.³ Thus, for example, it rationalizes the anchoring of the H_A scale, which previously had been misplaced by 0.3 units due to inadequate anchoring indicators.¹ The rationale behind this approach and its potential value are self-evident.

Comparison of the Two Methods. The purpose of this paper is to subject the merits of both procedures to objective and empirical analysis as far as the present state of experimental knowledge will allow and thus to show whether there is any evidence to indicate the choice of one rather than the other. This, of course, will not preclude further research and elucidation, indicating another conclusion in the future. We therefore compare the pK_a values derived from the two methods, the Hammett acidity function method (HAFM), on the one hand, and the excess acidity method (EAM), on the other. If, in general, values correspond, arguments as to which is the more significant become of academic interest only, the method of choice, for all practical purposes, then being merely the pragmatic question of which is the more easy to manipulate mathematically. For example, studies⁷ on the conjugate acids of 5-substituted thiophene-2-carboxamides (which obey the H_A acidity function), using the two different approaches, give pK_a values which agree closely, values being at the most 0.18 units apart, and such deviations as there are being random. Correlation of substituent effects give similar ρ values of similar accuracy. Another example giving close agreement is afforded by the conjugate acids of 5-substituted 3-nitro-2-(dimethylamino)thiophenes⁸ which follow H_0''' .

If, in general, such correspondence was observed, EAM would certainly come into its own, in particular for situ-

(1) Cox, R. A.; Yates, K. *Can. J. Chem.* 1983, 61, 2225.

(2) Arrowsmith, S. N. Ph.D. Thesis, University of East Anglia, 1980.

(3) Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M. F. *Can. J. Chem.* 1983, 61, 249. See also: Greig, C. C. Ph.D. Thesis, University of East Anglia, 1970.

(4) Marziano, N. C.; Tomasin, A.; Traverso, P. G. *J. Chem. Soc., Perkin Trans. 2* 1981, 1070 and references therein.

(5) (a) Cox, R. A.; Yates, K. *J. Am. Chem. Soc.* 1978, 100, 3861, (b) Supplementary material to ref 5a.

(6) Bunnett, J. F.; Olsen, F. P. *Can. J. Chem.* 1966, 44, 1899. Lucchini, V.; Modena, G.; Scorrano, G.; Cox, R. A.; Yates, K. *J. Am. Chem. Soc.* 1982, 104, 1958.

(7) Alberghina, G.; Amato, M. E.; Fisichella, S.; Occhipinti, S. *J. Chem. Soc., Perkin Trans. 2* 1980, 1721.

(8) De Maria, P.; Consiglio, G.; Arnone, C.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* 1983, 481.

(9) Johnson, C. D.; Katritzky, A. R.; Shapiro, S. A. *J. Am. Chem. Soc.* 1969, 91, 6654.

(10) Yates, K.; Wai, H.; Welch, G.; McClelland, R. A. *J. Am. Chem. Soc.* 1973, 95, 418.

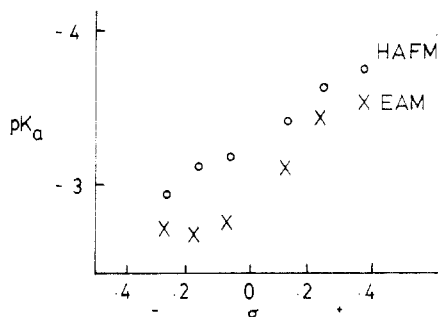


Figure 1. pK_a values of thiobenzamides H^+ vs. σ (4-OMe, 4-Me, 3-OMe, 3-Me, 4-Cl, 3-Cl).

ations in which a conjugate acid ionization followed no known acidity function.

However, doubts arise because frequently there are quite dramatic (up to one or two pK_a units or even more) deviations between the two approaches. For example, although the definition of pK_a demands values for a given conjugate acid should be the same regardless of the aqueous acid in which it is determined¹ and although HAFM demonstrates this within experimental error, EAM often furnishes values which differ quite markedly. The degree of this variation is illustrated for H_0 indicators in Table I, and other scales, H_0''' and H_A , show similar discrepancies using EAM. In this respect, HAFM appears more convincing than EAM but one must not jump to conclusions; HAFM could be more uniform, but it could be more uniformly incorrect. It may be noted that the Marziano (MCPM) version⁴ of the excess acidity function method specifically attempts to take uniformity of pK_a values in different aqueous acids into account, but this has not yet been incorporated into EAM.

There is really only one fundamental criterion to decide which method is the "best", namely which one yields pK_a values from the experimental data that most accurately predict the extent of ionization in the dilute aqueous reference state. Obviously this cannot be measured. If it could, we would not have the problems posed by acidity functions in the first place. Some secondary criterion is therefore required, which is amenable to experimental definition, on which to base the decision. Such a proposal has been made previously:^{11a} do the pK_a values obtained by any given procedure correlate in the "expected" manner with other physicochemical properties of the substrates not dependent on acidity function theory in any way for their definition? Obviously the most commonly used physicochemical parameter to test for correlation will be σ , modified to σ^+ or σ^- as the electronic demands of the reaction center require, but, as we shall see, other parameters can be employed, and often the question boils down to which approach provides numbers which make the best "chemical sense". Such a procedure is clearly arbitrary and inexact, and the extent to which it affords meaningful comparisons must be judged from the discussion given below for individual cases.

Before we outline such correlations, it should be emphasized that a satisfactory correlation, indicating that the pK_a 's involved stand in a reasonable relationship to one another, may suggest that those pK_a 's are thermodynamically correct but certainly does not prove it. A poorer correlation does imply greater errors in the assessment of pK_a 's; however, any individual value need not necessarily be further from the true thermodynamic pK_a than one

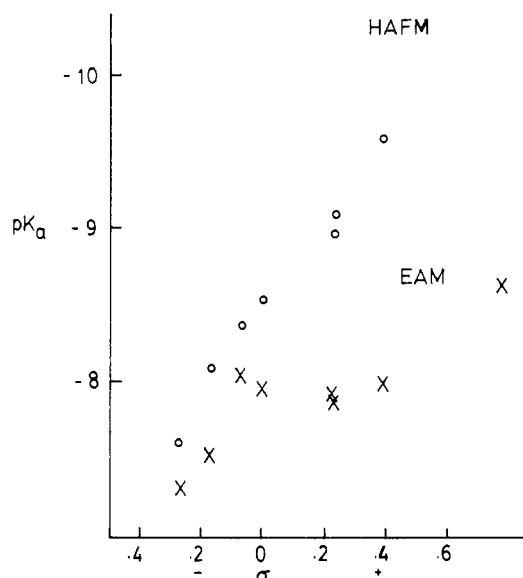


Figure 2. pK_a values of thiobenzoates H^+ vs. σ (4-OMe, 4-Me, 3-Me, H, 4-Cl, 4-Br, 3-Br, 4-NO₂).

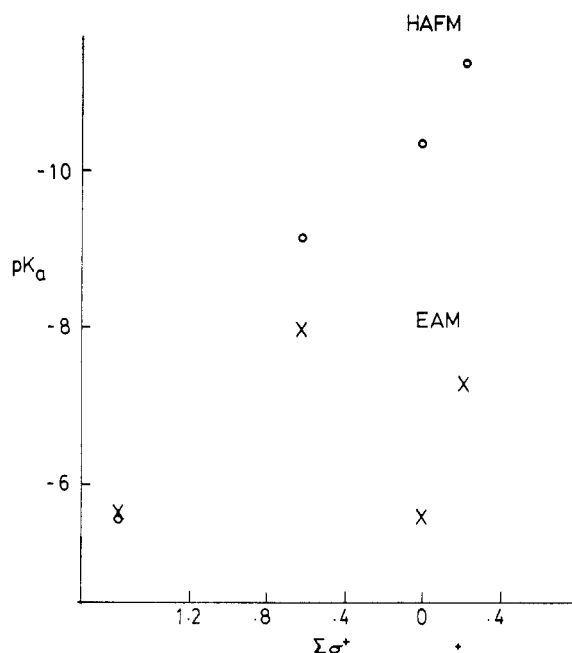


Figure 3. pK_a values of 1,1-diarylethyl cations vs. $\Sigma\sigma^+$ (*p*-OMe₂, -Me₂, and -Cl₂, H).

contained within a more satisfactory correlation.¹²

Discussion

By use of this criterion, therefore, sets of data for protonation of bases requiring an acidity function approach for their appraisal may be examined and the two methods compared. These are set out below. First of all we deal with pK_a -substituent constant correlations and then with correlations of pK_a series with enthalpy measurements, half-neutralization potentials, complexation factors, and the like.

pK_a 's of Thiobenzoates H^+ and Thiobenzamides H^+ .^{5,13} Correlation with σ (Figures 1 and 2):

(12) Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: Orlando, FL, 1985; Chapter 3.

(13) Edward, J. T.; Lantos, I.; Derald, G. D.; Wong, S. C. *Can. J. Chem.* 1977, 55, 812. Edward, J. T.; Derald, G. D.; Wong, S. C. *Can. J. Chem.* 1977, 55, 2331.

(11) (a) Gilbert, T. J.; Johnson, C. D. *J. Am. Chem. Soc.* 1974, 96, 5846.

(b) The EAM calculations for this set of experimental data were carried out by Dr. R. A. Cox.

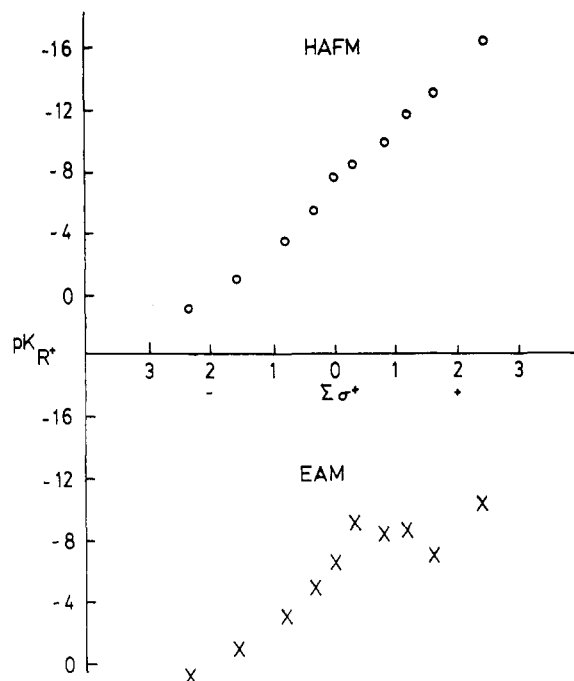


Figure 4. pK_{R^+} values of triarylcaminols vs. $\Sigma\sigma^+$ (4,4',4''-OMe₃, 4,4'-OMe₂, 4-OMe, 4-Me, H, 4,4',4''-Cl₃, 4-NO₂, 3,3',3''-Cl₃, 4,4'-(NO₂)₂, 4,4',4''-(NO₂)₃).

HAFM (H_T thiobenzamides), $\rho = -1.29 \pm 0.07$ (0.9937); EAM (thiobenzamides), $\rho = -1.53 \pm 0.20$ (0.9658); HAFM (H_T thiobenzoates), $\rho = -2.66 \pm 0.10$ (0.9955); EAM (thiobenzoates), $\rho = -0.99 \pm 0.23$ (0.8715). The variation in ρ values apparent from HAFM is reasonable: the C=SH function will be stabilized much more by NH₂ in thiobenzamides than by OEt in ethyl thiobenzoates, so the latter should register a much larger substituent response than the former.¹⁴ EAM shows a small variation in the opposite direction.

pK_a 's of 1,1-Diarylethyl Cations.^{5,15} Correlation with $\Sigma\sigma^+$ (Figure 3): HAFM (H_R), $\rho = -2.92 \pm 0.32$ (0.9885); EAM, $\rho = -0.49 \pm 0.91$ (0.3501).

pK_{R^+} 's of Triarylmethanols.^{16,21} Correlation with $\Sigma\sigma^+$ (Figure 4): HAFM (H_R), $\rho = -3.74 \pm 0.12$ (0.9962); EAM, $\rho = -2.37 \pm 0.34$ (0.9257).

The 4,4',4''-tris(trimethylammonio) compound has been excluded from these correlations because the σ_p^+ value of NMe₃⁺ is uncertain.¹⁷ The 4',4'',4'''-trimethoxy and -trichloro derivatives have been included, but their omission from the above statistical correlations could be justified on the grounds that lack of coplanarity of all three rings will restrict them from exerting their full resonance stabilization of the carbenium ion. In their absence, the correlations become the following: HAFM (H_R), $\rho = -3.91$

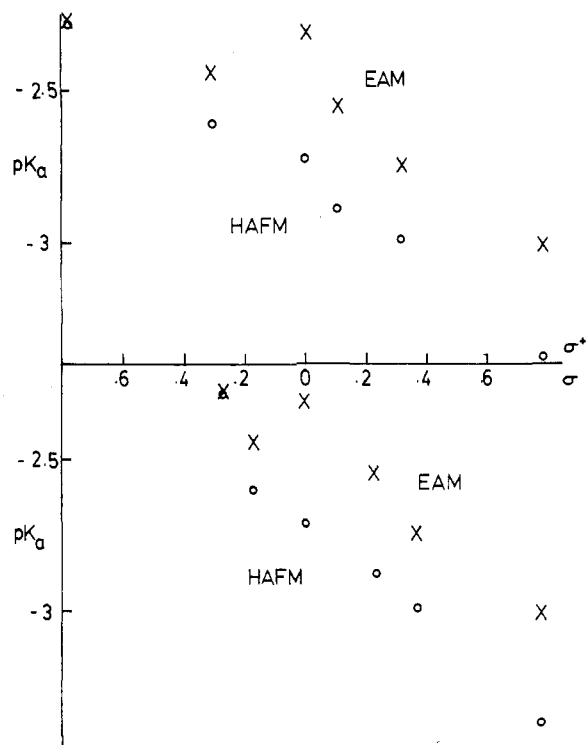


Figure 5. pK_a values of arylmethyl sulfoxides H^+ vs. σ and σ^+ (4-OMe, 4-Me, H, 4-Cl, 3-Cl, 4-NO₂).

Table II. pK_a Values for *p*-Alkyl- and *p*-Methoxyacetophenones

substituent	σ^+	m^a	$-pK_a^a$	m^{*b}	$-pK_a^b$
Me	-0.31	0.67	3.78	0.41	3.00
Et	-0.30	0.62	3.71	0.57	3.73
<i>i</i> -Pr	-0.28	0.67	3.69	0.45	3.05
<i>t</i> -Bu	-0.26	0.70	3.97	0.45	3.24
<i>p</i> -OMe	-0.78	0.59	3.02	0.51	3.04

^a See eq 3. ^b See eq 6.

± 0.11 (0.9975); EAM, $\rho = -2.21 \pm 0.32$ (0.9424).

pK_a 's of Acetophenones H^+ .^{11a,18} Correlation with σ^+ : HAFM (eq 3),¹¹ $\rho = -1.45 \pm 0.10$ (0.9848); EAM,¹⁸ $\rho = -0.93 \pm 0.18$ (0.9188). Here each equation refers to different measurements. The HAFM correlation is shown in Figure 3 of ref 11 (para substituents OMe, SMe, Me, Et, *i*-Pr, *t*-Bu, F, Cl, and NO₂). The EAM correlation is shown in Figure 7, ref 18 (substituents, *p*-OMe, *p*-Me, *m*-Me, H, *p*-Br, and 4-NO₂). If the experimental log *I* values used for the HAFM correlation^{11b} are treated by using the EAM approach, the correlation with σ^+ gives $\rho = -1.49 \pm 0.28$ (0.8982). It is perhaps illuminating to look at the values afforded by either method for the *p*-alkyl series of acetophenones Me, Et, *i*-Pr, and *t*-Bu, groups which might be expected to have a very similar influence on the acid function behavior and pK_a value, since their σ^+ values are very similar, and no steric effects are possible. Table II shows the relevant figures. The table also shows that the predicted strong acid weakening effect of *p*-OMe relative to *p*-Me, revealed by HAFM, is lost when EAM is used.

pK_a 's of Benzophenones H^+ .¹⁹ Correlations with σ^+ and σ . Stewart has recently discussed these results.¹² From HAFM $r = 0.974$ (σ^+) and 0.976 (σ); From EAM $r = 0.716$ (σ^+) and 0.747 (σ). Stewart concludes that the poor correlations with EAM are due to much greater error in determining pK_a values by extrapolative techniques than the "beguilingly" small standard errors for the individual compounds would suggest.

(14) This phenomenon of nonadditive substituent effects or cross-interaction has been discussed previously. See, for example: More-O'-Ferrall, R. A.; O'Brien, M. O. *J. Chem. Soc., Perkin Trans. 2* 1978, 1045. Johnson, C. D. *Tetrahedron* 1980, 36, 3471. Dubois, J.-E.; Ruasse, M.-F.; Argile, A. *J. Am. Chem. Soc.* 1984, 106, 4840. Goethals, G.; Membrey, F.; Ancian, B.; Doucet, J. P. *J. Org. Chem.* 1978, 43, 4944.

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(18) Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* 1979, 57, 2952.

(19) Bonner, T. G.; Phillips, J. *J. Chem. Soc. B* 1966, 650.

(20) Landini, D.; Modena, G.; Scorrano, G.; Taddei, F. *J. Am. Chem. Soc.* 1969, 91, 6703.

(21) Cox, R. A.; Yates, K. *Can. J. Chem.* 1984, 62, 2155.

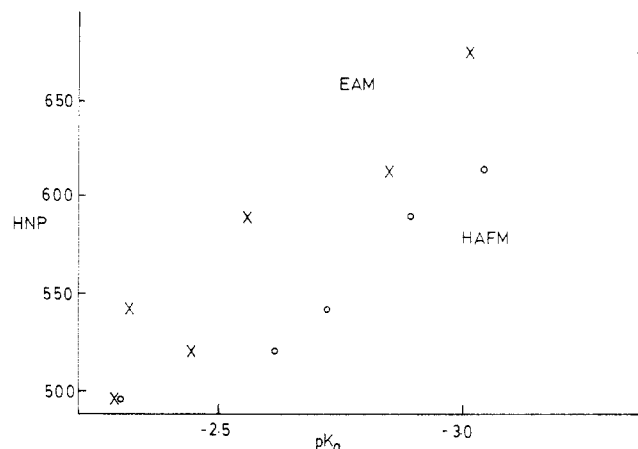


Figure 6. HNP values of arylmethyl sulfoxides H^+ vs. pK_a (substituents as for Figure 5).

pK_a 's of Arylmethyl Sulfoxides H^+ .²⁰ **Correlations with σ^+ and σ .** It is difficult to assess the change in through-conjugation between the protonated and unprotonated sulfoxides and thus to choose between σ^+ and σ for correlation. Therefore both are listed and shown in Figure 5. For these correlations, we averaged the UV and NMR data for both aqueous H_2SO_4 and $HClO_4$. It would appear that σ^+ rationalizes the relationship best using HAFM. HAFM (H_A): $\rho^+ = 0.67 \pm 0.04$ (0.9912); $\rho = 0.92 \pm 0.10$ (0.9775). EAM: $\rho^+ = 0.46 \pm 0.12$ (0.8941); $\rho = 0.69 \pm 0.11$ (0.9515).

pK_a 's of Arylmethyl Sulfoxides H^+ .²⁰ **Correlation with Half-Neutralization Potentials (HNP's)** (Figure 6): HAFM (H_A), HNP (mV) = $-178 (\pm 18) pK_a + 74 (\pm 14)$ (0.9810); EAM, HNP (mV) = $-227 (\pm 34) pK_a - 6 (\pm 21)$ (0.9579).

pK_a 's of Anilinium Ions. Correlation with Steric and Electronic Effects.^{9,21,22} Results for the H_0 acidity function⁹ give pK_a values for 3-methyl- and 3-bromo-2,4,6-trinitroaniline and 2,4,6-trinitroaniline of -8.33, -9.34, and -10.03 respectively. Applying the EAM to these results gives the corresponding values -8.20, -10.82, and -10.35.²¹ It is pointed out^{21,22} that the latter sequence is more reasonable, because 3-methyl is an electron donor, 3-bromo an electron acceptor ($\sigma_m = -0.07, 0.39$, respectively). But this neglects steric effects, which are well-known to possess the ability to disrupt the interpretation of series with otherwise consistent structural changes of known electronic effect: it is quite certain that in the 3-methyl and 3-bromo compounds the flanking nitro groups will be twisted, thereby losing much of their resonance electron-withdrawing capacity, which makes a large contribution to the overall effect ($NO_2, \sigma_1 = 0.63, \sigma^- = 1.27$). The steric influence of Me and Br are rather similar (van der Waal's radii 2.00 and 1.95 Å, respectively). A combination of the two influences will thus readily explain this sequence of pK_a values as calculated by HAFM.

pK_a 's of Anilinium Ions. Correlation with ΔH°_{25} .^{9,21,23} Linear correlations between ΔG and ΔH are the norm for a uniform reaction series of constant mechanism and are a necessary presumption for any LFER.²⁴ Thus Bolton and Hall²⁵ have demonstrated that 16 out of

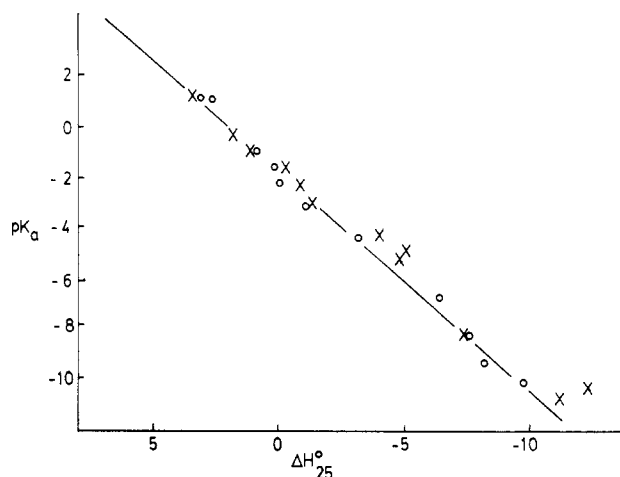


Figure 7. pK_a vs. ΔH°_{25} (kcal mol⁻¹) for anilinium dissociation. The line is drawn by using eq 7. (O) HAFM; (X) EAM.

19 monosubstituted anilines gave an exact linear correlation, eq 7, between pK_a , determined under standard-state

$$pK_a = 8.81 (\pm 0.08) \times 10^{-4} \Delta H^\circ_{25} - 1.97 (\pm 0.06) \quad (0.9994) \quad (7)$$

conditions, and their enthalpies of proton ionization, ΔH°_{25} . The remaining three points deviated only marginally from the line. Figure 7 shows the line calculated from eq 7 extended from the pH region to the acidity function region, together with the points obtained from temperature-variation studies on the H_0 aniline indicators. HAFM⁹ gives a fairly close correspondence, eq 8. By

$$pK_a = 8.66 (\pm 0.27) \times 10^{-4} \Delta H^\circ_{25} - 1.89 (\pm 0.38) \quad (0.9953) \quad (8)$$

EAM,²¹ the relevant equation is

$$pK_a = 7.64 (\pm 0.30) \times 10^{-4} \Delta H^\circ_{25} - 1.71 (\pm 0.50) \quad (0.9923) \quad (9)$$

The smooth transition of this correlation from the pH to the H_0 region by using HAFM is discussed by Stewart¹² and supports the idea that pK_a values within it do, in fact, refer to the dilute aqueous standard state. It would seem therefore that results of the form expressed in eq 7 and 8 would be particularly significant, since they indicate that not only are the relative pK_a changes, produced by systematic structural alteration, correct but that the values themselves represent thermodynamic quantities.

pK_{R^+} 's of Carbinols. Correlation with ΔH°_{25} .^{16,21,26} Early work²⁶ on the temperature variation of H_R using HAFM gave a correlation for which eq 10 expresses the best straight line, shown in Figure 8. Later experimental

$$pK_{R^+} = -7.25 (\pm 1.40) \times 10^{-4} \Delta H^\circ_{25} - 7.09 (\pm 2.91) \quad (0.8906) \quad (10)$$

studies,¹⁶ again using HAFM, were in marked contrast, as given by eq 11 and shown in Figure 8, and linearity is much

$$pK_{R^+} = 3.54 (\pm 0.15) \times 10^{-4} \Delta H^\circ_{25} + 1.23 (\pm 0.77) \quad (0.9913) \quad (11)$$

more closely approximated. The distinction between the two sets of data is lost on application of the EAM.²¹ Thus for tris(4-methylphenyl)methanol, ΔH°_{25} is 3860²⁶ and 18485¹⁶ cal mol⁻¹ by using HAFM for the two sets of experimental data. By using EAM, the values become 8720

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Table III. Equilibrium Acidities of Carbon and Nitrogen Acids Determined by the H_- Method in H_2O/Me_2SO and in Pure Me_2SO ³⁰

carbon acid ^a	$pK_a(Me_2SO)^b$	$pK_a(H_-)^c$	nitrogen acid	$pK_a(Me_2SO)$	$pK_a(H_-)$
9-CNFIH	8.3	11.4	2,4-(NO ₂) ₂ C ₆ H ₃ NH ₂	15.9	15.0
9-CO ₂ MeFIH	10.35	12.8	4-NO ₂ C ₆ H ₄ NHPh	16.85	15.6
(CN) ₂ CH ₂	11.05	11.1	2-NO ₂ -4-ClC ₆ H ₃ NH ₂	18.9	17.1
(<i>p</i> -NO ₂ C ₆ H ₄) ₃ CH	12.7	14.3	3-ClC ₆ H ₄ NHPh	23.4	20.7
(<i>p</i> -NO ₂ C ₆ H ₄) ₂ CH ₂	15.1	15.85	Ph ₂ NH	24.95	22.4
9-(<i>m</i> -ClC ₆ H ₄)FIH	16.85	18.1	4-CNC ₆ H ₄ NH ₂	25.5	22.7
9-C ₆ H ₅ FIH	17.9	18.6	4-NH ₂ -pyridine	26.5	22.3
2-CNFIH	18.2	19.0	3-CNC ₆ H ₄ NH ₂	27.5	24.6
2-BrFIH	20.0	20.6	2-NH ₂ -pyridine	27.7	23.5
9-PhCH ₂ FIH	21.4	21.2	3-CF ₃ C ₆ H ₄ NH ₂	28.2	25.4
9-MeFIH	22.3	21.8	3-ClC ₆ H ₄ NH ₂	28.5	25.6
HF1H	22.6	22.1			
2-MeOF1H	22.75	22.4			
9- <i>t</i> -BuFIH	24.35	23.4			

^a HF1H is used as an abbreviation for fluorene. ^b Reference 30a. ^c Reference 30b.

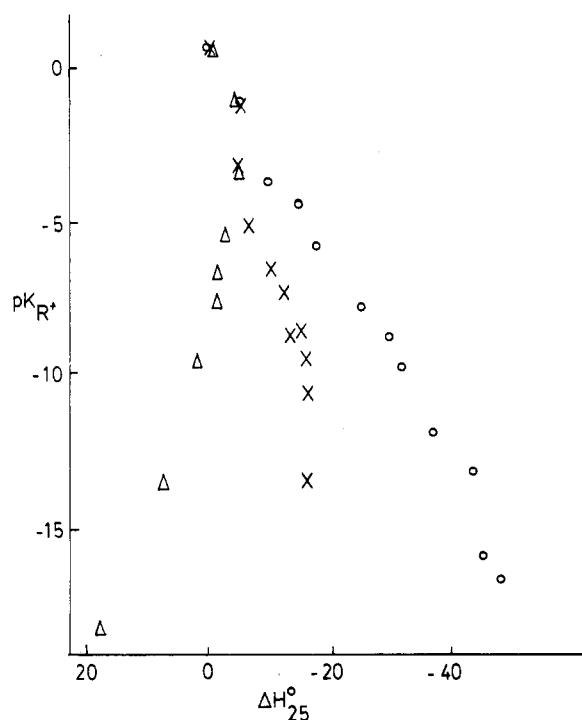


Figure 8. pK_{R^+} vs. ΔH_{25}° (kcal mol⁻¹) for carbinol ionization. (O) HAFM;¹⁵ (Δ) HAFM;²³ (X) EAM.¹⁸

± 440 and 8150 ± 230 , respectively, within two standard deviations of each other. The resultant EAM correlation combining the two sets of experimental data is also shown in Figure 8 and given in eq 12. A decision has to be made $pK_{R^+} = 7.90 (\pm 0.96) \times 10^{-4} \Delta H_{25}^\circ - 2.56 (\pm 1.44) (0.9461)$ (12)

whether the later work¹⁶ is more accurate than the earlier work,²⁶ and therefore HAFM performs here better than EAM in that the latter completely fails to differentiate between them, or whether the results offer support for the EAM approach in that it rationalizes discrepancies between two equally inaccurate sets of results.

pK_a 's of Anilinium Ions.^{9,21} Correlation with ΔH (FSO₃H).²⁷ Arnett has measured the heats of transfer of a series of primary aniline bases from inert solvent to FSO₃H (see Table III of ref 27). About half are sufficiently

basic for the pK_a 's to be determined under ideal conditions; the other half require an acidity function approach and indeed serve as indicators for H_0 .⁹ The correlations are as follows: HAFM, $\Delta H = 1.67 (\pm 0.07)$, $pK_a + 27.99 (\pm 1.35)$ (0.9823); EAM, $\Delta H = 1.70 (\pm 0.07)$, $pK_a + 27.90 (\pm 1.35)$ (0.9822).

Correlations with H_- Indicators. It is theoretically possible to compare the HAFM and EAM approaches to data for weak acids, that is those giving measurable ionization ratios in the H_- region, using the sorts of criteria discussed above. However, the Cox-Yates EAM has not yet been extended into the excess basicity range, although the closely related MCPM^{4,22} has been used by Cox and Stewart for this purpose.²⁸

A more serious point also arises: it has been pointed out²⁹ that "most chemists appear to have abandoned the H_- approach in favor of working in pure solvents. Examination of Table III indicates that the H_- method is exhibiting nonideal behavior. Nonideality has been recognized by experts in the field.²⁸ The H_- derived value of the pK_a of 9-phenylfluorene is 18.59 in EtOH/ Me_2SO , 18.49 in H_2O /sulfolane, and 18.38 in H_2O/Me_2SO . The pK_a determined in Me_2SO , the wider acidity range covered, and the simplicity of the method combine to make measurements in pure Me_2SO the method of choice. No pK_a determinations by the H_- method appear to have been published since 1977 when the method in Me_2SO was established."³⁰

Thus any comparison of the HAFM and EAM in this area would seem to be premature, although it is hoped to make this the subject of a subsequent publication.

Conclusion

In the examples of structure-reactivity correlations which we have been able to find, HAFM performs as well as EAM and, in some cases, somewhat better. This fact, taken in conjunction with the noncorrespondence of EAM pK_a values for the same compounds in different aqueous

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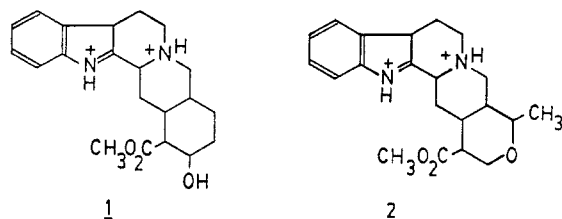
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acids, might appear to cast doubt on the authenticity of the latter method in some instances, *provided of course one accepts, first, that it is likely that pK_a values should follow such correlations and, second, that the examples given here, if not exhaustive, are representative and typical.* Both of these suppositions are open to question and debate and further experimentation. To the extent that such criticism of EAM is justified, however, it would also extend of course to treatment of acid-catalyzed reactions, because such reactions involve either a slow protonation step or a rapid preequilibrium protonation step. Thus, for example, the deduction¹⁸ that the mechanism of acid catalyzed enolization of 4-nitroacetophenone is different to that of other substituted acetophenones is dependent on treatment of the thermodynamic ionization behavior of the compound protonating at carbonyl oxygen (see previous discussion). Kresge has suggested⁹ that EAM performs most efficiently in dilute acid solutions, and the results reported here tend strongly to agree with this: it is in the middle and higher regions of acidity that discrepancies most markedly arise. In other words, the further one has to go into strong acid or strong base to make experimental measurements of ionization ratios, the greater the chances of discrepancies in pK_a evaluation between EAM and HAFM. This has been rationalized by Cox.³¹ As he points out "this arises from the extrapolative nature of EAM. It is much easier, and more precise, to measure differences at the half-ionization point; when anchored and added these will in general give better LFER's than those obtained by extrapolations each of a different length. The vast majority of existing measurements were obtained with HAFM in mind, and usually do not have accurate values at large and small ionization ratios which would lend confidence to an X-function extrapolation." We agree completely with this rationalization.

Its validity as the basic drawback to EAM is well illustrated by recent results³² on the ionization of indolenium cations of the Rauwolfia alkaloids yohimbine 1 and ajmalicine 2, results which also serve to pinpoint the concomitant defects of the HAFM.



Consideration of the above structures and examination of molecular models strongly suggest that the variations in structure should have neither electronic nor steric influence on the ionization of the indolenium nucleus. In keeping with this, HAFM using H_1 ^{32,33} gives pK_a 's of -8.30 and -8.31, a conclusion that at the same time requires that $-d \log I/dH_1$ values of 0.97 and 1.07 both indicate conformity to the H_1 acidity scale. As Figure 9 also shows, however, the lengthy extrapolation of EAM gives values of -6.38 and -6.85, values well separated from one another and even further separated from the HAFM values. The

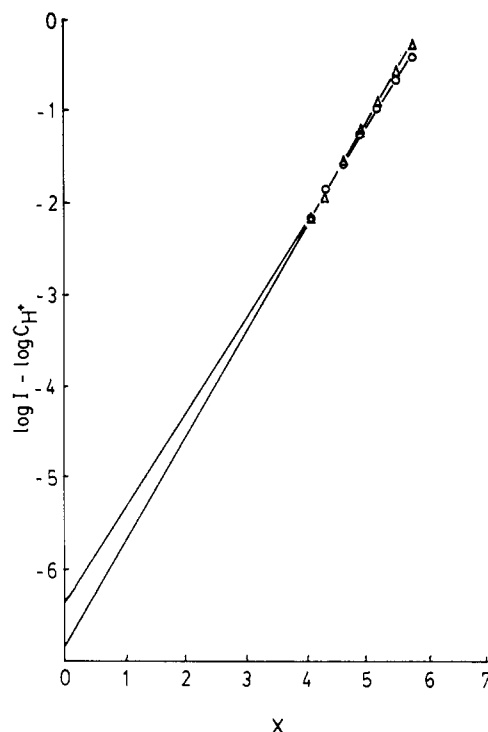


Figure 9. Application of HAFM and EAM to ionization data for Rauwolfia alkaloids. (O) yohimbine; (Δ) ajmalicine.

authenticity of Cox's conclusion is also well illustrated by the carbenium plots given in Figure 3, where pK_a values for each carbenium ion are based on only three or four log I value determinations and thus the extrapolative method is very likely to perform inefficiently: accordingly, this might well be an area for more extensive investigations. Of course, log I values necessarily decrease in accuracy as they diverge from 0, becoming totally unreliable much beyond the range ± 1.5 when measured under even optimum conditions, and medium effects may further reduce accuracy of measurement. Further experimentation on series of strong or weak acids, whose pK_a 's fall in the acidity function region, and consideration of their correlation with either structural parameters or other properties³⁴ might thus reverse the tentative conclusion reached here. Such experimental results are awaited with interest.

It is therefore generally to be expected that speculation about the most accurate way to define pK_a values of strong and weak acids whose regions of observable ionizations lie outside the pH range will continue; the fundamental character of the quantity to be defined means that such enquiries will not be without significance and that, within the discussion entailed, the concept of an acidity function as defined by Hammett, even if by now over 50 years old, may still have a degree of relevance.

Acknowledgment. It is a pleasure to thank Professor K. Yates and Dr. R. A. Cox for helpful and lengthy discussions, Professor M. Balon and Professor G. Scorrano for supplying unpublished ionization data for indole alkaloids and sulfoxides, and SERC for a grant to B.S. We regret that no reprints are available for this article.

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