Co.; the second indene sample was obtained from Neville Chemical Co. and was twice distilled, taking the middle cut each time. The poduct was isolated to confirm that only the nonaromatic double bonds of 1 were reduced during the heat of hydrogenation determination. IR, UV, and NMR spectra, as well as GC retention time, confirmed its identity with 1,1'-spirobiindane.[2]

Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.41; H, 7.54.

Registry No. 1, 165-42-4; 6, 205-12-9; 6·picrate, 70667-77-5; 6·1,3,5-trinitrobenzene, 75299-14-8; 6·2,4,7-trinitrofluorenone, 75311-34-1.

Effects of Alkyl Groups on Rates of Acyl-Transfer Reactions

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The Taft equation in σ_I (or σ^*) and E_s has been examined critically for two major purposes: to provide a definitive evaluation of the significance of polar or other nonsteric effects of alkyl groups and to determine what types of steric effects can be correlated among acyl-transfer reactions. The evaluation has led to several conclusions of general interest. (1) The σ^* values of alkyl groups are an artifact; they represent a residual steric effect plus an error component. (2) The apparent need for the $\rho_I\sigma_I$ term or other nonsteric term for alkyl groups is also an artifact. (3) A recent sophisticated statistical analysis which purports to show a need for a nonsteric $\beta_2\theta_2$ term is based on a seriously flawed data set. (4) Proposed alternatives to E_s such as E_s^c, υ, or θ_2 are without special merit and should be abandoned. (5) The Dubois E_s' values extend the E_s set but are based on a slightly different scale. Except for values which correct erroneous experimental data, correlations with the E_s' (Dubois) set are comparable to correlations with the E_s (Taft) set. (6) Procedures are suggested and implemented for reevaluating E_s values and for determining new E_s values. (7) The Taft equation is applicable to steric effects in the alkoxyl group and in the entering nucleophile as well as in the acyl group. (8) All types of acyl-transfer reactions are, in principle, suitable for the measurement of steric effects of alkyl groups. (9) Variations in the ρ_s constant are interpreted in terms of limitations on additivity of steric effects.

Although steric effects play a major role in controlling rates of reactions, research on steric influences has been discouraged by recognition of the possibility of nonadditivity and by doubts about the validity of the available linear free-energy relationships (LFER's).[1-3] Recent developments in the theoretical computation of steric effects on reaction rates promise to provide a firm theoretical underpinning.[4-8] Further progress will depend on new experimental efforts designed to improve the reliability of the data for sterically crowded reactants and to extend the range and the variety of steric effects for which quantitative values are available.

There is also a major role for empirical LFER treatments of steric effects. It becomes of interest, therefore, to carry out a detailed critical evaluation of the presently available LFER treatments in order to assess the importance of nonsteric effects and to point up a number of potentially useful extensions.

It has been recognized that four major factors determine the reactivity of a functional group. These have usually been identified as polar, steric, resonance, and solvation.[1-3] Steric effects and solvation are clearly through-space effects and for several systems polar effects have been computed theoretically as through-space effects by the Kirkwood–Westheimer equation or by related expressions.[9-13] Resonance effects are through-bond effects, but there are other through-bond effects, and the more general term bonding effects may be used to designate all types. A bonding effect is a through-bond effect that alters the free energy of formation of a molecule or of a transition state. Hyperconjugation is a further example.[2,14] Less well recognized is the branching effect which alters enthalpies of formation as in the pentane series: $\Delta H_f = -35.0$ (pentane), -36.9 (2-methylbutane), and -39.7 kcal/mol (2,2-dimethylpropane).[15] Additional examples are to be found in S_N2 reactions,[16] and an example directly pertinent to acyl transfer is given below.

Interactions among the several effects can lead to complexities, but if the main effects can be sufficiently well isolated, then interactions become relatively unimportant.

The proper sorting out of polar effects has long been a goal;[1-3,17,18] we propose instead to sort out steric effects. The primary emphasis is on alkyl groups and on cycloalkyl systems since these constitute a particularly rich popula-

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tion from which to select molecules having any desired range of steric effects.

It is relatively easy to avoid the complications of bonding effects by limiting the systems to saturated molecules having the same atoms attached to the reaction center. In addition to avoiding molecules where resonance is possible, it is necessary to avoid comparisons between formic esters and other esters. The system H—C=O has a different bonding at the reaction center than does the system C—C=O, and as a result formic esters differ from substituted acetic esters in steric effects, in polar effects, and in bonding effects of unknown magnitude. Failure to take cognizance of this complication has led to questionable assignments of steric and polar effects to H. We shall later on take a further look at hyperconjugation.

Solvation effects among substrates designed for studies of steric effects may be expected to remain constant or perhaps may tend to parallel the steric effects. In either event it is possible to obtain unambiguous relative values of steric effects.

What remains to be considered is the separation of polar effects and steric effects. Taft's pioneering dissection is based on the definition of steric constants (E_s, eq 1) derived

$$\log [k(\mathrm{RCOOEt})/k(\mathrm{CH_3COOEt})] = E_s \qquad (1)$$

from rate constants of acid-catalyzed hydrolysis of esters.[1] The general LFER is eq 2 or eq 3 in the older notation.[1,19]

$$\log k = a + \rho_s E_s + \rho_I \sigma_I \qquad (2)$$

$$\log k = a + \delta E_s + \rho^* \sigma^* \qquad (3)$$

Standards of reference were established for eq 3 by defining $E_s = 0$ for R = Me and $\delta = 1.000$ for acid-catalyzed hydrolysis of RCOOEt (actually in 70% aqueous acetone). Equation 1 follows from these two assignments plus also setting $\rho^* = 0$ for acid-catalyzed hydrolysis of esters, a choice based on experimental data. Of the many examples which justify this choice the following is typical: for HCl in H_2O, the ratio of relative rate constants $k(\mathrm{CH_3CH_2COOEt}):k(\mathrm{CH_2ClCOOEt}):k(\mathrm{CHCl_2COOEt})$ is 1.00:0.64:1.02.[20,21] Rate constants are nearly the same in spite of major differences in polar effects.

It is the definition of polar terms that has been the principal source of controversy.[2,3] The original definition was by direct comparison of acid-catalyzed and base-catalyzed hydrolyses, eq 4, with $\sigma^* = 0$ for Me and $\rho^* = 2.48$.

$$\log (k/k_0)_B - \log (k/k_0)_A = \rho^* \sigma^* \qquad (4)$$

There are two problems with eq 4. As a practical matter there are relatively few examples of parallel data for k_B and k_A. This is partly for the experimental reason that many esters of interest do not undergo simple hydrolysis under acidic conditions. A second problem is that this specialized definition of σ^* violates the principle of generalization implied in eq 2 and 3. It defines ρ_s or δ as 1.000 for base-catalyzed hydrolyses, and that proves to be incorrect for some reactions.

The trend has been to abandon the σ^* and ρ^* scale in favor of σ_I polar constants having $\sigma_I = 0$ for H. The σ_I scale is indirectly tied to eq 4 through the expression $\sigma_I = \sigma^*/6.22$, a relationship that holds for strongly polar groups.[1,22,23] Likewise $\rho_I = 6.22\rho^*$.

There are conflicting claims about the significance of σ_I and σ^* values for alkyl groups. They represent polar effects that can be used to interpret mechanisms.[3,26–28] Or, on the contrary, the polar effects of alkyl groups are zero.[2,29c] As a third alternative, σ_I or σ^* represents some as yet unidentified property of alkyl groups. There are also conflicting claims about steric constants. Various suggestions have been made for replacing E_s by other sets such as E_s^c [30–32] and E_s',[28] or by υ,[29] or by θ_1.[33] Some of these proposals have been reviewed.[3] The lack of constancy of ρ_s (or δ) values has led to some to question the whole rationale for the LFER approach through eq 2 or 3.[2,3] And the proper application of statistical evaluations is a continuing issue.[33]

We seek to put these several matters into perspective through a critical analysis of the Taft equation. The first stage is to consider the characteristics of the steric term and of the polar term and the range of structural variation susceptible to correlation. The next stage is to examine the evidence relating to polar effects or other nonsteric effects of alkyl substituents, in particular the significance of σ^*, σ_I, and θ_2. Then evaluation of the E_s steric constants is considered, and a proposed procedure is illustrated by reevaluation of E_s values for nine alkyl groups. The merits of certain other proposed measures of steric effects are considered, including E_s^c, E_s', υ, and θ. Inasmuch as these several stages are intertwined, it will not be possible to achieve a complete separation.

It has been known from the outset that ρ_s values are not unity for all acid-catalyzed acyl-transfer reactions. Ester exchange of RCOO-β-naphthyl has $\rho_s = 1.37$ in MeOH, 1.46 in *n*-PrOH, and 1.89 in *i*-PrOH.[34] These values agree with those of Table XIV of ref 1, except for *n*-PrOH. Acid-catalyzed hydrolysis of $\mathrm{RCOOC_6H_4NO_2}$-*p* has $\rho_s = 0.59$.[35] We shall consider the significance of these values after the ρ_s values for base-catalyzed reactions have been examined.

Typical data for base-catalyzed hydrolyses of esters are summarized in Tables I–IV. Tables I and II include a representative range of polar substituents while Tables III and IV involve the behavior of alkyl-substituted esters in partly nonaqueous solvents. Tables I and III present data for R of the acyl group RCOOR′ while Tables II and IV

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Table I. Alkaline Hydrolysis of RCOOEt in Water with NaOH at 25 °C Except from Source *f*

R	σ_I	$-E_s$[a]	log k_{rel} (obsd)	log k_{rel} (calcd)		source	
						k_{rel}	σ_I
CH_3	−0.046	0	2.00[b]	1.98[c]	1.90[d]	*e,g,h*	*k*
CH_3CH_2	−0.057	0.07	1.95	1.92	1.73	*e*	*k*
CH_3CH_2			1.86			*f*	
$CH_3CH_2CH_2$	−0.061	0.36	1.72	1.68	1.53	*e*	*k*
$CH_3CH_2CH_2$			1.57			*f*	
$(CH_3)_2CH$	−0.065	0.47	1.69	1.59	1.43	*e*	*k*
$(CH_3)_2CH$			1.45			*f*	
$(CH_3)_2CHCH_2$	−0.065	0.93	1.40	1.21	1.19	*e*	*k*
$(CH_3)_2CHCH_2$			1.02			*f*	
$CH_3CH_2CH(CH_3)$	−0.069	1.13	0.90	1.04	1.04	*f*	*k*
$(CH_3)_3C$	−0.074	1.54	.53	0.70	0.77	*f*	*k*
CH_3OCH_2	0.10	0.19	3.29	3.36	3.62	*e*	*l*
$C_6H_5CH_2$	0.03	0.38	2.28	2.13	2.65	*e*	*l*
FCH_2	0.18	0.24	4.10[m]	4.55	4.59	*g*	*l*
FCH_2			4.15[m]			*h*	
F_2CH	0.32	0.67	6.43	6.35	6.11	*h*	*l*
F_2CH			6.61			*i*	
F_3C	0.43	1.16	7.22	7.64	7.23	*h*	*l*
$ClCH_2$	0.16	0.24	4.48	4.24	4.34	*j*	*l*
$ClCH_2$			4.41			*h*	
$ClCH_2$			4.44			*g*	
$ClCH_2$			4.52			*i*	
Cl_2CH	0.31	1.54	5.79	5.47	5.54	*j*	*l*
Cl_2CH			5.69			*h*	
Cl_2CH			5.91			*i*	
Cl_3C	0.41	2.06	6.37	6.58	6.52	*j*	*l*
Cl_3C			6.26			*h*	
$BrCH_2$	0.17	0.27	4.66	4.37	4.45	*j*	*l*
$BrCH_2$			4.53			*h*	
$BrCH_2$			4.65			*g*	
Br_2CH	0.30	1.86	5.27	5.05	5.26	*j*	*l*
ICH_2	0.18	0.37	4.17	4.44	4.52	*j*	
ICH_2			4.13			*h*	*l*
ICH_2			4.28			*g*	
$NCCH_2$	0.18	0.20	4.29	4.58	4.61	*g*	*l*

[a] Table VI of R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. Newman, Ed., Wiley, New York, 1956, p 556. [b] Observed standard deviation 0.11 (16 DF). [c] Log $k = 1.979 + 15.39\sigma_I + 0.830E_s$, $s = 0.24$, $r^2 = 0.984$, $s_a = 0.06$, $s_{\rho_I} = 0.36$, $s_{\rho_s} = 0.08$; setting $\sigma_I = 0$ for all alkyl groups (37 points, initial point used three times). [d] Log $k = 2.474 + 12.429\sigma_I + 0.508E_s$, $s = 0.26$, $r^2 = 0.982$, $s_a = 0.06$, $s_{\rho_I} = 0.3$, $s_{\rho_s} = 0.08$ (37 points, Me point included three times). [e] H. Olsson, *Z. Phys. Chem., Abt. A*, **133**, 233 (1928). [f] J. P. Idoux and J. O. Schreck, *J. Org. Chem.*, **43**, 4002 (1978); data are for $RCOOCH_3$ at 20 °C in 40% aqueous dioxane; values are relative to $k(CH_3COOCH_3) = 100$. [g] J. Ashworth and B. A. Coller, *Trans. Faraday Soc.*, **67**, 1069, 1077 (1971); for CH_3COOEt in H_2O with NaOH, log k_{OH} (M^{-1} s^{-1}) = −0.97 (25 °C). [h] J. Barthel, G. Bäder, and G. Schmeer, *Z. Phys. Chem.* (*Weisbaden*) **62**, 63 (1968); for CH_3COOEt in H_2O with NaOH, log k_{OH} (M^{-1} s^{-1}) = −0.95, (25 °C). [i] W. P. Jencks and J. Carriulo, *J. Am. Chem. Soc.*, **83**, 1743 (1961). [j] E. K. Euranto and A. L. Moisio, *Suom. Kemistil. B*, **37**, 92 (1964). [k] R. W. Taft and L. S. Levitt, *J. Org. Chem.*, **42**, 916 (1977). [l] Table 10.4 of O. Exner, "Correlation Analysis in Chemistry", N. B. Chapman and J. Shorter, Eds., Plenum Press, New York, 1978, p 439. [m] Values from here to the end of table are log k_{25} (M^{-1} s^{-1}) of the paper cited plus 2.96.

have data for the alkoxy group OR′. For sake of clarity the tables list the specific values we have adopted for σ_I, E_s, and log k.

There are minor ambiguities about application of eq 2 to the data of Table I; these are a representative sample of the data used to define σ^* values for polar groups on the basis of the assignment of $\rho^* = 2.48$ and $\delta = 1.00$ (eq 3). However, the best line has $\rho_I = 12.4$ (standard deviation 0.3, equivalent to $\rho^* = 1.99$) and $\rho_s = 0.51$ (standard deviation 0.08), the error limits being based on 0.26 as the standard deviation of log k(calcd). (The replicate standard deviation is 0.11.) If, however, the σ_I value is taken as zero for every alkyl group, then $\rho_I = 15.4$ (standard deviation 0.4, equivalent to $\rho^* = 2.48$) and $\rho_s = 0.83$ (standard deviation 0.08); these values of ρ_I and ρ_s are reasonably consistent with the slopes assigned in the defining equation. In other words the "best" σ_I values for alkyl groups, and likewise the older σ^* values for alkyl groups, are not consistent with the defining equation for σ^* for polar groups while zero σ_I or σ^* values for alkyl groups are consistent.

Turning next to the properties of the OR′ groups, we note that although E_s of R′ does not properly represent the steric properties of OR′,[30,36] E_s of CH_2R' is a plausible surrogate.[29d,31] By use of this assignment, the data of Table II are correlated by eq 2 with $\rho_I = 5.36$ (±0.4) and $\rho_s = 1.2$ (±0.07) based on 0.14 as the standard deviation of log k. The spread in rate constants is rather narrow. If we assign $\sigma_I = 0$ for all alkyl groups, then $\rho_I = 7.87$ (±0.9) and $\rho_s = 1.32$ (±0.09) based on 0.19 as the standard deviation of log k. There is a fall-off factor of about 2 for a polar group once removed. The data of Table IV are also correlated reasonably well by using E_s of CH_2R'.

The polar term of eq 2 shows the proper behavior for strongly polar groups. The fact that E_s values can be computed directly from molecular structure[5] provides additional evidence that steric effects are properly treated. The validity of eq 2 can therefore be regarded as well established. We turn next to an examination of the significance of the ρ_s values, a topic that has received little prior consideration.

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Table II. Alkaline Hydrolysis of Esters Alkoxyl Group Substituents[a]

R	σ_I of R	$-E_s$ of RCH_2	log k_{OH^-} (rel, obsd)	log k_{OH^-}[b] (rel, calcd)	source		
					σ_I	E_s	k_{rel}
		Lactates					
CH_3	−0.046	0.07	2.00	2.06	c	e	j
CH_3CH_2	−0.057	0.36	1.59	1.65	c	e	j
$CH_3CH_2CH_2$	−0.061	0.39	1.50	1.59	c	e	j
$CH_3CH_2CH_2CH_2$	−0.063	0.41	1.49	1.55	c	e	j
$(CH_3)_2CHCH_2$	−0.065	0.43	1.52	1.52	c	f	j
$CH_3CH_2CH(CH_3)$	−0.069	1.05	0.75	0.75	c	g	j
$(CH_3)_3C$	−0.074	1.74	−0.23	−0.11	c	e	j
$CH_3OCH_2CH_2$	0.10/2.8	0.41	2.00	2.08	d	h	j
$ClCH_2CH_2$	0.16/2.8	0.40	2.35	2.21	d		j
		Acetates					
CF_3CH_2	0.14	0.07	2.74	3.05	d	i	k
$CF_3CH(CH_3)$	0.13	0.81	2.14	2.11	d	i	k
CH_3OCH_2	0.10	0.39	2.57	2.45	d	f	l
$CH_3CH_2OCH_2$	0.10	0.41	2.50	2.43	d	h	l
$CH_3OCH_2CH_2$	0.10/2.8	0.41	2.17	2.08	d	h	l
$CH_3CH_2OCH_2CH_2$	0.10/2.8	0.41	2.15	2.08	d	h	l
$C_6H_5CH_2$	0.03	0.38	2.10	2.09	d	e	l
$(CH_3)_2CH$	−0.065	0.93	1.21	0.91	c	e	l
$(CH_3)_2CHCH_2$	−0.065	0.43	1.65	1.52	c	e	l
$(CH_3)_3C$	−0.074	1.74	0.01	−0.11	c	e	l
CH_3CH_2	−0.057	0.36	1.68	1.65	c	e	m
$(CH_3)_2CH$	−0.065	0.93	0.97	0.91	c	e	m
$(CH_3)_2CHCH_2$	−0.065	0.43	1.37	1.52	c	e	m
$(CH_3)_3C$	−0.074	1.74	−0.36	−0.11	c	e	m

[a] Second-order rate constants in H_2O at 25 °C are relative to the methyl ester ($k_{OH^-} = 100$). [b] Log $k = 2.387 + 1.209E_s + 5.361\sigma_I$, $s = 0.14$, $r^2 = 0.9755$, $s_a = 0.05$, $s_{\rho_s} = 0.07$, $s_{\rho_I} = 0.4$. Taking $\sigma_I = 0$ for alkyl groups: log $k = 2.175 + 7.866\sigma_I + 1.318E_s$, $s = 0.19$, $r^2 = 0.9545$, $s_a = 0.08$, $s_{\rho_I} = 0.9$, $s_{\rho_s} = 0.09$. [c] L. S. Levitt and H. F. Widing, *Prog. Phys. Org. Chem.*, 12, 119 (1976); R. W. Taft and L. S. Levitt, *J. Org. Chem.*, 42, 916 (1977). [d] Table 10.4 of O. Exner in "Correlation Analysis", N. B. Chapman and J. Shorter, Eds., Plenum Press, New York, 1978. [e] Table VI of R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, p 556. [f] *n*-Pe value. [g] Slightly greater than *i*-Bu, J. P. Idoux and J. O. Schreck, *J. Org. Chem.*, 43, 4002 (1978). [h] *n*-Pe value plus 0.01. [i] Value for $CF_3CH_2CH_2$ computed as −0.36; value for *t*-$BuCH_2CH_2$ = −0.34 and for *n*-Pr = 0.36; $CF_3CH(CH_3)CH_2$ should have an $-E_s$ larger than that for *i*-Bu; assumed value −1.10. Since log *k* is relative to that for the ethyl ester, these were increased by 0.29, the Me–Et difference. [j] K. H. Vogel and J. C. Warner, *J. Am. Chem. Soc.*, 75, 6072 (1953). [k] These values are relative to the ethyl ester. A. L. Henne and R. L. Pelley, *ibid.*, 74, 1426 (1952). [l] H. Olsson, *Z. Phys. Chem., Abt. A*, 133, 233 (1928). [m] J. P. Idoux and J. O. Schreck, *J. Org. Chem.*, 43, 4002 (1978).

The variability of ρ_s values suggests that for a given ester RCOOR′ the ρ_s value for the R component may depend on the steric requirements of R′. Thus, ρ_s increases as the size of OR′ increases or as the size of the entering nucleophile increases. The following values are consistent with this hypothesis: ρ_s for base-catalyzed hydrolysis of RCOOMe in 40% dioxane is about 1, while ρ_s for RCOOEt in either 70% acetone or in 85% ethanol is about 1.25. The steric difference between OCH_3 (for CH_2CH_3, $E_s = -0.07$) and OCH_2CH_3 (for $CH_2CH_2CH_3$, $E_s = -0.36$) is appreciable. The progression from MeOH ($E_s = 1.37$) to *n*-PrOH ($E_s = 1.46$) to *i*-PrOH ($E_s = 1.89$) shows another parallel. The alternative suggestion has been made that steric effects are additive (eq 5).[31] This appears to work if limited to

$$\log k = a + \rho_{s,\text{acyl}}E_{s,\text{acyl}} + \rho_{s,\text{OR}'}E_{s,\text{CH}_2\text{R}'} \qquad (5)$$

the set R = R′, but it fails if applied to the total data set. If it is instead postulated that $\rho_{s,\text{acyl}}$ is proportional to $E_{s,\text{CH}_2\text{R}'}$, then a quadratic term, $bE_{s,\text{acyl}}E_{s,\text{CH}_2\text{R}'}$, would be introduced.

We now take up the controversial question of polar effects of alkyl groups, first summarizing the evidence in favor. (1) The recent work of Levitt and Widing[26] and of Taft and Levitt[27] has established a set of polar σ_I constants for alkyl groups that are applicable to gas-phase equilibria and ionization phenomena. Perhaps these should more properly be classed as polarization effects.[26b] (2) Levitt and Widing have established a functional relationship between σ_I and the older σ^* constants for alkyl groups; this can be reformulated as $\sigma^* = 0.482 + 10.05\sigma_I$ ($s = 0.03$, $r^2 = 0.906$).[23] (3) Some applications of eq 2 show statistical significance for inclusion of the $\rho_I\sigma_I$ term. This can be seen in a reduced standard deviation for log *k* in examples presented in the footnotes of Table III. (4) The detailed statistical study by Sjöström and Wold,[33] which is examined later, shows need for the $\beta_2\theta_2$ term in addition to the steric $\beta_1\theta_1$ term for their data set. (5) Other workers have reported rate correlations with σ^* or σ_I of alkyl groups.[25,37]

In spite of these lines of evidence which tend to argue for a polar effect of alkyl groups in reactions in solution, we now summarize stronger evidence to the contrary. The arguments involve two stages: (a) if there is some effect, σ_x, of alkyl groups on rates of reactions in solution that is experimentally distinguishable from the steric effect described by E_s, then that effect is not a polar effect, nor is it hyperconjugation; (b) in fact, the effect σ_I does not exist; it is an artifact due to systematic errors in the data sets.

We begin the analysis by examining the correlation between σ^* and E_s (noted qualitatively by Taft[1]) and the correlation between σ_I and E_s: $\sigma^* = -0.756 + 0.104E_s$ ($s = 0.054$, $r^2 = 0.66$) and $\sigma_I = -0.0556 + 0.0103E_s$ ($s = 0.0048$, $r^2 = 0.71$). The correlation is, of course, reasonable for a polarization effect; the larger the alkyl group the larger the magnitude of σ_I. Joint correlation with E_s implies direct correlation between σ^* and σ_I, and the existence of such correlation is therefore of diminished significance.[26]

To examine the issue directly, one finds it best to strip off the steric component from σ^* to yield a "true polar" residual σ_P^* and likewise to determine σ_{IP}; these are sum-

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(37) C. G. Screttas, *J. Org. Chem.*, 44, 3332 (1979).

Table III. ρ_S Values for Alkaline Hydrolysis of Esters RCOOR′ (Acyl Group)[a]

R	log k[b]	log k[c]	$-\log k_{25}$[d]	$-\log k_{25}$[e]
CH_3	0.903	1.286	2.204	1.327
CH_3CH_2	0.765	1.167	2.436	1.650
$CH_3CH_2CH_2$	0.475	0.872	2.763	2.050
$(CH_3)_2CH$	0.356	0.719	3.095	2.254
$CH_3CH_2CH_2CH_2$	0.427	0.775	2.712	2.174
$(CH_3)_2CHCH_2$	−0.080	0.326	3.369	2.656
$CH_3CH_2CH(CH_3)$	−0.201	0.173	3.509	
$(CH_3)_3C$	−0.570	−0.170	(4.600)	3.646
$(C_2H_5)_2CH$			4.804	4.073

[a] See footnotes of Tables I and II for references to E_s and σ_I. [b] J. P. Idoux and J. O. Schreck, *J. Org. Chem.*, **43**, 4002 (1978); NaOH, 40% aqueous dioxane at 20 °C; $k(RCOOCH_3)$ in units of $M^{-1}\ min^{-1}$; $\log k - 15.426\sigma_I = 1.6627 + 0.718E_s$, $s = 0.04$, $r^2 = -0.990$; $\log k = 0.828 + 0.930E_s$, $s = 0.045$, $r^2 = 0.993$; $\log k = 1.269 + 8.154\sigma_I + 0.818E_s$, $s = 0.031$, $r^2 = 0.997$, $s_a = 0.16$, $s_{\rho_I} = 2.9$, $s_{\rho_S} = 0.05$; $\log k = 0.860 + 0.956E_s$(new), $s = 0.042$, $r^2 = 0.994$. [c] C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211 (1961); NaOH, 40% aqueous dioxane at 35 °C; $k(RCOOCH_3)$ in units of $M^{-1}\ min^{-1}$; $\log k - 15.426\sigma_T = 2.043 + 0.7110E_s$, $s = 0.040$, $r^2 = 0.991$; $\log k = 1.207 + 0.922E_s$, $s = 0.054$, $r^2 = 0.990$ [d] D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938); NaOH, 85% EtOH, 25 °C, for RCOOEt, log k (k in units of $M^{-1}\ s^{-1}$) from least-squares Arrhenius equation. See also Figures 1 and 2. $\log k = -2.294 + 1.227E_s$, $s = 0.13$, $r^2 = 0.977$ (omitting *t*-Bu); $\log k = -2.274 + 1.314E_s$, $s = 0.18$, $r^2 = 0.965$ (*t*-Bu included); $\Delta\log k = 0.157 - 0.140m$, $s = 0.14$ [residuals (from equation including *t*-Bu) vs. m where $m = 3 -$ number of αH's]; $\log k = -2.228 + 1.248E_s$(new), $s = 0.052$, $r^2 = 0.997$ (omitting *i*-Pr and *t*-Bu). [e] G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940); NaOH, 70% acetone, 25 °C; log k (k in units of $M^{-1}\ s^{-1}$), based on least-squares Arrhenius equation. $\log k = -1.531 + 1.321E_s$, $s = 0.125$, $r^2 = 0.985$; $\log k = -1.559 + 1.267E_s$(new), $s = 0.08$, $r^2 = 0.9927$ (Me not included).

Table IV. Alkaline Hydrolysis of CH_3COOR

	$-E_s$-(RCH_2)[a]	log k[b]	log k[c]	log k[d]
CH_3	0.07	−0.967	0.903	1.286
CH_3CH_2	0.36	−1.332	0.586	0.949
$CH_3CH_2CH_2$	0.39	−1.569	0.453	0.829
$CH_3CH_2CH_2CH_2$	0.40	−1.638	0.379	0.731
$(CH_3)_2CH$	0.93	−2.151	−0.127	0.265
$(CH_3)_2CHCH_2$	0.43	−1.740	0.274	0.597
$CH_3CH_2CHCH_3$	1.05	−2.485	−0.417	−0.020
$(CH_3)_3C$	1.74	−3.577	−1.455	−0.987
cyclic C_6H_{11}	0.98	−2.341		

[a] See footnotes in Tables I and II for other references to to σ_I and E_s. [b] R. W. A. Jones and J. D. R. Thomas, *J. Chem. Soc. B*, 661 (1966); NaOH, 70% aqueous acetone at 24.7 °C; k in units of $M^{-1}\ s^{-1}$; $\log k - 5.509\sigma_I = -0.6327 + 1.408E_s$, $s = 0.11$, $r^2 = 0.980$; $\log k = -0.936 + 1.442E_s$, $s = 0.15$, $r^2 = 0.966$. [c] J. P. Idoux and J. D. Schreck, *J. Org. Chem.*, **43**, 4002 (1978); NaOH, 40% aqueous dioxane, 20 °C; $\log k(CH_3COOR)$, k in units of $M^{-1}\ min^{-1}$; $\log k - 5.509\sigma_I = 1.287 + 1.2956E_s$, $s = 0.09$, $r^2 = 0.986$; $\log k = 0.933 + 1.368E_s$, $s = 0.10$, $r^2 = 0.985$. [d] C. K. Hancock, E. A. Meyers, and B. J. Yager, *J. Am. Chem. Soc.*, **83**, 4211–4216 (1961); MaOH, 40% aqueous dioxane, 35 °C; $\log k(CH_3COOR)$, k in units of $M^{-1}\ min^{-1}$; $\log k = 1.332 + 1.305E_s$, $s = 0.11$, $r^2 = 0.980$.

marized in Table V. The following observations can now be made. (a) There is still a correlation between σ_P* and σ_{IP}; $\sigma_P^* = -0.0001 + 9.7\sigma_{IP}$ ($s = 0.027$, $r^2 = 0.75$). (b) The maximum relative "polar" effect is about 0.2 in log k between Me and *i*-Pr for a reaction having $\rho_I = 15$; the steric difference between Me and *t*-Bu is 1.5 in log k for $\rho_s = 1$. (c) There is no obvious connection between σ_P* or σ_{IP} values and structure; it would be a guess to try to predict a value for, say, cyclohexyl. Although there is justification for ignoring a 13% "polar" effect, it is more sensible to probe further to seek underlying causes.

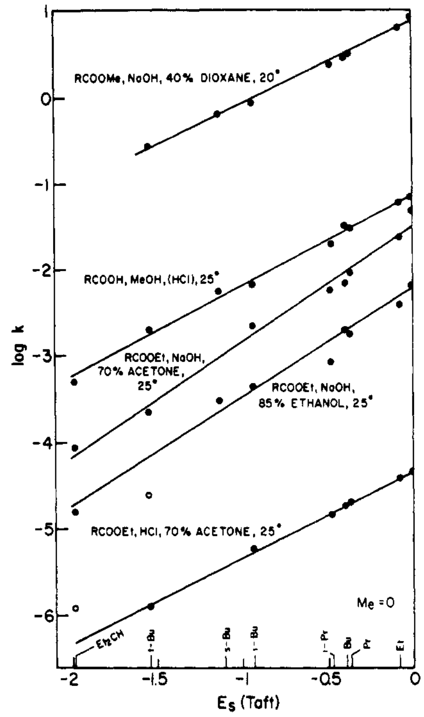

Figure 1. Log k plotted against original Taft E_s values (Table V).

For alkyl groups the several constants σ* and σ_I lack the characteristics that these constants imply for more polar groups. The pK_a for ZCOOH and the σ_I of Z are so closely correlated for polar groups that the proposal has been made that pK_a should be taken to define σ_I(Z).[22,38] Yet the correlation between pK_a for RCOOH[39] and the σ_I of R is very poor: p$K_a = a + \rho_I\sigma_I$ has $r^2 = 0.36$ for Me, Et, Pr, Bu, *i*-Bu, *i*-Pr, *sec*-Bu, Et_2CH, and *t*-Bu. The correlation with σ_{IP} is no better; it has $r^2 = 0.32$. If the estimated Et_2CH value is omitted, $r^2 = 0.21$. The general lack of correlation with pK_a has been noted before. The total range of pK_a values for RCOOH is small, 0.32 between Me and *t*-Bu, a factor of 2 in K. There is little obvious correlation between pK_a and structure; pK_a increases in the series Me, Et, *i*-Pr, and *t*-Bu and decreases in the series *i*-Pr, *sec*-Bu, and Et_2CH, but other sensible series show a scatter.

Which reactions will show improvement in the calculated log k value by addition of a $\rho_I\sigma_I$ term cannot be predicted in advance. Of the reactions shown in Table I and in Figure 1, there is apparent improvement for alkaline hydrolysis of RCOOMe in 40% dioxane at 20 °C[30,31] and for alkaline hydrolysis of RCOOEt in 70% acetone[40] but not in 85% ethanol.[41] There is also improvement for the primary defining reaction for E_s where there should be no polar effect. This is the acid-catalyzed hydrolysis of RCOOEt in 70% acetone, if the errant $Et_2CHCOOEt$ value is included.[40]

There is a risk of confusion in applying a "four-term" equation such as eq 2 when parameter sets E_s and σ_I are partly correlated. The better procedure is to remove the

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[38] L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, 1970, p 376.

[39] G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961.

[40] G. Davies and D. P. Evans, *J. Chem. Soc.*, 339 (1940).

[41] D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1439 (1938).

Table V. Constants Proposed for Alkyl Groups

R	$-\sigma_I{}^a$	$-\sigma^{*b}$	$-E_s{}^b$	$\sigma_P{}^{*c}$	$\sigma_{IP}{}^d$	$-E_s{}'^e$	$-E_s$(new), no. ^{f}
Me	0.046	0	0	0.076	0.0096	0	0 (0.02), 5
Et	0.057	0.100	0.07	−0.017	−0.0007	0.08	0.118 (0.015), 5
n-Pr	0.061	0.115	0.36	−0.002	−0.0017	0.31	0.391 (0.01), 5
n-Bu	0.063	0.130	0.39	−0.014	−0.0034	0.31	0.417 (0.02), 5
i-Bu	0.065	0.125	0.93	−0.047	0.0002	0.93	0.933 (0.03), 5
i-Pr	0.065	0.190	0.47	−0.066	−0.0046	0.48	0.535 (0.01), 4
sec-Bu	0.069	0.210	1.13	−0.017	−0.0018	1.00	1.074 (0.03), 3
t-Bu	0.074	0.300	1.54	−0.064	−0.0025	1.43	1.560 (0.02), 4
Et_2CH		0.225	1.98	0.057	0.0050	2.00	2.033 (0.06), 3

[a] R. W. Taft and L. S. Levitt, *J. Org. Chem.*, 42, 916 (1977). [b] Tables VI and XII of R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, 1956, p 556. [c] $\sigma_P{}^* = \sigma^* + 0.0756 - 0.104E_s$ (σ^* with steric component removed). [d] $\sigma_{IP} = \sigma_I + 0.0556 - 0.0103E_s$ (σ_I with steric component removed). [e] Reference 28, based on RCOOH + MeOH, acid, 40 °C, and eq 2 using $\rho_s = 1.000$ and $\rho_I = 0$. The Taft E_s values define $\rho_s = 1.05$ for this esterification. [f] Revised E_s values; see text. Values in parentheses are standard deviations of the averages. The number averaged is 3-5 as shown.

steric component from σ_I and to test what improvement, if any, comes from the residual σ_{IP} set of constants (eq 6).

$$\Delta \log k = a + b\sigma_{IP} \qquad (6)$$

With this constraint the only reaction to show improvement, and it is marginal, is alkaline hydrolysis of RCOOEt in 40% aqueous dioxane.

Hyperconjugation has held a fascination for many workers who have evaluated LFER treatments of alkyl groups.[30,31,42] Since the residual term $\rho_I\sigma_I$ does not represent steric effects nor polar effects, it could perhaps represent hyperconjugation. This can be tested by eq 7

$$\Delta \log k = a + b(n - 3) \qquad (7)$$

in which n represents the number of α hydrogens. Equation 7 gives no appreciable correlation for the residuals for base-catalyzed hydrolysis of RCOOEt in 70% acetone, but there is an improvement for 85% ethanol (Table III, footnote *d*) if the "bad" value for *t*-BuCOOEt is included. However, the correction is in the wrong direction for hyperconjugation. The correction would be in the correct direction for hydrolysis of amides $RCONH_2$.[42-44] Little credence can be placed in such arbitrary behavior, and the $\rho_I\sigma_I$ term or another correction term cannot reasonably be construed as evidence of hyperconjugation.

These several lines of evidence—inconsistency with the definition of σ^* for polar groups, lack of predictability of σ_{IP} or $\sigma_P{}^*$ with respect to the structure of the alkyl group, lack of predictability with respect to reaction, and demonstrated connection in several instances that the need for a $\rho_I\sigma_I$ term arises from inclusion of outlier points—all strongly indicate that this minor "13%" polar effect is indeed an artifact.

We complete the argument by taking a closer look at the origins of and meaning of σ^* values. A primary source for the σ^* values for alkyl groups appears to be hydroxide-catalyzed hydrolysis of esters, particularly the data of Davies and Evans in 70% acetone[40] and the data of Evans, Gordon, and Watson in 85% ethanol[41] (Table III). The computation[1] based on eq 4 is equivalent to use of the expression $\sigma^* = [\log (k/k_0)_B - E_s]/2.48$; that is, ρ_s is taken to be 1.000. Now it so happens that these two reactions have ρ_s values of about 1.25 (cf. Table III, footnote *d*, and Figures 1 and 2). The result of the assumed unity value is to produce a set of σ^* values that parallel the E_s values and which mirror any error as well.

If the σ^* values had instead been computed from the hydrolyses of RCOOMe in 40% dioxane ($\rho_s = 0.93$, data not available in 1956),[30,31] then the range of "σ^*" values would have been only one-third as great (ratio of standard deviation from the averages for Me, Et, Pr, Bu, *i*-Pr, *sec*-Bu, and *t*-Bu), and the sign would generally have been inverted: the value for *t*-Bu = +0.030, and for *n*-Bu = −0.059, but that for Me = 0. Since the computational procedure, consistently applied, leads to contradictory results, the conclusion follows that the set of σ^* values for alkyl groups is based on an artifact of computation.

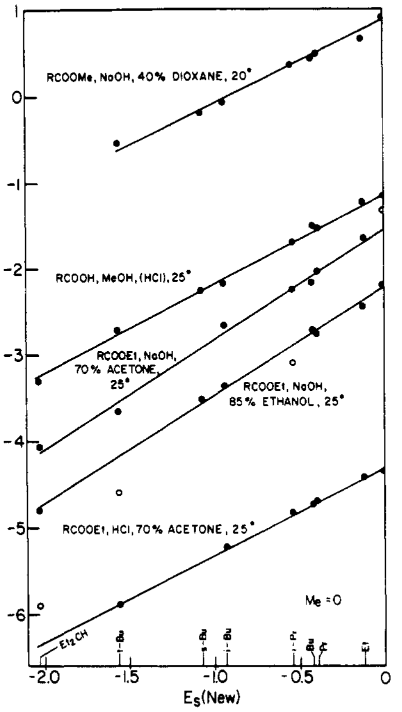

Figure 2. Log k plotted against averaged E_s values (Table V).

We continue the examination of the Taft equation with an evaluation of the steric substituent constants E_s and some of the proposed "improvements", $E_s{}^c$,[30] $E_s{}'$,[28] υ,[29] and θ_2.[33] We present first our proposed procedures for reevaluating E_s values and for computing new E_s values. Then the origins of and significance of the other constants are considered.

The first step, and the most important, is to identify appropriate reaction series that are considered to be representative of the population. It is also necessary to examine the series for deviant points and to adopt an averaging procedure to make best use of the available data.

To reevaluate E_s for the first several alkyl groups, we have selected the following reactions: (1) acid-catalyzed hydrolysis of RCOOEt in 70% acetone,[40] (2) acid-catalyzed

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(42) P. D. Bolton, *Aust. J. Chem.*, **19**, 1013–1021 (1966).

(43) P. D. Bolton and G. J. Jackson, *Aust. J. Chem.*, **22**, 527–532 (1969); **24**, 471–477 (1971).

(44) De Roo and A. Bruylants, *Bull. Soc. Chim. Belg.*, **63**, 140–157 (1954).

esterification (RCOOH + MeOH),[45] (3) base-catalyzed hydrolysis of RCOOEt in 70% acetone,[40] (4) base-catalyzed hydrolysis of RCOOEt in 85% ethanol,[41] and (5) base-catalyzed hydrolysis of RCOOMe in 40% dioxane.[31] Reaction 1 appears to be the only viable example of the reaction adopted to define the E_s scale. The disposal of the need for $\rho_I\sigma_I$ terms makes it possible to include the base-catalyzed reactions, setting $\rho_I = 0$ in eq 2 and giving eq 8, which will be used throughout.

$$\log k = a + \rho_s E_s \qquad (8)$$

The best average k values are obtained by fitting a least-squares Arrhenius equation to the available data and computing k, usually at 25 °C, as the average best value for that substituent. If data are available at only two temperatures, then the average log k value is appropriate.

The presence of outlier points is evaluated by computation or by plotting according to eq 8 as illustrated in Figure 1. It appears that the point for t-BuCOOEt in reaction 4 is too low by a factor of 2 or more and that the point for $Et_2CHCOOEt$ for hydrolysis by HCl in 70% acetone is too high by a factor of about 2.5. The value for i-PrCOOEt is suspect. The value for MeCOOEt in reaction 3 also seems off. These four points were therefore not used in the recomputation of E_s (see Figures 1 and 2).

It is relatively straightforward to adopt a comprehensive statistical approach to evaluating the best E_s values while maintaining $\rho_s = 1.00$ for reaction 1.[46] It is also possible to proceed as follows: Step 1 is to calculate a primary set of E_s values, E_s(primary), based on reaction 1 by using eq 8 with $\rho_s = 1.000$ and $a = \log k(CH_3COOEt)$. Step 2 treats each of the other reactions to get E_s(secondary) values. This is accomplished by computing best values of a' and b' for eq 9 by setting E_s equal to E_s(primary) for each alkyl

$$E_s = a' + b' \log k \qquad (9)$$

group. Then each E_s(secondary) is computed from its corresponding log k. The last step is to average E_s(primary) and the several E_s(secondary) for each alkyl group and to reset the origin (by about 0.03) to $E_s = 0.00$ for Me. The resultant reevaluated E_s values, designated E_s(new), are summarized in Table V, and their characteristics are shown in Figure 2 and in the footnotes in Table III.

These values do not represent a serious break with the E_s(Taft) values, and they are compatible with the remaining E_s(Taft) set. The procedure is generally applicable to deriving new E_s values or reevaluating older ones.

We now take a look at proposed alternatives to E_s. In a series of papers, Charton[29] has examined his variants of the Taft equation on the basis of υ values in place of E_s. The impression that υ values have somehow been related to van der Waals radii and that they have been evaluated statistically turns out on closer examination not to be correct. In any event, the van der Waals radius of a group of atoms is a variable quantity that is definable only in relationship to specific interactions.

Charton does not clearly indicate the derivation of υ values; they simply appear in his tables. The following procedure serves to define some 25 of the constants in Table III of ref 29b. A point for Me is defined by assignment of the arbitrary value $\upsilon = 0.52$ and the value log 1.219 for CH_3COOH. A second point is defined by assignment of the value $\upsilon = 1.24$ for t-Bu plus the value log 0.00858 for t-BuCOOH. These two points define a line. From this line and from the log k values listed in data set 15 of Table I of ref 29b it is possible to compute the corresponding υ values. Values so computed show an average deviation of less than 0.01 from the υ values presented in Table III of ref 29b. That these υ values are not statistical averages can be seen by applying a similar approach to other data sets; the resultant υ values show large deviations.

The E_s^c values of Hancock[30] have achieved a certain popularity;[31,32,42] they supposedly correct for hyperconjugation and remedy a presumed deficiency of the E_s values. The apparent success of the E_s^c values arose initially through a misunderstanding of the proper steric representation to be used for an OR′ group. Any continuing success comes through incorporation of an additional adjustable constant. The theoretical computation of E_s values[5] provides a way to test the steric hyperconjugation hypothesis. If hyperconjugation is a significant factor, then there should not be a single correlation between E_s and theoretically computed steric effects, but, instead, there should be separate correlations for each of the three alkyl types; one for RCH_2, one for R_2CH, and one for R_3C, with differences that define the hyperconjugation. However, the plot of E_s vs. ΔSE defines a single line. There is no separation, and there is, therefore, no evidence that hyperconjugation is involved. E_s^c values, therefore, serve no useful purpose and should be abandoned.

Recently, Dubois has derived a set of E_s' values based on eq 2 with $\rho_I = 0$, $\rho_s = 1.000$, and $a = \log k(CH_3COOH)$ for acid-catalyzed esterification of RCOOH in methanol at 40 °C.[28] This study has the advantage of bringing together the values for a large number of substituent groups. It should be noted that on the basis of E_s(Taft), the value of ρ_s is 1.05 for this reaction, and E_s' values are therefore on a slightly different scale.

Acid-catalyzed esterification is subject to several complications that can be surmounted by appropriate techniques. These include the need for the Goldschmidt correction, the variation of k with concentration of RCOOH, and possible competing reactions that consume catalyst.[28,45,47] The available data for RCOOH (R = alkyl or aryl) appear to be good to about 0.12 in log k.

There are a few rather large differences between E_s(Taft) and E_s'(Dubois) such as for Cl_2CH (−1.54 vs. −0.58) and Br_2CH (−1.86 vs. −0.76). In spite of these differences, eq 2 correlates the data of Table I equally well with E_s or with E_s': taking $\sigma_I = 0$ for all alkyl groups, $\log k = 2.068 + 14.40\sigma_I + 0.996E_s'$ ($s_{\log(k)} = 0.23$, $r^2 = 0.986$). This may be compared with the E_s correlation (footnote c of Table I).

While acid-catalyzed reactions are particularly suitable for evaluating polar groups, base-catalyzed reactions are better for treatment of steric effects of alkoxyl groups of RCOOR′. As the treatment of steric effects by LFER techniques matures, we can expect to have a proliferation of E_s scales. The E_s' scale of Dubois is the first significant proposed alternative to the Taft E_s set. We see no clear superiority to correlations based on the Dubois E_s' set apart from extended range and correction of errors in certain experimental data. (There are further corrections in ref 47.) Further experience will be needed to answer questions as to the most suitable set of steric constants for correlating a given reaction set.

We now consider the more general philosophical question about the best ways for determining parameters for LFER equations.

Two different approaches have been advocated. One is to establish a chemical model and to use statistical techniques as a tool for evaluating the model. The other is to

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[45] H. A. Smith, *J. Am. Chem. Soc.*, **61**, 254–260, 1176–1180 (1939); **62**, 1136 (1940); **63**, 605 (1941).

[46] D. F. DeTar, "Computer Programs for Chemistry", Vol. 4, D. F. DeTar, Ed., Academic Press, 1972, p 71.

[47] P. J. Sniegoski, *J. Org. Chem.*, 41, 2058 (1976).

place primary emphasis on the statistical apparatus as a means of revealing trends.

The Hammett ρ–σ relationship, the Taft equation,[1] and the recent study of Ehrenson et al.[17] on the setting up of a four-parameter polar-resonance treatment are examples of the chemical-model approaches. The recent study of Sjöström and Wold[33] is an example of the statistical approach, and the QSAR studies are necessarily statistically oriented.[48]

The Sjöström and Wold study was designed to evaluate the effects of alkyl substituents on acyl-transfer reactions and to establish what sorts of linear terms are needed to correlate the data. The major emphasis was on application of eq 10, chemically neutral but mathematically identical

$$\log k = \alpha + \beta_1\theta_1 + \beta_2\theta_2 \qquad (10)$$

with the Taft equation (eq 2 and 3). The θ's are properties of the alkyl substituents and the β's are reaction constants.

Sjöström and Wold reached the following conclusions. The equation correlated the reactions well (but not the pK_a equilibrium set). The θ_1 and θ_2 constants are uncorrelated. There is a strong correlation between θ_1 and E_s; but σ^* is dependent on both θ_1 and θ_2 jointly. The $\beta_2\theta_2$ term is required on statistical grounds. However, θ_2 does not behave quite like a polar term since it does not account for the pK_a values. Furthermore, the θ_1–θ_2 set is not the complete story for all groups since the benzyl group, for example, needs an additional term.

We approached an evaluation of the Sjöström and Wold study with special interest, since full statistical treatments are much talked about but seldom carried through. The major obstacle is lack of adequately complete data sets.

As a result of this evaluation, we conclude reluctantly that the data set is so flawed as to make the statistical treatment of little value. In technical statistical terms the data set does not represent the population of acyl-transfer reactions, and, furthermore, the data components do not meet the criterion of independence. Lest this study become quoted as having proved that LFER evaluations of alkyl groups require a nonsteric term, it is necessary to provide details.

Sjöström and Wold assembled a set of six reactions which were intended to be complete in the sense that for each reaction a rate constant was available for each of eight alkyl groups, Me, Et, Pr, Bu, *i*-Pr, *i*-Bu, *t*-Bu, and cyclohexyl. The statistical procedure requires a complete matrix of data.

Ostensibly, the data set included six reactions: (1) base-catalyzed hydrolysis of amides $RCONH_2$,[42,44] (2) HCl-catalyzed esterification of RCOOH plus MeOH,[45] (3) acid-catalyzed hydrolysis of RCOOEt in 70% acetone (mislabeled in the table as RCOOMe),[40] (4) base-catalyzed hydrolysis of RCOOEt in 85% ethanol,[41] (5) the pK_z's of RCOOH,[39] and (6) acid-catalyzed hydrolysis of $RCONH_2$.[43]

The data set is seriously deficient in the following respects. (a) The data used for reaction 1 are not from the set of alkaline hydrolysis constants; they are, instead, a partial duplicate of reaction set 6. The data for reaction 6 were measured by Bolton and his group using HCl as catalyst. The data for reaction 1 came from an older study of De Roo and Bruylants in dilute H_2SO_4[44] and were rescaled by Bolton.[42] These misassignments of reaction sets show up clearly when calculated log k's are compared to observed. More nearly correct α_1, β_1, and β_2 values for the alkaline hydrolysis are 0.5384, 0.3145, and −0.6015, with $s = 0.08$ and $r^2 = 0.975$. Data for cyclohexyl are not available in the Bruylants set, and the cyclohexyl points in reaction sets 1 and 6 were presumably both the Bolton value. (b) Reaction set 5 is a poor choice on chemical grounds for the reasons stated above and also since there is such a small range of pK_a values. (c) The data set is seriously biased by the erratic behavior of data for the *t*-Bu group. If we take as normal the Taft E_s value of −1.54, then in the following reactions *t*-Bu is normal: hydrolysis of RCOOEt in 70% acetone with HCl or with NaOH, hydrolysis of RCOOMe by base in 40% dioxane, and esterification of RCOOH with MeOH. In 85% ethanol the *t*-BuCOOEt rate constant is too low by a factor of 2 (Figures 1 and 2), and in both acid-catalyzed and base-catalyzed hydrolyses of $RCONH_2$, *t*-Bu is too high by factors in excess of 3.

The data set nominally included 48 points; eq 10 required evaluation of six α's, six β_1's, and six β_2's while the eight alkyl groups required eight θ_1's and eight θ_2's; after evaluation of this total of 34 constants, there nominally remain 14 degrees of freedom for use in making statistical tests. If reactions 1 and 5 are treated as a total loss, then there are only 32 points to support computation of 28 constants, and only four degrees of freedom. Statistical conclusions from such a slender data set are of dubious significance. The actual origin of the $\beta_2\theta_2$ term is to compensate for the erratic *t*-Bu values. Because error terms become dispersed throughout the total field of parameters, the actual major effect of $\beta_2\theta_2$ is to change *i*-Bu values in one direction and *t*-Bu values in the opposite direction. There are smaller changes for other substituents. It would certainly be difficult to decide from the values of the terms that it is the *t*-Bu values that are at fault. This illustrates the point that a statistical approach that ignores chemical insight is an inadequate tool.

We remark on an awkward consequence of adopting the rigid statistical approach; the sets of β's and θ's are unstable. Recomputation following any addition of a new reaction set or of data for a new substituent will lead to a different set of values, possibly a very different set. Stability is achieved in the usual LFER treatment through the definition of standards such as $\sigma = 0$ for H and $\rho = 1.000$ for the pK_a of benzoic acids in water at 25 °C.

In chemical research, it is chemical evaluation through chemical models that provides reliable guidance for further investigations. Elegant statistics applied to data of uncertain pedigree is apt to founder on unsuspected flaws in the data.

Conclusions

Steric effects of alkyl groups are cleanly separated from other effects and can be evaluated by a wide variety of acyl-transfer reactions. Since polar and other nonsteric effects of alkyl groups are negligible, the suitable reactions include base catalysis as well as acid catalysis. The Taft equation is applicable to correlation of steric effects in the acyl group, in the leaving group, and in the entering nucleophile. The evaluation of trends in ρ_s values may provide useful new information about steric effects. Where multiple steric effects are treated, they are not expected to be additive, but it may be possible to find useful trends of increasing ρ_s for RCOOR′ with progressively increasing group size of OR′. The availability of theoretical computational procedures for evaluating steric effects means that all types of steric interactions can in principle be examined, not just those that conform to LFER treatments. It therefore becomes interesting to examine steric effects in highly crowded systems rather than, as in the past, con-

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[48] See, e.g., S. H. Unger and C. Hansch, *Prog. Phys. Org. Chem.*, 12, 91–118 (1976); W. P. Purcell, G. E. Bass, and J. M. Clayton, "Strategy of Drug Design", Wiley, New York, 1973. QSAR stands for quantitative structure activity relationships.

fining attention to groups having E_s values in the limited range from 0 to −2.

Registry No. CH_3COOEt, 141-78-6; CH_3CH_2COOEt, 105-37-3; $CH_3CH_2CH_2COOEt$, 105-54-4; $(CH_3)_2CHCOOEt$, 97-62-1; $(CH_3)_2CHCH_2COOEt$, 108-64-5; $CH_3CH_2CH(CH_3)COOEt$, 7452-79-1; $(CH_3)_3CCOOEt$, 3938-95-2; CH_3OCH_2COOEt, 3938-96-3; $C_6H_5CH_2COOEt$, 701-97-3; FCH_2COOEt, 459-72-3; $F_2CHCOOEt$, 454-31-9; $F_3CCOOEt$, 383-63-1; $ClCH_2COOEt$, 105-39-5; $Cl_2CHCOOEt$, 535-15-9; $Cl_3CCOOEt$, 515-84-4; $BrCH_2COOEt$, 105-36-2; $Br_2CHCOOEt$, 617-33-4; ICH_2COOEt, 623-48-3; $NCCH_2COOEt$, 105-56-6; $CH_3CH(OH)COOCH_3$, 547-64-8; $CH_3CH(OH)COOCH_2CH_3$, 97-64-3; $CH_3CH(OH)COOCH_2CH_2CH_3$, 616-09-1; $CH_3CH(OH)COOCH_2CH_2CH_2CH_3$, 138-22-7; $CH_3CH(OH)COOCH_2CH(CH_3)_2$, 585-24-0; $CH_3CH(OH)COOCH(CH_3)CH_2CH_3$, 18449-60-0; $CH_3CH(OH)COOC(CH_3)_3$, 59854-10-3; $CH_3CH(OH)COOCH_2CH_2OCH_3$, 75066-30-7; $CH_3CH(OH)COOCH_2CH_2Cl$, 75066-31-8; $CH_3COOCH_2CF_3$, 406-95-1; $CH_3COOCH(CH_3)CF_3$, 400-37-3; $CH_3COOCH_2OCH_3$, 4382-76-7; $CH_3COOCH_2OCH_2CH_3$, 32665-19-3; $CH_3COOCH_2CH_2OCH_3$, 110-49-6; $CH_3COOCH_2CH_2OCH_2CH_3$, 111-15-9; $CH_3COOCH_2C_6H_5$, 140-11-4; $CH_3COOCH(CH_3)_2$, 108-21-4; $CH_3COOCH_2CH(CH_3)_2$, 110-19-0; $CH_3COOC(CH_3)_3$, 540-88-5.

Effects of Alkyl Groups on Rates of S_N2 Reactions

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Rates of S_N2 reactions are subject to steric effects that can be measured quantitatively providing that bonding effects are held constant and that polar effects are either negligible or else computed. It is shown for the first time that steric effects in the nucleophile can be correlated by the Taft equation $\log k = a + \rho_s E_s$.

S_N2 substitution reactions provide especially interesting examples for observation of steric effects.[1-3] The S_N2 halide exchange was an early target of theoretical computations of steric effects,[2-4] and recent studies have been successful with exchange[5] and with S_N2 ring closure of bromo amines.[6] In order to provide a proper foundation for more extensive experimental work aimed at evaluating steric effects, one finds it necessary to examine the ways in which substituent groups can influence the rates of S_N2 reactions. It is also of interest to ascertain whether certain S_N2 reactions can be correlated by linear free-energy relationships such as the Taft equation (eq 1).[7]

$$\log k = a + \rho_s E_s + \rho_I \sigma_I \qquad (1)$$

It is generally considered that substituents influence rates of reactions by four principal effects: steric, polar, resonance, and solvation.[1,7] Steric, polar, and solvation effects operate through space while resonance effects operate through bonds.[8] We present arguments elsewhere that through-bond effects can usefully be referred to as bonding effects in order to include the considerable variety of known effects.[8] These include hyperconjugation, the stabilization attendant on chain branching, and the differences between formic esters and acetic esters. Any substantial change in the bonding pattern at a reaction center may have a significant effect on rates that is distinct from polar, steric, or solvation effects.

If our interest is to measure steric effects, the objective will be either to maintain the other effects constant or else to find ways to evaluate them. Solvation is a major factor in S_N2 reactions.[1,9] The expectation is that when two sufficiently similar reactions are compared, the differential solvation effect will be small. A partial test is to compare relative rates in more than one solvent.

It is important to recognize bonding effects, and it is necessary to estimate the probable importance of polar effects. The discussion is organized as follows. (1) An example of bonding effects is evaluated. (2) Other examples of substituent effects in the substrate RBr are presented. (3) Polar effects in substrate RBr are evaluated. (4) Examples are presented of the application of the Taft equation to the correlation of S_N2 rates.

The example of bonding effects involves successive alkyl substitution at the electrophilic center as in the α series: MeBr, EtBr, *i*-PrBr, and *t*-BuBr. The rate of bromide exchange, for example, diminishes along this series.[2,3,10,11] Streitwieser suggested that this reflected a differential effect, a "resonance" acceleration with increasing alkyl substitution, and a dominating steric retardation.[1] Now that the steric effect has been estimated quantitatively,[5] it is possible to estimate the bonding effect at this saturated center. The data are summarized in Table I. The predicted increase in steric hindrance in the series is large, amounting to some 13 powers of ten from MeBr to *t*-BuBr. The S_N2 rate for bromide exchange of *t*-BuBr has not been measured; the reported rate constant for exchange is too large by a factor of about 50 because it pertains to an elimination–readdition process.[11]

The theoretical rates of exchange should be in the correct relative order, but the number of available examples for testing the theoretical calculations is small. Therefore, the numbers in the column labeled "bonding effects" must be considered approximations. In any event it is clear that direct replacement of hydrogen by methyl at the electrophilic carbon atom has a large effect on the rate. Just how the effect should be partitioned into polar and bonding effects is subject to discussion and perhaps to experimental study. If our interest is to evaluate steric effects, then the

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