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CAUTIONS REGARDING THE PHYSICAL INTERPRETATION OF STATISTICALLY BASED SEPARATION OF THE ORTHO SUBSTITUENT EFFECT INTO INDUCTIVE, MESOMERIC, AND STERIC COMPONENTS—III

SOME REMARKS CONCERNING THE SIGNIFICANCE OF STERIC EFFECTS IN ACIDIC AND ALKALINE ESTER HYDROLYSES

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Abstract—It is demonstrated that acidic and alkaline hydrolyses of *o*-substituted benzoates and acidic esterification of *o*-substituted benzoic acids depend upon inductive, "mesomeric", and steric effects. The "mesomeric" contribution is essentially connected with the nitro and the methoxy groups exerting special effects. The rate data of some acidic and alkaline reactions which may be regarded as being comparable yielded regression equations indicating that steric effects are the same in both reactions. The Taft–Ingold assumption seems to be correct for these reactions, whereas the averaging procedure applied by Taft is questionable. The results taken as a whole lend strong support to the hypothesis that the so-called ortho effect is essentially connected with the size of the substituents and not strictly electrical in nature.

We have previously shown[1] that the Taft E_s^0 parameters are mainly a function of steric effects. Furthermore, as might be expected, the hydrion catalysed esterification of *o*-substituted benzoic acids by methanol and cyclohexanol, respectively, depend essentially upon the inductive and steric properties of the substituents, after removing some strongly mesomeric substituents which exhibited special characteristics.[2] Since for this reason the reactions cited displayed no uniform pattern, the derivation of steric constants from acidic hydrolyses or esterifications of *o*-substituted compounds is questionable, especially if strong donors are regarded.

Charton[3,4] argued that neither the acidic nor the alkaline hydrolyses of *o*-substituted benzoates nor the acidic esterification of corresponding benzoic acids are a function of steric effects, setting aside large aliphatic groups (i-Pr, t-Bu) and concluded that steric contributions play a minor part in the ortho effect as a whole. This is a conclusion which cannot be taken lightly, since it is in sharp contrast to long held beliefs of organic chemists. Furthermore, the hypothesis that simple aliphatic and *o*-substituted esters should behave in such a different way is quite surprising. For this reason we reexamined most of the reactions listed by Charton[3,4] and where it seemed to have direct advantages additional material was included. Our concern consists in the estimation of the relative performances of inductive, mesomeric, and steric contributions. To this end the application of equations such as

$$y = b_0 + b_I x_I + b_R x_R + b_s x_s,$$

where x_I denotes an inductive, x_R a mesomeric, and x_s a steric substituent constant, constitutes the most useful treatment of the ortho effect in terms of LFER's.[4] The reactions examined in this paper are listed in Table 1.

By inspection of the results obtained for the acid catalysed reactions (Table 2) the following conclusions can be drawn:

(i) the steric effect contributes significantly to the overall variation of the rate constants in all reactions investigated;

(ii) generally, the resonance effect is of minor importance if such groups as NO_2 and OMe are deleted from the correlations (cp sets A1 and A2);

(iii) the inductive effect, although being significant in most cases, is of minor importance in relation to the steric effect. Furthermore, it should be noted that the use of the steric parameter ν defined by Charton[5] instead of the van der Waals radius r_v gives essentially the same results (cp sets C4 and C5; sets E1 and E2, etc.). From this result it can be concluded that the steric constants ν do not appear to have achieved the attention they deserve. Regarding the sets C1, C2 and C3, C4 it may be supposed that the use of σ_I and σ_R instead of $\mathscr{F}$ and $\mathscr{R}$ should not yield different results concerning the most important conclusions.

The correlations with the rate data for alkaline hydrolyses (see Table 3) clearly display a much more important contribution of inductive effects and in all reactions the regression coefficient for the steric parameter is significant at the 5% or the 10% level. The latter was applied if the sample size was very small (sets H, I, J). According to Taft[6] the steric effects in acidic and alkaline ester hydrolyses should cancel (Taft–Ingold assumption). This assumption may be examined by comparison of the regression coefficients of corresponding acidic and alkaline reactions, taking place at the same temperature, in the same solvent and involving the same ester. In addition, the substituents used in the correlations should be the same, since the results at least partly depend upon the sample structure (cp the extreme variation in sets A1 and A2).

Table 1. Sets studied

Set	Reaction§	Temp. °C	Substituents§§	Ref.
A	RCOOH + MeOH/HCl	15	1 - 6	a
B	RCOOH + MeOH/TsOH	60	1 - 5, 7, 8	b
C	RCOOMe + H_3O^+ (TsOH)	100.6	1 - 5, 7, 8	c
D	RCH_2COOH + MeOH/TsOH	40	1 - 5, 7, 8	d
E	RCOOMe + OH^-	34.8-35	1 - 5, 7, 8	c
F	RCOOMe + OH^-	44.8-45	1 - 5, 7, 8	c
G	RCH_2COOEt + OH^-	24.8	1 - 7, 9	e
H	RCOOEt + OH^-	25	1 - 3, 6, 7	f
I	RCOOEt + OH^-	35	1 - 3, 6, 7	f
J	RCOOEt + OH^-	50	1 - 3, 6, 7	f
K	1-menthyl benzoates + MeO^-	40	1 - 4, 6, 9	g

§R = o-X-C_6H_4-. §§1 = H, 2 = Me, 3 = Cl, 4 = Br, 5 = I, 6 = NO_2, 7 = F, 8 = Et, 9 = OMe. [a] J. J. Sudborough and M. K. Turner, *J. Chem. Soc.* **101,** 237 (1912). [b] N. B. Chapman, M. G. Rodgers and J. Shorter, *J. Chem. Soc.* (*B*) 157 (1968). [c] N. B. Chapman, J. Shorter and J. H. P. Utley, *J. Chem. Soc. Ibid.* 1291 (1963). [d] N. B. Chapman. [e] J. G. Watkinson, W. Watson and B. L. Yates, *J. Chem. Soc.* 5437 (1963). [f] D. P. Evans, J. J. Gordon and H. B. Watson, *J. Chem. Soc.* 1430 (1937). [g] R. W. Taft, M S. Newman and F. H Verhoeck, *J. Amer. Chem. Soc.* **72,** 4511 (1950).

We have correlated a vast amount of reactivity data for *o*-substituted compounds and feel that generally temperature has no great influence in relation to the relative performances of the independent variables. Since the reactions C and E, F involve the same ester and since the corresponding correlations have been based on the same substituents, a comparison among the regression coefficients for the steric constants should be of interest:

$$C3: -1.458(\pm 0.143 \quad E1: -1.638(\pm 1.066)$$

$$F1: -1.376(\pm 0.478)$$

and

$$C5: -1.537(\pm 0.314) \quad E2: -1.630(\pm 1.054)$$

$$F4: -1.514(\pm 0.411)$$

(values in parentheses are 95% confidence intervals).

From these values it can be concluded that at least in acidic and alkaline hydrolyses of *o*-substituted methyl benzoates given in Table 1, the steric effects approximately cancel and the Taft–Ingold assumption holds. However, it is not possible *a priori* to extrapolate this result to other substituents not included in the correlations and special care is needed if NO_2 and OMe are considered.

Correlation of the rate data for the alkaline hydrolysis of ethyl phenylacetates (excluding OMe and NO_2) gave set G1 which is not significant at the 5% level. Using a two-parameter equation sets G2 and G3 resulted demonstrating the predominance of inductive and steric effects as expected. Set G6 is a much improved correlation over set G4 (x_7 is a dummy variable with +1 for OMe and −1 for NO_2, cp part II[2]). Usually we have claimed that such dummy variables may account for special resonance effects,[2] but this is hardly true in this case, since the reaction center is insulated from the ring. Since the magnitude of the regression coefficient for x_7 lies relatively close to those of the dummy variables used in the correlations of the rate data for hydrion catalysed esterifications with methanol and cyclohexanol, respectively (methanol, 25°C: 0.775; cyclohexanol, 55°C: 0.430),[2] it might be suspected that in some reactions of *o*-substituted compounds OMe and NO_2 exert peculiar effects not directly related to their resonance capacities. But such a problem is outside the range of questions which can be treated by simple application of LFER's and speculations about hindered solvation of the excited state etc. (combined mesomeric-steric effect) should be prevented, if no additional and independent information is available. It is noteworthy that in set G6 the coefficient for r_x (−0.822) is close to those in sets D1 (−0.855) or D4 (−0.851). In sets H1, I1 and J1 the nitro group and in set K1 also the methoxy group are present. We expect a significant resonance contribution which is confirmed by regression analysis. The interpretation of sets H1, I1 and J1 should take into account that the sample size is too small for ultimate conclusions and for this reason the regression coefficients were tested at the 10% level. From the correlations displayed in tables 2 and 3 the following conclusion can be drawn:

(i) both acidic esterification of *o*-substituted benzoic acids and acidic and alkaline hydrolyses of *o*-substituted benzoates depend upon inductive, mesomeric, and steric effects;

(ii) after setting aside the nitro and the methoxy groups in most cases the resonance term becomes insignificant and may be dropped from the regression equations;

(iii) in all cases investigated where the resonance contribution proved to be significant, a dummy variable accounting for special "resonance" effects of

Table 2. Results of correlations for acidic hydrolyses and esterifications

Set	Regressand§	Regression equation and parameters§§
A1	all substituents	$y = 1.135 + 0.128\ x_I - 1.723\ x_R - 1.402\ r_v$ $R^2 = 0.9997\quad \hat{F} = 2125.33\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 5.17; 36.09; 42.23 $t_{2;0.95} = 4.30$
A2	NO_2 omitted	$y = 0.618 + 0.121\ x_I - 0.090\ x_R - 0.971\ r_v$ $R^2 = 0.9999\quad \hat{F} = 3567.59\quad F_{3;1;0.95} = 216$ $\hat{t}$: 13.69; 0.27; 8.88 $t_{1;0.90} = 6.31$
A3	NO_2 omitted	$y = 0.583 + 0.120\ x_I - 0.942\ r_v$ $R^2 = 0.9999\quad \hat{F} = 9983.53\quad F_{2;2;0.95} = 19.00$ $\hat{t}$: 19.15; 112.63
B1	Et omitted	$y = 2.826 + 0.118\ x_I - 0.474\ x_R - 1.131\ r_v$ $R^2 = 0.9953\quad F = 140.27\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 2.13; 2.76; 19.35
C1	Et omitted	$y = 2.681 + 0.516\ \sigma_I - 0.191\ \sigma_R - 1.359\ r_v$ $R^2 = 0.9983\quad \hat{F} = 395.26\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 7.13; 1.79; 31.52
C2	Et omitted	$y = 2.734 + 0.612\ \sigma_I - 1.365\ r_v$ $R^2 = 0.9930\quad \hat{F} = 201.77\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 6.15; 16.01
C3	Et omitted	$y = 2.807 + 0.369\ x_I - 0.351\ x_R - 1.458\ r_v$ $R^2 = 0.9990\quad \hat{F} = 657.18\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 11.68; 3.59; 43.79 $t_{2;0.95} = 4.30$
C4	Et omitted	$y = 2.835 + 0.438\ x_I - 1.459\ r_v$ $R^2 = 0.9925\quad \hat{F} = 197.51\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 7.87; 19.68
C5	all substituents	$y = 1.069 + 0.525\ x_I - 1.537\ \nu$ $R^2 = 0.9794\quad \hat{F} = 95.04\quad F_{2;4;0.95} = 6.94$ $\hat{t}$: 7.08; 13.61
D1	Et omitted	$y = 3.566 - 0.147\ x_I - 0.224\ x_R - 0.855\ r_v$ $R^2 = 0.9829\quad \hat{F} = 38.36\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 1.51; 0.74; 8.36
D2	Et omitted	$y = 3.585 - 0.103\ x_I - 0.855\ r_v$ $R^2 = 0.9782\quad \hat{F} = 67.28\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 1.45; 9.07
D3	Et omitted	$y = 3.656 - 0.926\ r_v$ $R^2 = 0.9629\quad \hat{F} = 103.71\quad F_{1;4;0.95} = 7.71$
D4	Et omitted	$y = 2.541 - 0.153\ x_I - 0.233\ x_R - 0.851\ \nu$ $R^2 = 0.9835\quad \hat{F} = 39.62\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 1.61; 0.79; 8.50
D5	Et omitted	$y = 2.559 - 0.107\ x_I - 0.852\ \nu$ $R^2 = 0.9783\quad \hat{F} = 67.68\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 1.52; 9.10

§cp table 1. §§For the substituent constants used cp ref 1, $x_I = \mathcal{F}$, $x_R = \mathcal{R}$, ν taken from Charton.[5]

Table 3. Results of correlations for alkaline hydrolyses

Set	Regressand	Regression equation and parameters
E1	Et omitted	$y = 0.937 + 1.569\ x_I + 0.121\ x_R - 1.638\ r_v$ $R^2 = 0.9744\quad \hat{F} = 25.41\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 6.67; 0.17; 6.61
E2	Et omitted	$y = -1.028 + 1.557\ x_I + 0.103\ x_R - 1.630\,\nu$ $R^2 = 0.9738\quad \hat{F} = 24.77\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 6.56; 0.14; 6.53
E3	Et omitted	$y = -1.036 + 1.536\ x_I - 1.630\,\nu$ $R^2 = 0.9735\quad \hat{F} = 55.19\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 9.98; 7.96
F1	Et omitted	$y = 0.995 + 1.482\ x_I + 0.114\ x_R - 1.376\ r_v$ $R^2 = 0.9938\quad \hat{F} = 106.77\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 14.04: 0.35; 12.37
F2	Et omitted	$y = 0.986 + 1.460\ x_I - 1.376\ r_v$ $R^2 = 0.9934\quad \hat{F} = 226.42\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 20.79; 14.71
F3	all substituents	$y = -0.669 + 1.661\ x_I + 0.286\ x_R - 1.507\,\nu$ $R^2 = 0.9823\quad \hat{F} = 55.64\quad F_{3;3;0.95} = 9.28$ $\hat{t}$: 9.97; 0.46; 7.63
F4	all substituents	$y = -0.693 + 1.613\ x_I - 1.514\,\nu$ $R^2 = 0.9811\quad \hat{F} = 103.92\quad F_{2;4;0.95} = 6.94$ $\hat{t}$: 13.93; 8.58
G1*	OMe, NO_2 omitted	$y = 1.875 + 0.309\ x_I + 0.097\ x_R - 0.782\ r_v$ $R^2 = 0.9489\quad \hat{F} = 12.38\quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 2.53; 0.26; 6.09
G2	OMe, NO_2 omitted	$y = 1.867 + 0.290\ x_I - 0.781\ r_v$ $R^2 = 0.9472\quad \hat{F} = 26.91\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 3.62; 7.33
G3	OMe, NO_2 omitted	$y = 0.930 + 0.286\ x_I - 0.779\,\nu$ $R^2 = 0.9487\quad \hat{F} = 27.71\quad F_{2;3;0.95} = 9.55$ $\hat{t}$: 3.65; 7.44
G4*	all substituents	$y = 1.915 + 0.456\ x_I + 1.150\ x_R - 0.768\ r_v$ $R^2 = 0.7804\quad \hat{F} = 4.74\quad F_{3;4;0.95} = 6.59$ $\hat{t}$: 2.07; 3.40; 2.56
G5*	OMe omitted	$y = 1.855 + 0.439\ x_I + 0.641\ x_R - 0.747\ r_v$ $R^2 = 0.8906\quad \hat{F} = 8.14\quad F_{3;3;0.95} = 9.28$ $\hat{t}$: 3.74; 2.72; 4.69
G6	all substituents	$y = 1.932 + 0.235\ x_I - 0.538\ x_7 - 0.822\ r_v$ $R^2 = 0.9344\quad \hat{F} = 19.99\quad F_{3;4;0.95} = 6.59$ $\hat{t}$: 1.95; 6.93; 5.00
G7	all substituents	$y = 1.736 - 0.558\ x_7 - 0.634\ r_v$ $R^2 = 0.8718\quad \hat{F} = 17.00\quad F_{2;5;0.95} = 5.79$ $\hat{t}$: 5.80; 3.81

Table 3. (*Contd.*)

Set	Regressand	Regression equation parameters
H1	all substituents	$y = 1.337 + 1.810\,x_I + 1.125\,x_R - 1.286\,r_v$ $R^2 = 0.9992 \quad \hat{F} = 400.55 \quad F_{3;1;0.95} = 216$ $\hat{t}$: 32.34; 8.91; 14.95 $\quad t_{1;0.90} = 6.31$
H2*	all substituents	$y = 0.673 + 1.712\,x_I - 0.920\,r_v$ $R^2 = 0.9332 \quad \hat{F} = 13.97 \quad F_{2;2;0.95} = 19.00$
I1	all substituents	$y = 1.789 + 1.768\,x_I + 1.132\,x_R - 1.303\,r_v$ $R^2 = 0.9987 \quad \hat{F} = 260.80 \quad F_{3;1;0.95} = 216$ $\hat{t}$: 26.27; 7.45; 12.59
J1*	all substituents	$y = 2.362 + 1.694\,x_I + 1.049\,x_R - 1.303\,r_v$ $R^2 = 0.9968 \quad \hat{F} = 104.67 \quad F_{3;1;0.95} = 216$ $\hat{t}$: 16.84; 4.62; 8.43
K1	all substituents	$y = 1.923 + 1.451\,x_I + 1.735\,x_R - 1.5195\,r_v$ $R^2 = 0.9914 \quad \hat{F} = 77.24 \quad F_{3;2;0.95} = 19.16$ $\hat{t}$: 10.91; 9.89; 8.02

*Not significant at the predetermined 5% level.

the nitro and the methoxy groups could replace $\mathscr{R}$ yielding a much enhanced goodness of fit. This is an indication that such reactions exhibit no uniform pattern;

(iv) generally, both acidic and the corresponding alkaline reactions cited above are essentially determined by inductive and steric effects (taken away OMe, OEt and NO_2), the former being of minor importance in acidic hydrolysis and esterification;

(v) an examination of the Taft Ingold assumption, namely that steric effects are approximately equal in both types of reactions is only strictly justified, if the same substituents are submitted to the statistical analyses;

(vi) at least in the reactions cited here the Taft-Ingold assumption could be verified, but it seems that this assertion holds only if the reactions are strictly comparable (acidic and alkaline hydrolyses of the same ester);

(vii) although the basic assumptions of Taft[6] seem to be approximately correct for the reactions investigated, the averaging procedure as applied by Taft should be refused (cp also MacPhee and Dubois[7]), since there may be some considerable differences between acidic hydrolyses and esterifications and, furthermore, "E_s°" values derived from esterification by cyclohexanol and, respectively, by methanol, are quite different in some cases (cp table 4). Therefore, instead of E_s° or other constants deduced from it, the application of the van der Waals radius or the steric parameter ν and, respectively, the STERIMOL parameters[8] is recommended.

Table 4. Esterification of ortho-substituted benzoic acids by methanol and cyclohexanol, respectively, at various temperatures (°C). "E_s°" values with $-CH_3$ as reference group.

	Esterification by MeOH/HCl				Esterification by c-$C_6H_{11}OH$/HCl			
Group	25°	40°	50°	60°	55°	65°	75°	85°
H	0.48	0.51	0.58	0.55	0.29	0.39	0.37	0.38
F	0.43	0.44	0.49	0.47	0.49	0.50	0.45	0.44
I	-0.29	-0.25	-0.26	-0.29	-0.06	0.03	-0.06	-0.09
OMe	1.11	1.11	1.10	1.04	0.83	0.86	0.81	0.84
OEt	1.01	1.09	0.97	0.96	0.78	0.83	0.79	0.82
Me	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
NO_2	-1.07	-0.92	-	-0.68	-0.43	-0.42	-0.41	-0.42
Br	-0.06	-0.03	-0.02	-	0.11	0.11	0.12	0.13
Cl	0.08	0.09	0.09	0.10	0.25	0.25	0.23	0.23

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