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Statistical Analysis of the Hammett Equation. III. Evidence against *para* Through-resonance for —M Substituents in Phenylacetic Acids and Phenylpropionic Acids

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Deviation from the Hammett equation for phenylacetic acids and β-phenylpropionic acids in aq. EtOH are studied with statistical methods. The deviations are explained as solvent dependent interactions between the reaction site and *meta* substituents with free electron pairs. No evidence for *para* through-resonance for $-$M substituents as claimed in literature is found.

The precise definition of σ-values to be used in the Hammett equation is important for several reasons. One important example is the use of σ-values to check the "homogeneity" of an aromatic reaction series. Thus, a reaction in an aromatic reaction series which does not fit a Hammett plot, is usually considered "abnormal". Since the σ-values are the basis for the Hammett equation, their values are crucial for the interpretation of these plots.

A frequently used way to define the σ-value for a particular substituent is to use directly, the pK_a-value for unsubstituted benzoic acid minus the observed pK_a of the corresponding substituted benzoic acid in water. Substituents for which these pK_a-values are ill-defined are customarily given so called secondary σ-values in the following way:

1. Select a well-behaved reaction series where the effect of the particular substituent can be observed.
2. Measure log k (or log K) for (*a*) primary substituents with σ-values defined by the benzoic acid series and *(b)* the new substituent.
3. Define a ϱ-value for the reaction series based on the values of step 2 *a*.
4. Define the secondary σ-values for the substituent as (log $k-$log $k_0)/\varrho$.

In our opinion, this way to define secondary σ-values has serious disadvantages:

(*a*) The analysis is based on the assumption that the standard reaction is free from model errors.

(*b*) A few, mostly *meta*, substituents are assumed to be representative for the Hammett equation as a whole.

However, these assumptions can never be fulfilled exactly. This makes both the ϱ-value and the calculated log k_0-value in a Hammett plot sensitive to unavoidable errors in the primary σ-values. This will, in turn, produce a large uncertainty for the calculated secondary σ-values, especially for reaction series with small ϱ-values and for substituents with large σ-values.

Recently Hoefnagel *et al.*[1,2] used this classical method to determine secondary σ-values for a number of substituents. They concluded that the systems $X-Ph-CH_2-COOH$ (*1*) and $X-Ph-CR_2-CH_2-COOH$ ($R= -H$ or $-CH_3$) (*2*) are unsuitable for the derivation of σ-values (σ^0 or σ^n) for *para* $-$M substituents. In the Hammett plots, they found large positive deviations for these substituents and explained this as a through-resonance effect. However, we believe the deviations for the *para* $-$M substituents to be a result of the way they made their data analysis. We claim that no through-resonance effect exists for the systems (*1*) and (*2*). This conclusion is based on a statistically correct analysis of these systems.

STATISTICAL METHOD AND CALCULATIONS

We have used the method described earlier by us.[3,4] This method makes it possible to analyse the Hammett equation on the form

$$\log k_{ik}=\phi_k+\varrho_k\,\sigma_i+e_{ik}$$

where e_{ik} are the residuals and ϕ_k is the calculated log k_0-value. The index i varies with the substituent and the index k with the reaction series. By this method, σ-values which best fit the total body of data are calculated. Furthermore, the residuals e_{ik} give information about the fit of both individual reaction series and individual substituents.[3,4]

To investigate whether a $-$M effect exists in the Hoefnagel data, we have included reaction series of (*1*) and (*2*) (see Table 1) in a data matrix which in addition consisted of about 60 reaction series of σ^0, σ and σ^- data earlier used in similar calculations.[3,4]

The *para* +M substituents in σ series and the *para* $-$M substituents in σ^- series have been excluded; see further Ref. 4. For each of the two types of series (*1*) and (*2*) two

Table 1. The analysed reaction series of *(1)* and *(2)*.

No.	Reaction	Ref.
Phenylacetic acids		
1a	H_2O[a]	5
1b	H_2O[a]	6,7
1c	10 % EtOH	2
1d	50 % EtOH	2
1e	75 % EtOH	2
β-Arylpropionic acids		
2a	50 % EtOH	1
2b	75 % EtOH	1
β-Arylisovaleric acids		
2c	50 % EtOH	1
2d	75 % EtOH	1

[a] $pK_a=3.89$ is used for the p-NO_2 compound, see Ref. 2, footnote 37.

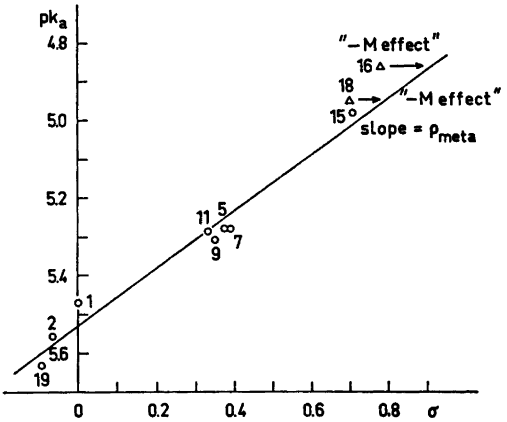

Fig. 1. The analysis of Hoefnagel *et al.* of ionization equilibria of phenylacetic acids in 50 % EtOH. Data for eight selected *meta* substituents, marked with O are plotted against the primary σ-values[1] for these substituents. Substituent numbers see Table 2. No. 19 is 3,5-di-CH_3. Calculated values: $\varrho_m=0.714$, $\log K_{0,\text{calc}}-\log K_{0,\text{exp}}=-0.058$, $s_\varrho=0.052$ and $s_e=0.038$. The two $-$M substituents p-NO_2 (No. 16) and p-CN (No. 18) are plotted against their primary σ-values. The difference between the primary σ-value and the σ-value determined from the equation of the line is explained in Ref. 2 as a "through-resonance" effect.

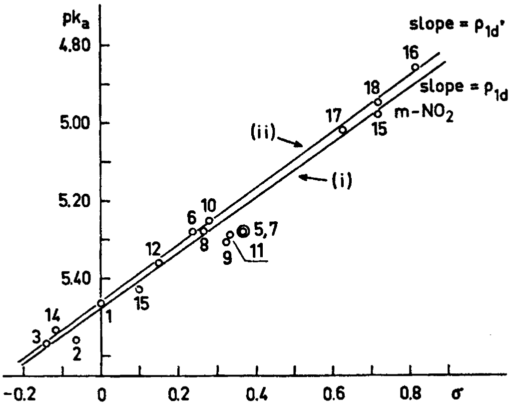

Fig. 2. Our analysis of ionization equilibria of phenylacetic acids in 50 % EtOH. The σ-values used are from Table 2 and are somewhat different from the primary σ-values used by Hoefnagel *et al.* Calculated values: (*i*) with all substituents included; $\varrho_{1d}=0.712$, $\log K_{0,\text{calc}}-\log K_{0\,\text{exp}}=-0.014$, $s_\varrho=0.030$ and $s_e=0.036$, (*ii*) without m-OCH_3, m-halogens, and m-NO_2; $\varrho_{1d'}=0.733$, $\log K_{0,\text{calc}}-\log K_{0,\text{exp}}=0.003$, $s_\varrho=0.017$ and $s_e=0.018$.

Table 2. Residuals e_{ik} for each reaction of system (*1*), (*i*) with and (*ii*) without the substituents m-OCH$_3$, m-halogens, and m-NO$_2$. For each computation, the ϱ-value, the C_ϱ-value [a] and the residual standard deviation s_e, are also given. Numbering, see Table 1. All values are derived with about 60 additional reactions of σ^0, σ, and σ^- type. The σ-values result from computation (*i*).[b]

			Reaction series									
Substituent		σ	1a	1a′	1b	1b′	1c	1c′	1d	1d′	1e	1e′
1	H	0.000	−0.012	−0.011	0.002	0.001	0.010	0.003	0.014	−0.003	0.009	−0.007
2	m-Me	−0.066			−0.017	−0.016	−0.015	−0.022	−0.029	−0.045	−0.005	−0.021
3	p-Me	−0.142	0.008	0.009	0.014	0.015	0.016	0.010	0.025	0.011	0.010	−0.005
4	p-Et	−0.121			0.001	0.001						
5	m-Cl	0.369	0.007		−0.009		−0.018		−0.059		−0.024	
6	p-Cl	0.238	0.005	0.005	0.006	0.002	0.012	0.004	0.035	0.013	0.057	0.040
7	m-Br	0.370					−0.018		−0.059		−0.025	
8	p-Br	0.264	−0.019	−0.020	−0.005	−0.009	0.008	−0.001	0.016	−0.007	0.024	0.007
9	m-I	0.324			−0.008				−0.057		−0.026	
10	p-I	0.278			−0.003	−0.007	0.001	−0.008	0.036	0.013	0.023	0.005
11	m-F	0.334	0.004				−0.009		−0.044		−0.035	
12	p-F	0.149	0.007	0.008	−0.006	−0.008	0.000	−0.008	0.016	−0.002	0.022	0.006
13	m-OCH$_3$	0.103					−0.035		−0.019		−0.069	
14	p-OCH$_3$	−0.122	0.003	0.004	0.012	0.013	0.025	0.019	0.041	0.027	0.012	−0.002
15	m-NO$_2$	0.717	−0.008		−0.009		−0.014		−0.007		−0.010	
16	p-NO$_2$	0.815	0.008	0.006	0.010	0.010	0.023	0.012	0.044	0.010	0.007	−0.014
17	m-CN	0.626					−0.005	−0.016	0.019	−0.011	0.008	−0.012
18	p-CN	0.715					0.017	0.007	0.025	−0.005	0.022	0.004
		s_e	0.0092	0.0102	0.0100	0.0099	0.0167	0.0117	0.0358	0.0179	0.0264	0.0152
		ϱ	0.493	0.496	0.496	0.507	0.535	0.541	0.712	0.733	0.849	0.856
		C_ϱ	0.045	0.066	0.042	0.051	0.056	0.046	0.090	0.050	0.060	0.037

[a] Criterion of goodness of fit, see Ref. 4. $C_\varrho = t_{n-2}$ (0.05) s_ϱ/ϱ. [b] The sigma values derived in case (*ii*) show small differences from case (*i*) due to the change in the data base from which they are calculated. The differences are, however, within 0.002 σ units.

Table 3. Residuals e_{ik} for each reaction of system (*2*), (*i*) with and (*ii*) without the substituents *m*-OCH_3, *m*-halogens, and *m*-NO_2. Notation same as in Table 2.

Substituents		2a	2a′	2b	2b′	2c	2c′	2d	2d′
1	H	0.021	0.008	0.006	−0.001	−0.002	−0.011	0.021	−0.001
2	*m*-Me	0.007	−0.007	0.008	0.002				
3	*p*-Me					0.004	−0.001		
5	*m*-Cl	−0.029		−0.025		−0.040		−0.026	
6	*p*-Cl					0.008	−0.011		
7	*m*-Br	−0.029		−0.005		−0.030		−0.007	
12	*p*-F					0.008	−0.003		
14	*p*-OCH_3					0.026	0.020		
15	*m*-NO_2	−0.012 [a]		−0.025 [a]		−0.019		−0.005	
16	*p*-NO_2	0.020	0.006	0.016	0.001	0.032	0.007	0.008	−0.004
17	*m*-CN	0.012	−0.002	0.009	0.004				
18	*p*-CN	0.009	−0.005	0.015	0.002	0.022	0.000	0.017	0.004
	s_e	0.0195	0.0059	0.0158	0.0024	0.0226	0.0101	0.0158	0.0033
	ϱ	0.382	0.384	0.491	0.500	0.399	0.420	0.481	0.471
	$C\varrho$	0.141	0.057	0.090	0.018	0.125	0.061	0.125	0.149

[a] Calculated σ-values for 3,5-di-NO_2 in reaction 2a; 1.39; 2: 1.27. The primary σ-value is 1.379. The statistical value based on 11 observations is 1.417 (to be published by the present authors). The σ-value for reaction 2a is within the uncertainty of the Hammett equation but the value for reaction 2b is too low. The 3,5-di-NO_2 group thus shows a strong solvent dependence when the alcohol content is increased from 50 % in reaction 2a to 75 % in 2b.

computations were made, denoted by 1a and 1a′ *etc:* (*i*) all substituents included and (*ii*) *meta* substituents with free electron pairs, *i.e. meta* halogens, *m*-OCH_3 and *m*-NO_2 excluded for series of (*1*) and (*2*); *m*-CN showed no anomaly and was not excluded.

RESULTS

The results of the computations are presented in Tables 2 and 3. Reactions 1a and 1b show very good fits in both computations and the deviations are of the normal size for the Hammett equation.[3,4] There is no improvement of the fit in the case 1a′ and 1b′. In reaction 1c, all substituents show good fits except *m*-OCH_3 and there is some improvement of the fit in the case 1c′. Reactions 1d and 1e show big negative residuals for the *meta* halogens and *m*-OCH_3 but the fit is greatly improved in the cases 1d′ and 1e′. The reaction 2c shows the same residual pattern as the reaction 1d and 1e and the fit is improved in case 2c′. In the reactions 2a′, 2b′ and 2d′ the substituents are too few to allow stringent interpretations. The results are, however, included for comparison.

DISCUSSION

The main pattern is best seen in Figs. 1 and 2, where the Hammett plot for the series 1d are made in (Fig. 1) the way corresponding to the analysis of Hoefnagel and (Fig. 2) corresponding to 1d and 1d′ in our analysis. In the plot corresponding to our analysis, the free electron substituents deviate and especially the *meta* halogens (Nos. 5, 7, 9, and 11). As seen in Fig. 1 the Hoefnagel plot relies very much on these substituents, which results in too low ϱ and log K_0 values and, consequently, far too large secondary σ-values for *p*-CN and *p*-NO_2. These abnormal values were interpreted by Hoefnagel *et al.* as due to through-resonance effects.

Since the deviations for the *meta* substituents are absent in the series 1a and 1b and increase through 1c and 1d with increasing amounts of alcohol in the solvent, we suggest that they are due to some solvent related effect. Hence, we claim that the poor fit for the phenylacetic acids in 50 % EtOH is likely to be a solvent dependent interaction between the *meta* substituents and the reaction site and not due to a through-resonance effect of the *para* substituents.

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