Substituent Effects. III.[1,2] Dissociation Constants of β-Arylpropionic Acids, β-Arylisovaleric Acids, *N*-Arylglycines, Aryloxyacetic Acids, *N*-Aryl-β-alanines, and Some Related Systems

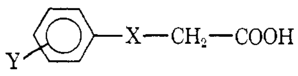
A. J. Hoefnagel, J. C. Monshouwer, E. C. G. Snorn, and B. M. Wepster*

Contribution from the Laboratory of Organic Chemistry, Technische Hogeschool, Delft, The Netherlands. *Received July 29, 1972*

Abstract: Dissociation constants of reaction series $ArXCH_2COOH$, with X = CH_2, CMe_2, NH, O, S, and $NHCH_2$, have been measured in water and/or ethanol–water mixtures. Deviations from the Hammett equation are found for −M substituents in the para position. These deviations, expressed in free energy terms $\Delta\Delta G_p$, are proportional to the resonance parameter $\Delta\sigma_R^-$ of the substituent as well as to the resonance parameter $\Delta\sigma_R^+(X\text{–}CH_3)$ representing the reaction center; the corresponding eq 5 is a special case of an expression for $\Delta\Delta G_p$ discussed previously. The reasons for the deviations from the Hammett equation are discussed and provide an explanation for the approximate equality of the exaltation of σ found for 4-NO_2 in the series with X = NH and $NHCH_2$, and in the arylhydrazines. The exaltations observed for X = CH_2 imply that such systems are not suitable to derive normal σ values (σ^n or σ^0) of −M substituents in the para position.

In a previous paper from this laboratory,[1] the Hammett ρσ relation was reevaluated on the basis of some assumptions regarding the consequences of mesomeric para interaction (through-resonance) as in 4-nitroaniline and 4-aminobenzoic acid. The results were encouraging, but for many reaction series there appeared to be a lack of data which would enable the calculation of reliable regression lines, or which would provide more detailed information on the para interaction; in other cases the experimental accuracy was doubtful. This combination of factors has led us into a program of research, part of which is a reinvestigation of reaction series which had been studied before.

In the present paper, we report on the dissociation constants of the carboxyl group in series of compounds of type I.



I

with X = CH_2, CMe_2, NH, O, S, and NH-CH_2

The first question was whether in these systems, in which the reaction center is conjugatively insulated from the Ar–X moiety, para substituents having −M effects (*e.g.*, NO_2, CN) would show a deviation from the Hammett equation, would show exalted σ_p values. If this would apply, the second question would be for the dependence of this deviation on the nature of X.

In fact, the first question had been studied, and answered in the affirmative, for X = O, by Hayes and Branch[3] in a paper which contains many insights which have been accepted only many years later. Unfortunately, the accuracy of some of the experimental data would seem not entirely satisfactory.

The systems with X = CH_2,[6,7] S,[4,5,8] and NH[9] have also been investigated previously. For our purposes, however, this work is not conclusive, either because the number of compounds studied is too small,[5–8] the accuracy of the data is in doubt,[4,5,8,9] or para substituents with −M effects have not been included.[9] The systems with X = CMe_2 and $NHCH_2$ have not been studied before.

Results

In dealing with the dissociation constants obtained, we shall make use of the following notions and notations:

$$\log K/K^0 = \rho\sigma^n \qquad (1)$$

the Hammett equation; *K*, dissociation constant of the substituted acid; K^0, dissociation constant of the unsubstituted acid, Y = H; σ^n, normal substituent constant, representing the substituent parameter to the exclusion of contingent through-resonance effects, as defined previously;[1] σ^0, normal substituent constant, in the notation introduced by Taft, *et al.*;[10] ρ, reaction constant, calculated using only "primary" meta-substituent parameters (see below), *i.e.*, defining $\rho \equiv 1$ for the acid–base equilibrium of ArCOOH in water, at 25°; σ, observed substituent parameter, calculated, as previously,[1] according to the statistical methods recommended and used by Jaffé;[11] $\tilde{\sigma}$, observed substituent parameter, calculated as $(\log K/K^0)/\rho$,[10] where K^0 is the experimental value for Y = H; $\sigma - \sigma^n$ and $\tilde{\sigma} - \sigma^n$, exaltations of substituent parameter;

$$\log K/K^0 = \rho\sigma^n + \rho r^+\Delta\sigma_R^+ \qquad (2)$$

$$\log K/K^0 = \rho\sigma^n + \rho r^-\Delta\sigma_R^- \qquad (3)$$

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[1] H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, 78, 815 (1959), is to be regarded as part I of this series.

[2] Part II: B. M. Wepster, *J. Amer. Chem. Soc.*, **95**, 102 (1973); part IV: A. J. Hoefnagel and B. M. Wepster, *ibid.*, **95**, 5357 (1973).

[3] N. V. Hayes and G. E. K. Branch, *ibid.*, **65**, 1555 (1943); for X = O see also ref 4 and 5.

[4] D. J. Pasto, D. McMillan, and T. Murphy, *J. Org. Chem.*, **30**, 2688 (1965).

[5] O. Behaghel, *J. Prakt. Chem.*, **114**, 287 (1926).

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[10] R. W. Taft, Jr., and I. C. Lewis, *ibid.*, **81**, 5343 (1959); R. W. Taft, Jr., S. Ehrenson, I. C. Lewis, and R. E. Glick, *ibid.*, **81**, 5352 (1959); R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

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Table I. Thermodynamic pK_a* Values^a of the COOH Group in Ar–X–CH_2COOH, in Water and Ethanol–Water Mixtures, at 25°

X	CH_2		CMe_2		NH		$NHCH_2$		O		S	
Solvent^d Substituent	50%	75%	50%	75%	50%	75%	50%	75%	H_2O	50%	10%	50%
3,5-Di-Me	5.82	6.56			(4.97)^b	5.56^c			3.20	4.26		
3-Me	5.77	6.53								4.22		
H^{e,f}	5.73	6.50	6.26	6.97	(4.88)^b	5.53	5.55^b	6.19	3.16	4.19	3.76	4.62
3-Cl	5.64	6.35	6.15	6.84	4.77	5.37			3.04	4.04		
Br	5.64	6.33	6.14	6.82	4.76	5.35			3.04	4.03		
NO_2^{e,f}	5.49	6.18	5.99	6.65	4.64	5.24	5.38	6.02	2.91	3.81	3.50	4.26
3,5-Di-NO_2^{f}	5.22	5.89			4.38	4.96	5.23	5.85		3.48		
4-NO_2	5.42	6.09	5.90	6.59	4.38	4.96	5.26	5.88	2.81	3.68	3.38	4.06
COMe					4.56	5.11			2.91	3.85		
SO_2Me					4.50	5.07			2.85	3.75		
CN	5.47	6.14	5.95	6.63	4.53	5.09			2.87	3.76		
3,5-Di-Me-4-NO_2	5.57	6.23			4.56	5.22				3.90		
3-$CH_2NH_3^+Cl^-$^{e,f}	5.06	5.52										
CN	5.50	6.19										
NH_2		6.57^c										
NMe_3^+ I^-^{e,f}	4.88	5.36										
4-Me			6.31									
t-Bu			6.31									
$CH_2NH_3^+$ Cl^-^{e,f}	5.20	5.75										
NH_2	(5.83)^b	6.62^c	(6.33)^b	7.09								
NHAc			6.20									
NMe_3^+ I^-^{e,f}	5.06	5.57	5.49	5.98								
OH			6.31									
OMe			6.28									
F			6.19									
Cl			6.16		4.76							
I										4.01		
3,5-Di-*t*-Bu	5.91	6.58										
3,5-Di-Cl					4.65							

^{a} If, with the amino acids, the sum of the corrections for zwitterion and ammoniocarboxylic acid is larger than 0.02 unit, the corrected pK_a* value is bracketed; for details see footnotes *b* and *c*, and Experimental Section. Where brackets and superscripts are absent, the correction is negligible. ^{b} "Overall" pK_a* value in 50% ethanol: X = CH_2, 4-NH_2 5.93; X = CMe_2, 4-NH_2 6.37; X = NH, 3,5-Me 5.06; H 4.92; X = $NHCH_2$, H 5.56. ^{c} "Overall" pK_a value in 75% ethanol: X = CH_2, 3-NH_2 6.58, 4-NH_2 6.63; X = NH, 3,5-di-Me 5.57. ^{d} 10, 50, and 75%: 10, 50, and 75 volumes of absolute ethanol in 100 volumes of final solution; *cf.* Experimental Section. ^{e} In water: X = CH_2, H 4.67 (ref 6 4.66); 3-NO_2 4.53; 3-$CH_2NH_3^+$ 4.22; 3-NMe_3^+ 4.17; 4-$CH_2NH_3^+$ 4.28; 4-NMe_3^+ 4.22. ^{f} In 10% ethanol: X = CH_2, H 4.85; 3-NO_2 4.67; 3,5-di-NO_2 4.48; 3-$CH_2NH_3^+$ 4.36; 3-NMe_3^+ 4.31; 4-$CH_2NH_3^+$ 4.42; 4-NMe_3^+ 4.37.

the Yukawa–Tsuno equations;[12] $\Delta\sigma_R^+ = \sigma^+ - \sigma^n$, standard exaltation of +M substituents; σ^+, value of σ for +M substituents in the para position in the S_N1 reaction of $ArCMe_2Cl$ in 90% acetone, at 25°, or of a similar reaction and brought to the same scale using the Yukawa–Tsuno proportionalities; $\Delta\sigma_R^- = \sigma^- - \sigma^n$, standard exaltation of −M substituents; σ^-, value of σ for −M substituents in the para position in the acid–base equilibrium of $ArNH_3^+$ in water, at 25°; r^+, Yukawa–Tsuno resonance proportionality constant applying when a +M substituent is involved in through-resonance, $r^+ = (\sigma - \sigma^n)/(\sigma^+ - \sigma^n)$; r^-, resonance proportionality constant applying when a −M substituent is involved in through-resonance, $r^- = (\sigma - \sigma^n)/(\sigma^- - \sigma^n)$;

$$-\Delta\Delta G_p = \rho(\sigma - \sigma^n)2.3RT = \rho r^{\pm}\Delta\sigma_R^{\pm}2.3RT \quad (4)$$

the deviation from the Hammett equation, taken to be due to the (para) through-resonance, and expressed in terms of free energy differences.[1,2]

In Table I all the thermodynamic pK_a* values measured in this work are listed. The reaction constants ρ were calculated on the basis of the following "primary" σ^n values,[1] all from the benzoic acid dissociation data of Dippy and coworkers:[13,14] (1) 3,5-di-Me, −0.098; (2) 3-Me, −0.069; (3) H, 0; (4) 3-F, 0.337; (5) 3-Cl, 0.373; (6) 3-Br, 0.391; (7) 3-I, 0.352; (8) 3-COMe, 0.376; (9) 3-NO_2, 0.710; (10) 3,5-di-NO_2, 1.379. The values for 3,5-di-Me and 3,5-di-NO_2 were added to those used previously in order to widen the range of σ^n values. thus compensating for the relatively low values of ρ, Table II gives the ρ values and the usual statistical data including those of relevant work from other laboratories. All correlations of our own data are such that comparison of the derived values of σ and $\Delta\Delta G_p$ seems warranted, although with even more care than usual considering the values of ρ.

The calculated σ values are collected in Table III. Table IV gives the deviations from the Hammett equation, in terms of both $\sigma - \sigma^n$ and $-\Delta\Delta G_p$. The actual values of σ^n and $\Delta\sigma_R^-$ used are: for σ^n, 4-NO_2, 0.78; 4-SO_2Me, 0.73; 4-COMe, 0.50; 4-CN, 0.70; and for $\Delta\sigma_R^-$, 4-NO_2, 0.45; 4-SO_2Me, 0.32; 4-COMe, 0.32; 4-CN, 0.29. These figures will be accounted for in the accompanying part IV of this series,[2] as will

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(12) Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Jap.*, **32**, 960 (1959); Y. Yukawa and Y. Tsuno, *ibid.*, **32**, 965, 971 (1959); Y. Yukawa, *Yuki Gosei Kagaku Kyokai Shi*, special ed, 69 (1962); M. Yoshioka, K. Hamamoto, and T. Kubota, *Bull. Chem. Soc. Jap.*, **35**, 1723 (1962); Y. Yukawa, Y. Tsuno, and M. Sawada, *ibid.*, **39**, 2274 (1966).

(13) J. F. J. Dippy, *Chem. Rev.*, **25**, 151 (1939); J. F. J. Dippy, S. R. C. Hughes, and J. W. Laxton, *J. Chem. Soc.*, 1470 (1954); 2995 (1956); J. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, **19**, 1527 (1963).

(14) After this paper had been submitted, the work of P. D. Bolton, K. A. Fleming, and F. M. Hall [*J. Amer. Chem. Soc.*, **94**, 1033 (1972)] came to our attention. Using their data, covering the substituents numbered 2, 3, 5, 6, and 9 here, somewhat better standard deviations and correlation coefficients are obtained, and ρ is 1–4% lower (see also Experimental Section under dissociation constants). The conclusions of the present paper are not affected.

Table II. Reaction Constants and Other Statistical Data[a] of the pK_a* Values of Ar–X–CH_2COOH and $ArNHNH_3^+$, at 25°

Acid	Solvent	$\rho \pm s_\rho$	s	R	pK_a^0	Substituents
$ArCH_2CH_2COOH$	10%	0.268 ± 0.009	0.009	0.999	4.85	3, 9, 10
	50%	0.385 ± 0.019	0.025	0.994	5.76	1, 2, 3, 5, 6, 9, 10
	50%	0.334 ± 0.056	0.028	0.974	5.75	3, 5, 6, 9
	75%	0.448 ± 0.007	0.009	0.999	6.51	1, 2, 3, 5, 6, 9, 10
	75%	0.450 ± 0.020	0.010	0.998	6.51	3, 5, 6, 9
$ArCMe_2CH_2COOH$	50%	0.377 ± 0.043	0.021	0.988	6.27	3, 5, 6, 9
	75%	0.448 ± 0.047	0.024	0.989	6.99	3, 5, 6, 9
$ArNHCH_2COOH$	H_2O[b]	0.296 ± 0.038	0.024	0.977	3.98	2, 3, 5, 8, 9
	50%	0.383 ± 0.016	0.019	0.997	4.91	1, 3, 5, 6, 9, 10
	75%	0.408 ± 0.007	0.009	0.999	5.52	1, 3, 5, 6, 9, 10
$ArNHCH_2CH_2COOH$	50%	0.232 ± 0.005	0.005	1.000	5.55	3, 9, 10
	75%	0.247 ± 0.004	0.004	1.000	6.19	3, 9, 10
$ArOCH_2COOH$	H_2O[c]	0.313 ± 0.014	0.009	0.997	3.18	2, 3, 4, 5, 9
	H_2O[c]	0.297 ± 0.042	0.027	0.954	3.19	2, 3, 4, 5, 6, 7, 9
	H_2O	0.350 ± 0.014	0.009	0.998	3.17	1, 3, 5, 6, 9
	50%	0.522 ± 0.019	0.025	0.997	4.20	1, 2, 3, 5, 6, 9, 10
$ArSCH_2COOH$	H_2O[d]	0.213 ± 0.063	0.040	0.810	3.60	2, 3, 4, 5, 6, 9
	10%	0.37				3, 9
	50%	0.51				3, 9
	50% dioxane[d]	0.494 ± 0.040	0.025	0.987	5.59	2, 3, 4, 5, 6, 9
$ArNHNH_3^+$	H_2O[e]	1.263 ± 0.087	0.056	0.993	5.33	2, 3, 5, 6, 9
	H_2O[f]	1.159 ± 0.030	0.019	0.999	5.19	2, 3, 5, 9
	50%[g]	1.56				3, 9

[a] ρ, reaction constant; s_ρ, standard deviation of ρ; s, standard deviation of the experimental points; R, correlation coefficient; pK_a^0, intercept of the regression line with the ordinate ($\sigma = 0$); substituents, actual substituents in the compounds involved in the calculation of ρ, identified according to their number mentioned in the text. [b] Reference 9. [c] Reference 3. [d] Reference 4; the statistical data given there are in error. [e] H. H. Stroh and G. Westphal, *Chem. Ber.*, 96, 184 (1963); *cf. ibid.*, 97, 83 (1964). [f] A. Fischer, D. A. R. Happer, and J. Vaughan, *J. Chem. Soc.*, 4060 (1964). [g] pK_a* values: H 4.87; 3-NO_2 3.76.

Table III. Calculated σ Values[a] of Substituents in Ar–X–CH_2COOH

X	CH_2		CMe_2		NH		O	
Solvent Substituent	50%	75%	50%	75%	50%	75%	H_2O	50%
4-NO_2	0.89[b]	0.93	0.98	0.87	1.38	1.38	1.02	1.00
COMe					0.91	1.01	0.73	0.68
SO_2Me					1.06	1.11	0.90	0.87
CN	0.76[b]	0.82	0.85	0.78	0.99	1.06	0.84	0.85
3,5-Di-Me-4-NO_2	0.50	0.62			0.91	0.74		0.58
3-$CH_2NH_3^+$[c]	1.81	2.20						
CN	0.68	0.70						
NH_2		−0.14						
NMe_3^+[c]	2.27	2.56						
4-Me			−0.08					
t-Bu			−0.08					
$CH_2NH_3^+$[c]	1.45	1.69						
NH_2	(−0.17)	−0.26	(−0.14)	−0.22				
NHAc			0.20					
NMe_3^+[c]	1.81	2.09	2.04	2.20				
OH			−0.08					
OMe			−0.01					
F			0.23					
Cl			0.30		0.39			
I								0.37
3,5-Di-(*t*-Bu)	−0.37	−0.16						
3,5-Di-Cl					0.68			

[a] All values are from our own data, and, as far as more than one regression line is given in Table II, relate to the line obtained for the larger number of substituents. Values in parentheses are considered to be somewhat less reliable due to uncertainties in the corresponding pK_a* values (*cf.* Table I). Calculated σ values for 4-NO_2 with X = $NHCH_2$, 1.24 (50%) and 1.26 (75%); with X = S, 1.04 (10%) and 1.10 (50%). [b] Using the substituents 3, 5, 6, and 9 only (*cf.* Table II), the σ value of 4-NO_2 is calculated as 0.95, that of 4-CN as 0.81. [c] σ values in 10% ethanol for X = CH_2, 3-$CH_2NH_3^+$ 1.84; 3-NMe_3^+ 2.03; 4-$CH_2NH_3^+$ 1.62; 4-NMe_3^+ 1.80.

the following $\Delta\sigma_R^+$ values: 4-NHMe, −1.33; 4-OMe, −0.71; 4-SMe, −0.71; 4-Et, −0.19; 4-*t*-Bu, −0.12.

The solvent in which all reaction series were measured is 50 vol % ethanol, and most of the discussion will be restricted to the data in this solvent. This medium was chosen for reasons of solubility and for comparability with other studies. It has the added advantage over water that with amino acids much less difficulty is experienced with zwitterions; 75% ethanol is even considerably better in this respect (see Table I).

The data in the other solvents generally display the same trends as observed in 50% ethanol. The variations with solvent of $\Delta\Delta G_p$ and σ are mostly small and within experimental error. The variations of ρ con-

Table IV. Values of $\sigma - \sigma^n$ and $-\Delta\Delta G_p$ (kcal/mol) for Para-Substituted Ar–X–CH_2COOH and $ArNHNH_3^+$

X	Solvent	4-NO_2 $\sigma - \sigma^n$	4-NO_2 $-\Delta\Delta G_p$	4-COMe $\sigma - \sigma^n$	4-COMe $-\Delta\Delta G_p$	4-SO_2Me $\sigma - \sigma^n$	4-SO_2Me $-\Delta\Delta G_p$	4-CN $\sigma - \sigma^n$	4-CN $-\Delta\Delta G_p$
CH_2	50%	0.11	0.06					0.06	0.03
	75%	0.15	0.09					0.12	0.07
CMe_2	50%	0.20	0.10					0.15	0.08
	75%	0.09	0.06					0.08	0.05
NH	50%	0.60	0.31	0.41	0.21	0.33	0.17	0.29	0.15
	75%	0.60	0.33	0.51	0.28	0.38	0.21	0.36	0.20
$NHCH_2$	50%	0.46	0.15						
	75%	0.48	0.16						
O	H_2O	0.24	0.11	0.23	0.11	0.17	0.08	0.14	0.07
	50%	0.22	0.16	0.18	0.13	0.14	0.10	0.15	0.11
S	10%	0.26	0.13						
	50%	0.32	0.22						
$ArNHNH_3^+$	H_2O^a	0.30	0.52						
	H_2O^b	0.51	0.81					0.11^b	0.17^b
	$50\%^c$	0.43	0.92					0.22	0.46

[a] See footnote *e*, Table II. [b] See footnote *f*, Table II; the values for 4-CN are probably in error (N analysis; our values in 50% ethanol). [c] pK_a^* values: 4-CN 3.44; 4-NO_2 2.98.

firm trends observed before[15] and will not be discussed here. The data on the thioacetic acids mainly serve to show that the results obtained for aqueous solution by Pasto, *et al.*,[4] are probably in error.

Discussion

(1) From cursory inspection of Tables III and IV it is plain that in the systems under consideration the σ_p values of $-M$ substituents are exalted, and that the degree of exaltation is dependent on the nature of X. Thus, in 50% ethanol, σ(4-NO_2) is found to be 0.89, 1.00, and 1.38 for the series with X = CH_2, O, and NH, respectively. Exaltation and multiplicity of exaltation, therefore, also hold for these conjugatively insulated systems.

Following Hayes and Branch,[3] we correlate these observations with the mesomeric para interactions present. As will appear from the following more detailed analysis, the available data are in (semi-)-quantitative agreement with this interpretation.

(2) Within each reaction series (X constant, Y variable) the deviation from the Hammett equation can be described as proportional to $\Delta\sigma_R^-$(Y). In other words, the systems I follow the Yukawa–Tsuno proportionalities. This has been illustrated in Figure 1, using $\Delta\Delta G_p$ (which within each reaction series is proportional to $\sigma - \sigma^n$ through eq 4) as the measure of deviation. The proportionality factors r^- vary from about 0.2 for X = CH_2 to about 1.2 for X = NH. The statistical data pertaining to the "overall" Yukawa–Tsuno relation, eq 3, are essentially the same as those for eq 1 (Table II) and are, therefore, not given; the corresponding r^- values have been included in the caption of Figure 1.

We note here that, contrary to the contention of Yukawa and Tsuno who regard r to be a measure of the through-resonance, we regard only $\Delta\Delta G_p$ to be significant as such;[16] r is, by definition, a dimensionless measure of the exaltation of σ within a reaction series, relative to the exaltation observed in an arbitrary standard reaction. A good illustration of the difference of opinion is provided by a comparison of the *N*-arylglycines with anilinium ions, at 25°. The r^- values are 1.2 (in 50% ethanol) and 1.0 (in water) and would suggest a larger (change in) para interaction for *N*-(4-nitrophenyl)glycine than for 4-nitroanilinium ion. The $-\Delta\Delta G_p$ values, on the other hand, are 0.31 and 1.8[1,2] kcal/mol. Of course, this lack of parallelism between r and $\Delta\Delta G_p$ is implicit in eq 4, and in the present example can be said to be due mainly to the large difference in ρ of the systems involved.

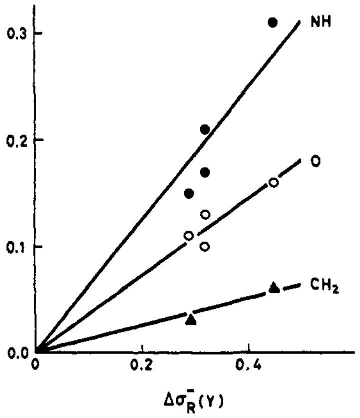

Figure 1. Correlation of $-\Delta\Delta G_p$ in 50% ethanol with $\Delta\sigma_R^-$(Y) for three reaction series. The slopes, the standard deviations, and the correlation coefficients of the least-squares line through the origin are for X = NH, 0.62, 0.03, 0.97; X = O, 0.36, 0.01, 0.98; X = CH_2, 0.13, 0.01, 0.99. The corresponding values of r^-, and the values of r^- calculated for the "overall" Yukawa–Tsuno relation (eq 3) are, in 50% ethanol: X = NH, 1.20 and 1.24; X = O, 0.50 and 0.51; X = CH_2, 0.23 and 0.24; and X = CMe_2, 0.47 and 0.49. In 75% ethanol: X = NH, 1.34 and 1.37; X = CH_2, 0.36 and 0.35; X = CMe_2, 0.22 and 0.25. In water: X = O, 0.56 and 0.60. The other values of r^-, calculated directly from the exaltations of σ(4-NO_2), are for X = $NHCH_2$, 1.02 and 1.07 in 50 and 75% ethanol; for X = S, 0.58 and 0.71 in 10 and 50% ethanol, respectively.

(3) When considering the dependence of $\Delta\Delta G_p$[17] on the nature of X (keeping Y constant), a fairly obvious choice as a parameter for X is $\Delta\sigma_R^+$(X–CH_3), *e.g.*, $\Delta\sigma_R^+$(OCH_3) for X = O. As illustrated in Figure 2,

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[15] *Cf.*, *e.g.*, K. Bowden, *Can. J. Chem.*, **41**, 2781 (1963); J. D. Sharp Ritter and S. I. Miller, *J. Amer. Chem. Soc.*, **86**, 1507 (1964).

[16] Reference 1, especially pp 817, 835, and 841.

[17] When comparing the deviations in different reaction series having different ρ values, as in this section, the choice between $\sigma - \sigma^n$ and $\Delta\Delta G_p$ is no longer arbitrary (as it was in section 2 with regard to the question of adherence to the Yukawa–Tsuno proportionalities) and $\Delta\Delta G_p$ must be used.

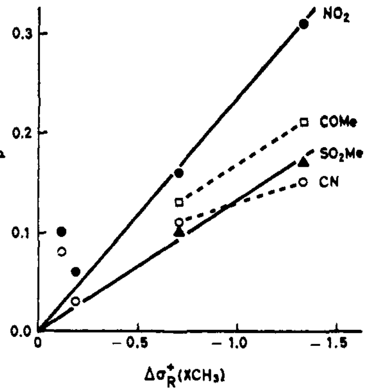


Figure 2. Correlation of $-\Delta\Delta G_p$ in 50% ethanol with $\Delta\sigma_R^+$-(XCH_3), for four para substituents. The slopes, the standard deviations, and the correlation coefficients of the least-squares line through the origin are for Y = NO_2, −0.24, 0.04, and 0.95; Y = COMe, −0.16, 0.02, and 0.99; Y = SO_2Me, −0.13, 0.01, and 1.00; Y = CN, −0.13, 0.04, and 0.81. For clarity's sake only the lines for NO_2 and SO_2Me have been drawn.

Table V. Effect of Proton Loss on the Uv Spectra[a] of Some 4-Nitroaniline Derivatives in 50 Vol % Ethanol

Compd	Form	λ_{max}, nm	ϵ_{max}	$\Delta\lambda$	$\Delta\nu$, cm^{-1}
N-(4-Nitrophenyl)-	COOH	384.5	16000		
glycine	COO^-	400.5	20000	16.0	1040
N-(3,5-Dimethyl-4-	COOH	390.0	5500		
nitrophenyl)glycine	COO^-	397.0	8900	7.0	450
N-(4-Nitrophenyl)-β-	COOH	396.0	19500		
alanine	COO^-	404.5	20700	8.5	530
4-Nitrophenylhydrazine	$NHNH_3^+$	331.0	10000		
	$NHNH_2$	392.0	14000	61.0	4700

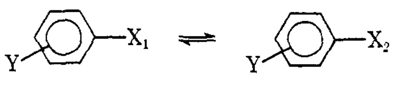
[a] $\Delta\lambda$ and $\Delta\nu$ refer to the differences in the maxima of absorption of the acids (at $pH^* \approx pK_a^* - 2$) and their conjugate bases (at $pH^* \approx pK_a^* + 2.5$).

this parameter is (also) approximately linearly related to $\Delta\Delta G_p$, with different slopes for each individual Y. Some details will be discussed in section 8.

(4) The proportionalities observed in sections 2 and 3 imply the more general expression[18a]

$$-\Delta\Delta G_p = (\text{constant})\Delta\sigma_R^-(Y)\Delta\sigma_R^+(XCH_3) \quad (5)$$

This expression has been discussed[2] as a special case of a relation due to Hine,[18b] holding for through-resonance in the systems II which relation can be written[2] as



II

$$-\Delta\Delta G_p = 2.4\Delta\sigma_R^{\pm}(Y)[\Delta\sigma_R^{\mp}(X_1) - \Delta\sigma_R^{\mp}(X_2)]2.3RT \quad (6)$$

From the point of view of this relation the applicability of eq 5 means that $\Delta\sigma_R^+(XCH_3)$ is proportional to $\Delta\sigma_R^+(XCH_2COOH) - \Delta\sigma_R^+(XCH_2COO^-)$.[19] We shall return to this in section 6a.

(5) Independent evidence for the importance of through-resonance is obtained from the σ values of 3,5-dimethyl-4-nitro-substituted derivatives. It is well known[20] that the methyl groups exert a considerable steric inhibition of the resonance interaction of the nitro group with the rest of the system. In the present work this is further indicated by the low ϵ_{max} in the uv spectra of the *N*-arylglycines (Table V). If the through-resonance were unimportant for the pK_a values, the inhibition of the resonance would be unimportant, so that the σ values of the 3,5-dimethyl-4-nitro grouping would be expected to be $\sigma(4\text{-}NO_2) + \sigma^n(3,5\text{-di-Me}) = \sigma(4\text{-}NO_2) - 0.098$. In fact, the observed values are all smaller, well on their way to or approximately equal to 0.56, the σ value found in the benzoic acid series.[21] More direct comparisons between the substituent effect of the 4-nitro group in phenyl-X-CH_2COOH and in (3,5-dimethylphenyl)-X-CH_2COOH provide a similar picture.

(6) Accepting the above data as experimental proof that the deviations from the Hammett equation are caused by the mesomeric para interaction, we shall now discuss the "mechanism" of the influence on pK_a as a combination of two effects which are acting in a concerted way.

(a) Taking *N*-(4-nitrophenyl)glycine as an example, we can start out from the hypothetical acid and anion in which mesomeric para interactions are absent; the acid-base equilibrium between these two species would have a pK_a corresponding with $\sigma^n(4\text{-}NO_2) = 0.778$. If, now, mesomeric para interaction is allowed to occur in the nitrophenylamino grouping, an extra dipole is formed along the C_1C_4 axis with the positive side directed to the glycine moiety; this dipole, therefore, certainly increases the dissociation constant. A crude estimate of the magnitude of this increase can be obtained from the extra mesomeric dipole moment in 4-nitroaniline which can be taken as about 1 D in benzene solution.[22] Placing the positive charge of this dipole on the amino nitrogen atom, and the negative charge at the midpoint between the oxygen atoms of the nitro group, *i.e.*, at a distance of 6.3 Å, these charges are +0.03 and −0.03, respectively. Neglecting the influence of the far-away negative charge, and taking the influence of a full positive charge to be 2.4 pK_a units,[23] the influence of the extra mesomeric dipole would be 0.07 pK_a unit. The observed increase of pK_a^* in 50% ethanol is [4.88 − 0.383(0.778)] − 4.38 = 0.20 pK_a^* unit,[24] so that it would seem reasonable to conclude that at least part of the exaltation can be accounted for in this way. Improvement of the calculation will not be attempted, but it should be pointed out that: (a) the decrease in the mesomeric interaction dipole moments in the order 4-nitroaniline,[22] 4-nitroanisole,[25] 4-nitrotoluene[26] corresponds qualitatively

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(18) (a) *Cf.* ref 2, and S. I. Miller, *J. Amer. Chem. Soc.*, 81, 101 (1959); (b) J. Hine, *ibid.*, 82, 4877 (1960).

(19) This difference, as calculated from the present data on 4-NO_2 derivatives in 50% ethanol, is 0.21 for X = NH, 0.11 for X = O, and 0.04 for X = CH_2.

(20) *Cf.* B. M. Wepster, *Progr. Stereochem.*, 2, 108, 123, 128, 144, 151 (1958); R. W. Taft, Jr., and H. D. Evans, *J. Chem. Phys.*, 27, 1427 (1957).

(21) Unpublished results, from measurements in 50% ethanol.

(22) *Cf.* M. J. Aroney, K. E. Calderbank, R. J. W. Le Fèvre, and R. K. Pierens, *J. Chem. Soc. B*, 561 (1968). An approximately equal extra moment follows from unpublished measurements by J. P. Iljas in this laboratory: aniline 1.53 D, nitrobenzene 3.98 D, 4-nitroaniline 6.25 D, 3,5-di-*tert*-butyl-4-nitroaniline 4.59 D; all in benzene at 25°.

(23) In water, at 25°, acetic acid has pK_a = 4.76, ammonioacetic acid 2.35; ρ_I for such substituted acetic acids is almost equal in water and in 50% ethanol (unpublished).

(24) Using ρ_I = 4 for substituted acetic acids (ref 23), this means that of the total "inductive constant" σ_I = 0.31 of the 4-nitrophenylamino grouping, 0.05 unit is due to the through-resonance.

(25) M. J. Aroney, R. J. W. Le Fèvre, R. K. Pierens, and M. G. N. The, *J. Chem. Soc. B*, 666 (1969).

(26) M. J. Aroney, K. E. Calderbank, R. J. W. Le Fèvre, and R. K. Pierens, *ibid.*, 159 (1969).

to the decrease in $-\Delta\Delta G_p$ found for X = NH, O, CH_2; (b) the decrease in the mesomeric moment from 4-nitroanisole[25] to 4-cyanoanisole[25] corresponds qualitatively to the decrease in $-\Delta\Delta G_p$ for Y = 4-NO_2 to Y = 4-CN.

(b) In the above considerations it was implicitly assumed that the polarization of the 4-nitrophenylamino grouping in the acid is the same as that in the anion. This cannot be correct, since, quoting Ingold,[27] "polarization effects . . . . are not carried unaltered from factor to product." In our case, with the mesomeric polarization developed fully in the acid, the negative charge formed upon dissociation will cause a further polarization. This implies a further extra stabilization of the anion, a further decrease of pK_a. The observation that the extra polarizability decreases in the order 4-nitroaniline,[22] 4-nitroanisole,[25] 4-nitrotoluene[26] shows that this polarizability effect can also account qualitatively for the decrease in the corresponding values of $-\Delta\Delta G_p$.

The reality of the differences in polarization between acid and conjugate base is demonstrated by the uv spectral data of Table V. In all cases, λ_{max} shifts to longer wavelengths upon removal of a proton, and when the resonance is sterically inhibited the shift is smaller.

(c) Reconsidering eq 5 of section 4, the applicability of this equation formally requires that both the dipole moment factor discussed in section 6a and the polarizability factor discussed in section 6b are approximately proportional to $\Delta\sigma_R^-(Y)$ and $\Delta\sigma_R^+(XCH_3)$. Although this extension of linear relationships is perhaps not unreasonable and provides an improvement in the description of these systems, it should be realized that many of the differences involved have large uncertainties, so that we cannot say more than that the observations are consistent with linearity; the data cannot, conversely, provide rigorous proof of the linearity or nonlinearity.

(7) Now, let us consider *N*-(4-nitrophenyl)-β-alanine with X = $NHCH_2$. In comparison with *N*-(4-nitrophenyl)glycine, the distance between the reaction center and the nitrophenylamino moiety has increased; therefore, the influences of both the extra dipole and the extra polarization in the anion will be smaller (*cf.* Table V, $\Delta\nu$), and consequently $-\Delta\Delta G_p$ should be smaller, as observed. However, since ρ is approximately proportionally smaller, the exaltations of σ(4-NO_2) are not very different for X = NH and X = $NHCH_2$.

The consequences of shortening the distance to the reaction center, while retaining the same 4-nitrophenylamino grouping, can be observed with the arylhydrazinium ions. Here $\Delta\nu$ and $-\Delta\Delta G_p$ for the deprotonation of the β-N-atom are much larger, as expected, but so is ρ, and the changes in $-\Delta\Delta G_p$ and ρ once more "compensate" with respect to the effective σ value.[28] Thus, an extension of the chain length by three bonds has relatively little effect on the degree of exaltation of σ.

(8) In the above discussion we have accepted the systems with X = CH_2 and X = CMe_2 as systems in which $-$M substituents show exalted σ values. This implies that we do not consider these systems (or the arylacetic acids[28]) as entirely satisfactory for the direct determination of σ^n or σ^0 as usually assumed,[29] although we have no evidence for deviations of +M substituents. The exaltations for $-$M substituents are small and only slightly outside experimental error and the approximations inherent in the Hammett equation, including small differences between ρ_m and ρ_p. The deviations are, however, consistently in the same direction, independent of the method of calculation,[30] and also turn up in direct comparisons, such as the ratio of the influences of 4-NO_2 and 3-NO_2 or of 4-CN and 3-NO_2. Moreover, and this we judge decisive, the exaltations appear as natural from the relations discussed in sections 3 and 4. When accepting the data for X = NH and X = O as demonstrating the relations between $\Delta\Delta G_p$ and $\Delta\sigma_R^+(XCH_3)$, denying the exaltation for X = CH_2 would imply assuming $\Delta\sigma_R^+(Et) = 0$, and this implication will be accepted by few.

In Figure 2 the points for X = CH_2 and X = CMe_2 appear in the "wrong" order. We do not consider this as important evidence against the proportionalities discussed. Firstly, we deal here with differences between small differences; secondly, the order of alkyl groups is infamous for its inconstancy;[31] and thirdly, the conformational possibilities of the side chains tend to complicate interpretation even further. Therefore, we would rather stress that the points are where they should be: near the origin and even in the correct quadrant. In a similar vein the "normal" order found in 75% ethanol, although noteworthy, is not to be given too much weight. It needs hardly to be said that, conversely, these points near the origin can contribute little or nothing with regard to the question whether strict linearity obtains or not.

(9) The σ values of Table III which have not yet been discussed will be dealt with in forthcoming papers in conjunction with those for, *inter alia*, arylacetic acids.[2] Attention may be drawn already here to the very high values for the positive poles, the small negative values for the 4-amino group, and the remarkable behavior of the 3,5-di-*tert*-butyl derivative.

Experimental Section

Some data on preparation, melting point, elemental analysis, and uv spectrum of the compounds studied are given in the microfilm edition.[32]

Dissociation Constants. The thermodynamic $pK_a{}^*$ values were determined using the method described by van Veen, *et al.*,[33] with a complete Beckman apparatus: pH meter Type G, Type G.P. glass electrode, Type 270 calomel electrode (fiber), and NBS phthalate buffer (pH 4.01) and phosphate buffer (pH 6.865). The calculations are exemplified in Table VI for two acids, one with a neutral and one with a positively charged substituent.

The accuracy and precision of this method have been discussed.[33]

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[27] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 63.

[28] We note that the same holds for arylacetic acids relative to β-arylpropionic acids; see the accompanying part IV of this series.

[29] Reference 11, p 230; ref 10; ref 1, p 833, footnote 17.

[30] See, *e.g.*, footnote *b* of Table III, and ref 14.

[31] *Cf.*, *e.g.*, R. O. C. Norman and P. D. Ralph, *J. Chem. Soc.*, 5431 (1963); W. M. Schubert and D. F. Gurka, *J. Amer. Chem. Soc.*, **91**, 1443 (1969); J. M. A. Baas and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **91**, 285 (1972), and forthcoming papers.

[32] These data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JACS-73-5350. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

[33] A. van Veen, A. J. Hoefnagel, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **90**, 289 (1971).

Table VI. Examples of pK_a* Determination in 50% Ethanol[a]

Compd	Acid concn mmol/l.	NaOH concn mmol/l.	Reading R	pH* = $R - \Delta$	$\sqrt{I}$[b]	Log $(HA - c_{H^+})/(A^- + c_{H^+})$	pK_a*	pK_a* mean
P	3.106	2.068	5.90	5.75	0.0455	−0.301	5.487	5.49
	6.294	2.068	5.30	5.15	0.0456	0.308	5.496	
Q	3.046	2.068	5.59	5.44	0.0552	−0.328	5.067	5.06
	5.942	2.068	5.00	4.85	0.0771	0.268	5.057	

[a] Compound P, 3-(3-nitrophenyl)propanoic acid; Q, 3-(4-trimethylammoniophenyl)propanoic acid iodide. The notation used in the table is that of ref 33. [b] For P, $\sqrt{I}$ from concentration NaOH + c_{H^+}; for Q, $\sqrt{I}$ from concentration acid, treating the conjugate base as a neutral particle: *cf.* H. Zollinger, W. Büchler, and C. Wittwer, *Helv. Chim. Acta*, **36**, 1711 (1953); A. V. Willi, *Z. Phys. Chem.* (*Frankfurt am Main*), **26**, 42 (1960).

An impression of the relative precision is obtained from the statistical data pertaining to our pK_a* values in 10% ethanol, at 25°, of ten benzoic acids (H; 3-Me, OMe, Cl, Br, NO_2; 4-Me, OMe, Cl, NO_2) when plotted against the corresponding values in water due to (a) Dippy, *et al.*,[13] $\rho = 1.073 \pm 0.008$; $s = 0.009$; $R = 0.9998$; $\Delta^0 = 0.001$ ($\Delta^0 = \log K^0$ (calcd) $- \log K^0$ (obsd)), and (b) Bolton, *et al.*,[14] $\rho = 1.053 \pm 0.010$; $s = 0.010$; $R = 0.9996$; $\Delta^0 = 0.005$.

Amino Acids. In the notation used by Bryson, *et al.*,[9] the dissociation constants involved in the acid–base equilibria of amino acids are designated K_A, K_B, K_C, and K_D. These are related through $K_A/K_B = K_D/K_C = K_Z$, and composite constants are given by $K_1 = K_A + K_B$, and $1/K_2 = 1/K_C + 1/K_D$. In this work we are interested in K_D, relating to the amino acid and the amino carboxylate anion, but in several cases this constant is not directly obtained with sufficient accuracy from the pH* of partly neutralized acid. Accordingly, corrections had to be applied to derive pK_D from the "overall" pK_a value. For judging the accuracy of these corrections it is of assistance to note that pK_A − pK_B = pK_D − pK_C = pK_Z is increased by about 1 pK unit when changing the solvent from 50% ethanol to 75% ethanol,[34] so that if there is little zwitterion in 50% ethanol, there is hardly any in 75% ethanol. As far as the *N*-arylglycines are concerned, the smallness or absence of corrections in 50% ethanol is qualitatively supported by the data of Bryson, *et al.*,[9] for aqueous solution, taking into account that pK_Z increases about 2 pK units in going from water to 50% ethanol.[34] Again, the corrections are such that pK_D is smaller than the uncorrected, overall pK_a value; this implies that the σ values for the 3- and 4-amino substituents cannot be more negative than those calculated from the overall pK_a.

The overall pK_a values for 3-(3-aminophenyl)propanoic acid, 3-(4-aminophenyl)propanoic acid, and 3-(4-aminophenyl)-3-methylbutanoic acid were first corrected with respect to K_1 by the method of Los, *et al.*,[35] to obtain pK_2, and then for K_C (zwitterion) to obtain pK_D. For this purpose, pK_A was taken to be equal to the experimental value for the NMe_3^+ derivative, and pK_B equal to the value estimated or found for the corresponding methyl ester (see below); the estimated values are sufficiently accurate since the pK_a values of the esters measured are close to those of aniline.[34]

The corrections necessary for *N*-phenylglycine and *N*-(3,5-dimethylphenyl)glycine in 50% ethanol were estimated by uv spectroscopy. The molecular extinction coefficients of the amino acid forms (maxima at 240 and 245 nm, respectively) were taken to be 95% of those of the corresponding ethyl esters; this percentage corresponds with the molecular extinction coefficients observed for *N*-phenylglycine and its ethyl ester in 75% ethanol (at appropriate pH), in which solvent zwitterions are almost absent.

The correction applied with *N*-phenyl-β-alanine in 50% ethanol was derived from estimated values for K_A and K_B based on the known values of phenylglycine[9] and aniline[34] in water, normal attenuation factors, and the solvent dependence of pK_Z mentioned above. An alternative approach starting out from β-alanine, gives the same small correction.

pK_a* values not mentioned in the tables: methyl 3-(4-aminophenyl)propanoate in 50% ethanol, 4.20; in 75% ethanol, 3.99; methyl 3-methyl-3-(4-aminophenyl)butanoate in 50% ethanol, 4.17.

Acknowledgments. We thank Drs. J. M. A. Baas and A. P. G. Kieboom for valuable discussions, Dr. C. Rüchardt for samples of a number of arylisovaleric acids, I. F. F. (Nederland) for a gift of 3,5-di-*tert*-butylbenzaldehyde, M. van Leeuwen for carrying out the elemental analyses, and M. A. Hoefnagel for the preparation of some *N*-arylglycines.

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(34) *Cf.*, *e.g.*, ref 33.

(35) J. M. Los, R. F. Rekker, and C. H. T. Tonsbeek, *Recl. Trav. Chim. Pays-Bas*, **86**, 609 (1967).