THE ACIDITY OF N-ACIDS. SUBSTITUENT EFFECTS ON THE DISSOCIATION CONSTANTS OF IMIDES AND SULPHONAMIDES

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Apparent dissociation constants of several aromatic sulphonamides, their N-acetyl and N-benzoyl derivatives, sulphohydrazides, sulphohydroxamic acids, dibenzamides, N-acetylbenzamides, and benzohydroxamic acids have been measured in water and/or 80% methyl cellosolve. The effect of the two substituents on the acidity of N-acids may be rationalized as follows: The substituents SO_2R, COR, alkyls, and aryls act in a regular but non-additive manner according to the correlation equation (*1*); the total substituent effect is composite of the inductive and of the electron withdrawing mesomeric effects. Only within restricted ranges, *e.g.* for substituted sulphonanilides, for which also the Hammett equation holds, the additivity is fulfilled with an acceptable precision, see Eq. (*2*). An abnormal behaviour is encountered with oxygen and nitrogen substituents (OH, $OCH_2C_6H_5$, NH_2): When they are present together with SO_2R substituents, the resulting acids are weaker than expected; when they are together with acyl groups, the acidity is enhanced.

N-Acids are commonly considered to be much weaker than typical O-acids, although this is true only as far as monoderivatives of ammonia, RNH_2, are compared to the corresponding derivatives of water, ROH. However, the former molecule has the possibility of introducing the second substituent; in this way the range of accessible acidities is enlarged and as strong acids as the strongest O-acids may be produced. For this reason the N-acids would be a suitable object for structure-acidity correlations if these were not impeded by some technical difficulties, as too high or too low values of pK and the instability of some derivatives. Some recent studies[1-7] are mostly confined to series of structurally similar compounds and the double substitution was not studied systematically. Even so, the fact emerges from the available data that the activity does not depend on substitution according to a simple, *e.g.* additive scheme. Most striking is the acidity of hydroxamic acids, slightly greater than that of sulphohydroxamic acids[8], while sulphonamides are stronger acids than amides by 5 pK units at least; in all these compounds it is the NH proton which dissociates. The explanation was originally attempted[8] in terms of mutual interaction of the inductive and mesomeric effect; hence the hydroxamic acids were considered anomalous, *i.e.* too strong acids. Non-additive substituent effects were also observed with N-cyanoamides[9]; this behaviour agrees in general with the behaviour of polysubstituted methanes as C-acids[10].

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The present study was undertaken with the aim of giving a general picture of substituent effects on the acidity of N-acids by an empirical approach. If possible, the well-behaved and anomalous substituents should be distinguished and the effect of the former expressed by a correlation equation. It was felt that the effects of two adjacent substituents, acting from two sides, need not be expressed in the form of a sum but rather of a product, like *e.g.* the substituents effects on the IR frequencies[11].

For the mentioned purpose we had to complete the existing data on dissociation constants by measuring further derivatives: sulphohydrazides *II*, N-acetyl-and N-benzoylsulphonamides *III* and *IV*, sulphohydroxamic acids *V*, and diacylamides *VI* and *VII*. All the compounds belonged to the aromatic series; besides the unsubstituted phenyl derivatives (*a*), those with $3-NO_2$ (*b*), 4-Br (*c*), and $4-CH_3$ (*d*) substituents were prepared in each series in order to estimate approximately the Hammett constant ϱ. The corresponding sulphonamides *I* and hydroxamic acids *VIII*, investigated already several times in the literature[5,6,8,12,13] were included for comparison. Several other classes of compounds were prepared like disulphonamides *IX*, N-cyanosulphonamides *X*, and hydrazides *XI* but the pK values could not be obtained by the standard methods used. N-Cyanoamides are investigated in more detail in an accompanying paper[9].

EXPERIMENTAL AND RESULTS

Materials

All the derivatives were prepared by standard methods starting from a substituted benzenesulphonylchloride or a substituted benzoyl chloride. All the compounds were analyzed and their melting points compared with those given in the literature. The analyses are listed in Table I only for compounds not reported previously.

Benzenesulphohydrazides[14] (*IIa—d*), N-acetylbenzenesulphonamides[15] (*IIIa—d*), N-benzoylbenzenesulphonamides[16] (*IVa—d*), benzenesulphohydroxamic acid[17] (*Va*), 4-toluenesulphohydroxamic acid[17] (*Vd*), 3-nitro- and 4-bromobenzenesulphohydroxamic acids[18] (*Vb,c*) were prepared according to the respective literature methods. N-Acetylbenzamides *VIa*, *VIb*, and *VId* were prepared by acetylation with acetic anhydride[19], while for N-acetyl-4-bromobenzamide (*VIc*) the use of acetyl chloride in pyridine[20] was necessary (30% excess of 4-bromobenzamide, 50°C, 3 hours). Under the same conditions all the monosubstituted dibenzamides (*VIIa—d*) were prepared. From the two possible combinations of starting compounds, benzamide plus substituted benzoyl chloride was always preferable; the reversed combination gave only small yields. Benzohydroxamic acids (*VIIIa—d*) were obtained as previously[8]. Symmetrically disubstituted bis(benzenesulphonyl)imides were prepared by the known method[21] but isolated as potassium salts (*IXa—d*). During the reaction, pH of the mixture was held to c. 7 by addition of 5% potassium hydroxide. The attempts to obtain the free acid in a state of purity failed. The same problem was encountered with substituted N-cyanobenzenesulphonamides which were prepared according to a decsribed procedure[22] and isolated also as potassium salts (*Xa—d*). Substituted benzohydrazides (*XIa—d*) were obtained by the standard procedure[23].

TABLE I

Analytical Data of Compounds Not Prepared Previously

Compound	Yield, % m.p., °C	Formula (m.w.)	Calculated/Found		
			% C	% H	% N
IIIb	60 191—192	$C_8H_8N_2O_5S$ (244·2)	39·35 39·52	3·30 3·48	11·47 11·67
IVb	75 188—189	$C_{13}H_{10}N_2O_5S$ (306·2)	50·98 50·75	3·29 3·58	9·15 9·46
Vb	37 156—158	$C_6H_6N_2O_5S$ (218·2)	33·03 32·85	2·77 2·52	12·84 12·64
VIc	56 198—199	$C_9H_8BrNO_2$ (242·1)	44·65 44·24	3·33 3·26	5·79 6·00
VId	67 145—148	$C_{10}H_{11}NO_2$ (177·2)	67·78 67·89	6·26 6·42	7·90 7·60
VIIb	71 128—132	$C_{14}H_{10}N_2O_4$ (270·2)	62·22 62·05	3·73 3·82	10·37 10·13
VIIc	50 228—230	$C_{14}H_{10}BrNO_2$ (304·2)	55·29 55·14	3·31 3·36	4·61 4·42
VIId	30 132—133	$C_{15}H_{13}NO_2$ (239·3)	75·30 75·33	5·48 5·59	5·85 5·39
IXa	69 >300	$C_{12}H_{10}KNO_4S_2$ (335·4)	42·97 42·50	3·00 3·11	4·18 4·31
IXb	86 >300	$C_{12}H_8KN_3O_8S_2$ (425·4)	33·88 33·88	1·90 2·41	9·88 9·65
IXc	80 >300	$C_{12}H_8Br_2KNO_4S_2$ (493·3)	29·22 29·45	1·63 1·43	2·84 2·84
IXd	71 >300	$C_{14}H_{14}KNO_4S_2$ (363·5)	46·26 46·68	3·88 3·92	3·85 4·19
Xa	70 >300	$C_7H_5KN_2O_2S$ (220·3)	38·16 38·20	2·29 2·50	12·72 12·46
Xb	85 >300	$C_7H_4KN_3O_4S$ (265·3)	31·69 32·14	1·52 1·54	15·84 15·80
Xc	75 >300	$C_7H_4BrKN_2O_2S$ (299·2)	28·10 28·46	1·35 1·64	9·36 9·03
Xd	70 >300	$C_8H_7KN_2O_2S$ (234·3)	41·00 41·21	3·01 3·28	11·96 11·58

Physical Measurements

The apparent dissociation constants were determined by potentiometric titration using a Beck-mann Research pH-meter, a glass indication electrode Radiometer G 2222 and a calomel reference electrode Radiometer K 4112 DP. Solutions of the concentration $5 . 10^{-3}$M were titrated at $25 \pm$ $\pm 0.1°C$ with 0.1M aqueous tetramethylammonium hydroxide in the atmosphere of nitrogen saturated by vapour of the respective solvent. The solvents used were redistilled water or 80% by weight aqueous methyl cellosolve, the required concentration was always reached just at the half-neutralization point. The apparatus was calibrated using a phosophate buffer pH = 6.57. The full titration curve was recorded and evaluated in the case of compounds *III, IV, VII*, and *VIII*. The remaining compounds *I, II, V*, and *VI* did not exhibit a sufficiently distinct potential jump, hence the pK values were calculated from three points, at a 40%, 50% and 60% neutraliza-tion, respectively. The potassium salts *IX* and *X* could not be titrated by 0.1M hydrochloric acid in a $5 . 10^{-2}$M solution owing to their too low values of pK. On the other hand the hydrazides *XI* were too weakly acidic to be measured under our conditions, although some pK values were reported[7]. The pK values determined are listed in Table II. As indicated in the footnotes, they agree mostly quite well with previous determinations.

The electronic spectra were measured on a spectrophotometer Unicam SP-800 at the concen-tration of $5 . 10^{-4}$M in 0.1M hydrochloric acid or 0.1M potassium hydroxide, respectively. The absorption maxima are reported in Table II. Their shifts with ionization were in no case large enough to allow a convenient spectrophotometric determination of pK.

Calculations. The least-squares calculations according to the correlation equations (*1*) and (*2*) were performed on a Hewlett Packard calculator 9820 A. The details of the program will be reported elsewhere[26].

DISCUSSION

In order to rationalize the substituent effects on acidity we must first define the "well-behaved" substituents and select the pertinent data from Table II and from the literature, which are related to comparable conditions. With respect to the mentioned discrepancies in the acidity of hydroxamic and sulphohydroxamic acids[8], we tentati-vely excluded all the substituents of the type OR or NHR; from the remaining substi-tuents a selection was made as shown in Table III. We intended to obtain a reason-ably filled table and not to include several very similar substituents (*e.g.* all the substi-tuted phenyls). It was, however, unavoidable to complete the direct experimental data by some calculated ones, either deduced from measurements of other com-pounds in water, or of the same compound in another solvent. Care was always taken to use only reliable correlations, restricted to small series of similar compounds and any longer extrapolation was avoided. The details of the estimation are given in footnotes to Table III. With all the precautions mentioned the Table is filled up only to 50%. The only not dependable value is that for ammonia for which dif-fering estimations exist[27,31].

The substituent effects on acidity will be firstly explained from the data of Table III themselves, without referring to any fixed scale of constants (σ). The following equa-

TABLE II

Apparent Dissociation Constants (in Water and in 80% Methyl Cellosolve) and Ultraviolet Absorption Maxima of Some N-Acids

Compound		pK_{app}. (25°C)		λ nm (log ε)	
		H_2O	80% MCS	0·1M-HCl	0·1M-KOH
Ia	$C_6H_5SO_2NH_2$	$10·10^a$	11·54	260 (3·00)	260 (3·03)
Ib	$3-NO_2C_6H_4SO_2NH_2$	$9·40^a$	10·78	258 (3·34)	260 (3·92)
Ic	$4-BrC_6H_4SO_2NH_2$	$9·87^a$	11·31	234 (4·11)	234 (3·19)
Id	$4-CH_3C_6H_4SO_2NH_2$	$10·24^a$	11·65	269 (2·84)	269 (2·90)
IIa	$C_6H_5SO_2NHNH_2$	10·60	11·89	260 (3·15)	260 (3·44)
IIb	$3-NO_2C_6H_4NHNH_2$	9·78	11·30	255 (3·74)	260 (4·11)
IIc	$4-BrC_6H_4SO_2NHNH_2$	10·36	11·72	237 (4·30)	237 (4·28)
IId	$4-CH_3C_6H_4SO_2NHNH_2$	10·71	11·87	260 (3·03)	260 (3·30)
IIIa	$C_6H_5SO_2NHCOCH_3$	4·72	6·69	266 (3·07)	266 (3·02)
IIIb	$3-NO_2C_6H_4SO_2NHCOCH_3$	3·97	5·55	255 (3·46)	262 (3·66)
IIIc	$4-BrC_6H_4SO_2NHCOCH_3$	4·52	6·18	238 (3·62)	236 (3·46)
IIId	$4-CH_3C_6H_4SO_2NHCOCH_3$	$4·92^b$	6·86	262 (3·20)	258 (3·14)
IVa	$C_6H_5SO_2NHCOC_6H_5$	—	5·44	236 (4·25)	240 (4·37)
IVb	$3-NO_2C_6H_4SO_2NHCOC_6H_5$	—	4·30	239 (4·52)	246 (4·52)
IVc	$4-BrC_6H_4SO_2NHCOC_6H_5$	—	4·94	242 (4·60)	237 (4·06)
IVd	$4-CH_3C_6H_4SO_2NHCOC_6H_5$	—	5·66	239 (4·50)	241 (4·35)
Va	$C_6H_5SO_2NHOH$	$9·34^c$	$11·64^c$	258 (3·16)	260 (3·38)
Vb	$3-NO_2C_6H_4SO_2NHOH$	8·60	11·07	257 (3·93)	257 (3·94)
Vc	$4-BrC_6H_4SO_2NHOH$	9·08	11·58	245 (3·62)	247 (3·56)
Vd	$4-CH_3C_6H_4SO_2NHOH$	9·40	12·00	262 (3·42)	262 (3·37)
VIa	$C_6H_5CONHCOCH_3$	—	11·55	235 (4·32)	258 (3·30)
VIb	$3-NO_2C_6H_4CONHCOCH_3$	—	10·94	225 (4·58)	264 (4·10)
VIc	$4-BrC_6H_4CONHCOCH_3$	—	11·36	245 (4·44)	245 (4·44)
VId	$4-CH_3C_6H_4CONHCOCH_3$	—	11·81	250 (4·36)	260 (4·24)
VIIa	$C_6H_5CONHCOC_6H_5$	—	10·60	247 (4·49)	274 (4·13)
VIIb	$3-NO_2C_6H_4CONHCOC_6H_5$	—	9·43	238 (4·63)	273 (4·41)
VIIc	$4-BrC_6H_4CONHCOC_6H_5$	—	10·21	249 (4·18)	270 (4·22)
VIId	$4-CH_3C_6H_4CONHCOC_6H_5$	—	10·80	250 (4·60)	268 (4·10)

TABLE II
(*Continued*)

Compound		pK_{app}. (25°C)		λ nm (log ε)	
		H_2O	80% MCS	0·1M-HCl	0·1M-KOH
VIIIa	$C_6H_5CONHOH$	8.89^d	10.44^e	230 (3·94)	267 (3·91)
VIIIb	$3-NO_2C_6H_4CONHOH$	8·20	9.12^e	237 (4·48)	267 (4·27)
VIIIc	$4-BrC_6H_4CONHOH$	8·61	9·78	233 (4·41)	272 (3·95)
VIIId	$4-CH_3C_6H_4CONHOH$	8.99^d	10.55^e	239 (4·22)	265 (3·96)
IXa	$(C_6H_5SO_2)_2NK$	—	—	234 (3·99)	236 (4·03)
IXb	$(3-NO_2C_6H_4SO_2)_2NK$	—	—	232 (4·23)	232 (4·33)
IXc	$(4-BrC_6H_4SO_2)_2NK$	—	—	225 (4·57)	226 (4·59)
IXd	$(4-CH_3C_6H_4SO_2)_2NK$	—	—	232 (4·64)	233 (4·54)
Xa	$C_6H_5SO_2NKCN$	^{f}	—	226 (4·01)	226 (4·12)
Xb	$3-NO_2C_6H_4SO_2NKCN$	—	—	224 (4·20)	225 (4·31)
Xc	$4-BrC_6H_4SO_2NKCN$	—	—	230 (4·21)	229 (4·08)
Xd	$4-CH_3C_6H_4SO_2NKCN$	—	—	222 (4·22)	222 (4·32)
XIa	$C_6H_5CONHNH_2$	^{g}	—	232 (4·25)	267 (3·81)
XIb	$3-NO_2C_6H_4CONHNH_2$	^{g}	—	225 (4·59)	271 (4·28)
XIc	$4-BrC_6H_4CONHNH_2$	—	—	246 (4·37)	248 (4·11)
XId	$4-CH_3C_6H_4CONHNH_2$	^{g}	—	242 (4·31)	242 (4·18)

[a] Ref.[5] gives pK 10·10, 9·34, 9·79, and 10·21 for *Ia* — *Id*, respectively; [b] ref.[24] gives the approximate pK 4·8 at 22·5°C; [c] previously the pK values of 9·26 and 11·6 were found[8] in water and in 80% methyl cellosolve, resp.; [d] ref.[13] gives pK 8·80 and 8·93 for *VIIIa* and *VIIId*, resp; [e] exactly the same values were found previously[8]; [f] ref.[25] gives pK 4·89 but we were not able to confirm this value; [g] ref.[7] gives pK 12·52, 11·36, and 13·04 for *XIa*, *XIb*, and *XId*, resp.

tion was found to hold with an acceptable precision

$$pK = pK^0 + x_i x_j, \qquad (1)$$

where pK^0 and x's are empirical constants, each x_i characterizes a given substituent R_i. The pertinent statistics of the correlation are given in Table IV. According to the value[32] of the statistic ψ the correlation is "fair" but it improves to "good" if the two values for acetamide and benzamide, based on a rather old paper[28], are omitted.

A graphical representation of equation (1) is in Fig. 1 where the experimental pK values are plotted against the empirical constants x; the calculated values are represented by a family of lines intersecting in one point $(0, -5.30)$. The behaviour of the substituents is non-additive beyond any doubt; this statement is equivalent to the observation that the lines in Fig. 1 are not parallel. When substituent effects are related to hydrogen as a standard, then the second electron attracting substituent has always a smaller effect than the first one already present, and the cumulative effect is less than additive. The value of p$K^0 = -5.30$ represents the utmost limit of the acidity. (For electron releasing substituents the reverse should be true, the second substituent having a greater effect than the first; there is no limit of weak acidity. Of course, the electron releasing substituents are unimportant as compared to the electron withdrawing.)

Equations of the type (1) were previously used to correlate characteristic frequencies of the carbonyl[33] and sulphonyl[11] groups with substituent effects. In our opinion they are typical always when two adjacent substituents are operating from opposite sides, and hence their effect is relatively strong. If the substituents are more remote, or are restricted to a set of structurally similar groups, their effects may become approximately additive, or it may be at least difficult to prove the deviations from ad-
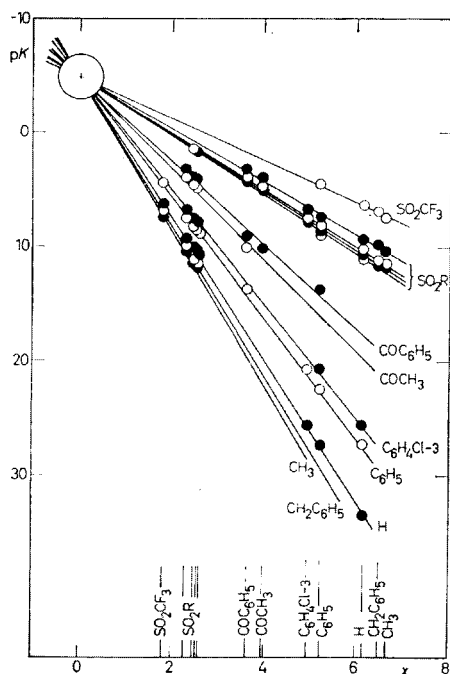

FIG. 1

Empirical Correlation of the Acidity of N-
-Acids R^1NHR^2 According to the Equation (1)

The pK values are plotted against the empirical constants of the substituents R^1; derivatives with a common substituent R^2 are situated on the same line.

ditivity with certainty. In the graphical representation it means that in a small seg-
ment of Fig. 1 the lines can be viewed as approximately parallel. Such cases are
encountered in Hammett correlations with double substitution: A non-additive
equation analogous to (1) has been suggested by Miller[34] to be a general solution
but in practiee it may be often difficult to prove firmly the deviations from additivity[35].
Sometimes an additive relationship is still used merely for traditional reasons and
even for quantities[36] treated previously by equation (1).

Although the non-additive character of the data of Table III is beyond discussion,
we carried out still a calculation according to the additive equation

$$pK = pK^0 + y_i + y_j. \qquad (2)$$

In this case the substituent constants y are different from x in equation (1) and one
of all the constants $(pK^0$ and $y_i)$ may be arbitrarily adjusted. For example if pK^0
equals the pK of ammonia then the constant y for hydrogen equals zero as usually.*
Hence the number of all empirical constants is one less than in equation (1). The
statistics given in Table IV, line 3, show conclusively that equation (2) is not ade-
quate for all the data of Table III.

On the other hand, various sub-groups may be selected within the area of N-acids,
for which the additive relationship (2) is a sufficient approximation. We have carried
out the calculation for several such sets:

The pK values of substituted benzenesulphonanilides with *meta* or *para* substituents in either
benzene nucleus (12 or 7 various substituents, respectively) were measured in 50% ethanol[6].
This set thus represents the range of validity of the classical Hammett equation[37] and the con-
stants y_i found must be proportional to Hammett's $\sigma_{m,p}$. The calculation revealed (Table IV,
line 4) that the additive relationship (2) is "very good" and is not significantly improved by using
equation (1), see line 5. The accuracy decreases only slightly when the set is extended by including
the corresponding N-methylsulphonamides, N-benzylsulphonamides, primary sulphonamides,
and derivatives of toluene-α-sulphonic acid from the same source[6] (line 6 in Table IV). Another
set is based on pK values (in water) of substituted sulphonamides $R^1SO_2NHR^2$ where $R^1 = CH_3$,
CH_2F, CHF_2, CF_3, C_6H_5, C_6H_4Br-4, $C_6H_4NO_2$-3, $C_6H_4CH_3$-4, and $R^2 = H$, C_6H_5,
$C_6H_4COC_6H_5$-3, CH_3, $CH_2C_6H_5$, $COCH_3$, and COC_6H_5 (see data in Tables II, III and ref.[1]).
Even in this case the additive relationship is completely sufficient (lines 7, 8 in Table IV). The
insignificant improvement achieved by applying equation (1) is well documented also from the
constants pK^0 which have very distant and very imprecise values.

A still more structurally restricted set based on the Hammett equation consists of eight series
I— VIII, each containing only four derivatives $a - d$ (Table II). The condition of additivity is equi-
valent to the postulate that all the ϱ constants are equal[35], while according to the equation (1)

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*   The number of empirical constants, and hence of degrees of freedom, is different according
to whether the set is symmetrical (the substituents R^1 and R^2 are the same and take equivalent
positions like in Table III) or unsymmetrical (like in the following examples). Also the calculations
differ in some detail in these two cases[26], but for the purpose of the present discussion the dif-
ference will be neglected.

TABLE III

Experimental and Estimated pK Values of Selected Bis-derivatives of Ammonia R^1NHR^2 (in water)

R^2/R^1	H[a]	CH_3	C_6H_5	$C_6H_4Cl\text{-}3$	$CH_2C_6H_5$	$COCH_3$	COC_6H_5	$SO_2C_6H_5$	$SO_2C_6H_4NO_2\text{-}4$	$SO_2C_6H_4CH_3\text{-}4$	SO_2CH_3	SO_2CF_3	Constant x
H[a]	33·5[b]	—	27·3[c]	25·6[c]	—	15·1[d]	~14·5[d]	10·10	9·40	10·24	10·8[e]	6·33[f]	6·25
CH_3	—	—	22·4[c]	—	—	—	—	11·43[g]	10·42[g]	11·69[g]	—	7·56[f]	6·61
C_6H_5	—	—	—	20·7[c]	—	—	13·70[h]	8·31[i]	7·50[i]	8·46[i]	8·85[f]	4·45[f]	5·25
$C_6H_4Cl\text{-}3$	—	—	—	—	—	—	—	7·66[i]	6·85[i]	7·85[i]	—	—	5·00
$CH_2C_6H_5$	—	—	—	—	—	—	—	11·25[g]	9·84[g]	11·55[g]	—	6·82[f]	6·45
$COCH_3$	—	—	—	—	—	—	10·15[j]	4·72	3·97	4·92	—	—	4·04
COC_6H_5	—	—	—	—	—	—	9·05[j]	3·95[j]	3·20[j]	4·10[j]	—	—	3·71
$SO_2C_6H_5$	—	—	—	—	—	—	—	1·45[g]	—	—	—	—	2·55
$SO_2C_6H_4NO_2\text{-}3$	—	—	—	—	—	—	—	—	—	—	—	—	2·38
$SO_2C_6H_4CH_3\text{-}4$	—	—	—	—	—	—	—	—	—	1·70[g]	—	—	2·58
SO_2CH_3	—	—	—	—	—	—	—	—	—	—	—	—	2·65
SO_2CF_3	—	—	—	—	—	—	—	—	—	—	—	—	1·90

[a] Statistically uncorrected, but the constants x were calculated from corrected values; [b] extrapolated using a relationship between RNH_2 and RNH_3^+ acid[27]; [c] ref.[4], the value for $C_6H_5NH_2$ is a relatively dependable extrapolation based on the Hammett equation; [d] ref.[28], approximate values; [e] ref.[29], [f] ref.[1], the value for $CF_3SO_2NHCH_2C_6H_5$ is estimated on the basis of titration in 67% dimethylformamide; [g] ref.[5], 20°C; [h] ref.[30], [i] ref.[12], 20°C, $\mu = 0·1$; the values for the 3-chlorophenylsulphonamides were estimated by us from the Hammett correlations; [j] estimated from the data of this paper determined in 80% methyl cellosolve.

one would predict that they would vary in the ratio $1 : 1.7$. Our calculation yielded ϱ in the range $0.96 - 1.06$ in water and $0.72 - 1.78$ in 80% methyl cellosolve; the lowest values in the latter case may be caused by experimental errors of very high pK's. Even the remaining ϱ's are loaded with large errors due to the small number of derivatives. Hence one cannot reject the hypothesis that they are equal. In addition, they are not in the sequence required by equation (1).

We conclude that some of these additive correlations according to the equation (2) are more precise than the general correlation according to the equation (1); this is of course outweighted by their closer range of validity. This high precision might show that the additive character is an intrinsic property of these special series rather than it is only approximately realized by their restricted range of validity. However, the question can hardly be answered, just because of this restricted range.

In the described correlations many empirical constants (x_i, y_i, pK^0) are involved from which only those of the most general relationship, *i.e.* x_i in equation (1), are of independent importance. By comparing their values (Table III, last column) with known scales[37] of the inductive (σ_I) or mesomeric (σ_R) effect or a combination of both $(\sigma_p, \sigma_p^-, \sigma_p^+)$ one can decide which effects are controlling the acidity of N-acids. The plot* of constants x from Table III against σ_I (Fig. 2) reveals the expected trend with significant deviations of the aryl and acyl substituents. These enhance the acidity more than would follow from their σ_I constants. This proves that the electron attracting conjugative effect of these substituents is also operative and is relatively strong. In principle it could be accounted for by replacing the σ_I constants by σ_p or σ_p^- which are also composed from the inductive and mesomeric effects[37]. However, not one of the possible plots (not shown) is completely satisfactory. The σ_p constants make proper allowance for the conjugation of acetyl as an acceptor but not of phenyl since the latter acts as a donor in biphenyl-4-carboxylic acid (definition of σ_p) but as an acceptor in our case. Similarly the σ_R scale gives the mesomeric effects of phenyl with the opposite sign. Nor does the σ_p^- scale do full justice to the effect of phenyl while it already overestimates the effect of acetyl.

We do not intend to define any new scale of constants because of the small number of our x values and their limited applicability. However, we must state that these values cannot be simply correlated with any kind of constants already known. It is well known that mesomeric effects are rather specific and not transferable in a quantitative manner from one series of compounds to another[37]. Note that in the non-additive model with symmetrical substitution — equation (1) — the constants are obtained unambiguously and there is no possibility to adjust some of them, *e.g.* to zero for hydrogen as usual with other equations.

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*   The values of σ_I for the composed substituents were not available in tables[37] and had to be estimated basing on the relations between the σ constants of the whole substituent and of its parts[38]. Details of estimating are not given here since the inaccuracy inherent in the procedure does not affect the final conclusions. For instance σ_I constant of $SO_2C_6H_4CH_3$-4 must be very close to that of $SO_2C_6H_5$ but slightly less positive; the exact value is immaterial.

The slope in Fig. 2 $(c. -5.6)$ cannot be directly compared with any known ϱ constant since the relationship (1) is not linear. We can only compare individual series of compounds R^1NHR^2 where one substituent is constant and the second variable. For hydrogen as the constant substituent we get $\varrho_I = 34.5$, for $SO_2C_6H_5$ we get only $\varrho_I = 13.8$. The former value may be compared to $\varrho_I = 19.5$ (recalculated from ref.[39]) for the acidity of ammonium ions $RNH_3^{(+)}$ with the conclusion that the second dissociation constant of these acids is almost twice $(1.77\times)$ as sensitive to substituent effects as the first one. Within a restricted series of compounds this ratio was found[27] to be 1.30.

The constant pK^0 of equation (1) is of theoretical interest since it is independent of any transformation of constants and could thus have a physical meaning. Any simple interpretation is, however, lacking like in similar equations for the infrared frequenceis[11,33].

At this point we are able to return to the substituents OR and NHR excluded from the above discussion as anomalous. They really do not obey equation (1) since they cannot be given a single-valued constant x. For the substituent OH this constant

TABLE IV

Statistics of Correlations of Acidity of N-Acids According to Equations (1) and (2)

Range of validity	Equation	N^a	M^b	s^c	$s_0^{\;d}$	$\psi = s/s_0$	pK^0
All N-acids (Table III)	(1)	39	13	0·77	7·01	0·11	-1.64
All N-acids; excluded data for acetamide and benzamide	(1)	37	13	0·30	7·18	0·042	-5.30
All N-acids; excluded data for acetamide and benzamide	(2)	37	12	1·98	7·18	0·28	
Substituted benzenesulphonanilides^e	(2)	82	18	0·022	1·04	0·022	—
Substituted benzenesulphonanilides^e	(1)	82	19	0·021	1·04	0·020	~ -60
N-Substituted benzenesulphonamides^f	(2)	111	22	0·038	1·44	0·026	—
N-Substituted sulphonamides^g	(2)	33	14	0·151	2·76	0·055	—
N-Substituted sulphonamides^g	(1)	33	15	0·141	2·76	0·051	~ -40

^{a} Number of experimental data; ^{b} number of independent empirical constants involved; ^{c} root-mean-square difference between predicted and experimental values; ^{d} standard deviation of the experimental values from their average; ^{e} data[6] in 50% ethanol by weight; substituents in either benzene nucleus of benzenesulphonanilide; ^{f} the preceding set extended by including N-methylsulphonamides, N-benzylsulphonamides and primary sulphonamides, and by adding toluene-α-sulphonic acid derivatives[6]; ^{g} pK's in water; derivatives of methanesulphonic, mono-, di-, and tri-fluoromethanesulphonic[1], benzenesulphonic, and 4-bromo-, 3-nitro and 4-methylbenzenesulphonic acids with the following substituents on nitrogen: H, C_6H_5, $C_6H_4COC_6H_5$-3, CH_3, $CH_2C_6H_5$, $COCH_3$, and COC_6H_5.

would be $x = 3.76$ if derived from benzohydroxamic acid (*VIIIa*) but 5.75 if derived from benzenesulphohydroxamic acid (*Va*). The corresponding values for $OCH_2C_6H_5$, 3.81 and 5.66, may be approximately estimated from the dissociation constants in 80% methyl cellosolve[8]. For NH_2 one gets $x = 4.76$ from benzohydrazide (*XIa*) and 6.27 from benzenesulphohydrazide (*IIa*). In other words all these sulphonyl derivatives are too weak acids in relation to the corresponding carboxylic acid derivatives. This fact is visualized in Fig. 3 where pK's of the corresponding derivatives $C_6H_5SO_2NHR$ and C_6H_5CONHR are plotted against each other. The four well-behaved substituents fall closely to the calculated line which is based on the whole set of N-acids. The deviations of these points reflect the inaccuracy of equation (*1*) in the enlarged scale, while the much larger deviations of the anomalous substituents are evident.

The unexpected ratio of acidity of hydroxamic and sulphohydroxamic acids was previously explained[8] in terms of specific effects enhancing the dissociation constant of the former; these effects were estimated referring to the additive relationships and to sulphohydroxamic acids as a standard. When it is now known that the substituent effects are not additive in any N-acids one must ask again the question which
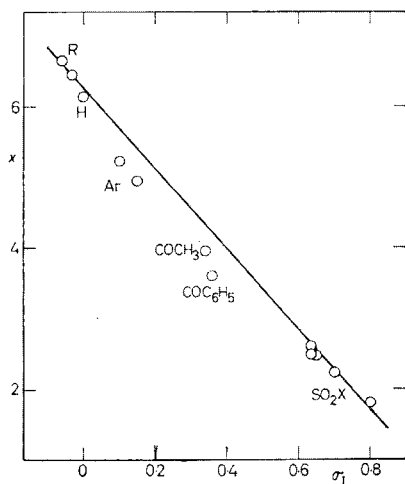

Fig. 2

Correlation of the Empirical Constants x with the Inductive Constants σ_I
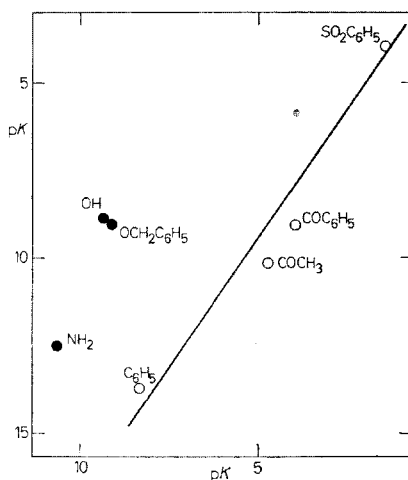
Fig. 3

Correlation of pK's of Corresponding Derivatives of Benzensulphonamide $C_6H_5SO_2$. .NHR (x-axis) and Benzamide C_6H_5CONHR (y-axis)

○ Well-behaved substituents, ● anomalous substituents; the line was calculated from equation (*1*).

derivatives are abnormal, hydroxamic or sulphohydroxamic. If the above values of x were plotted into Fig. 2 against the corresponding constants σ_I, the same results would be obtained for all three substituents OH, $OCH_2C_6H_5$. and NH_2: The values from benzoic derivatives are too high and those from benzenesulphonic derivatives too low, about in the same extent. For the time being we can offer only the same explanation of the high acidity of hydroxamic acids as previously[8] (which may apply also for hydrazides): It is a special cooperative action of the inductive effect of the hydroxyl (amino) group from one side and of the mesomeric effect of the acyl from the other side. On the other hand, we have no rational interpretation of the lowered acidity of sulphohydroxamic acids and sulphohydrazides, we only feel that the acidity of various derivatives and their conformation should be investigated in more detail. Note that hydrogen bonds in the anions of V and $VIII$ (formulae A, B) although possible[40] cannot explain the observed effects because these are not changed[8] when replacing hydrogen by $CH_2C_6H_5$. More relevant could be shifts in the electronic spectra with dissociation, observed only with hydroxamic acids $VIII$, hydrazides XI, and diacylamides VI, VII, see Table II. They prove an increase of the $C{\cdots}N$ double bond character in the anion and a partial transfer of the negative charge to oxygen (formula A); this behaviour has no parallel among the sulphonyl derivatives. Also the plot of pK's in water and in 80% methyl cellosolve against each other reveals a dissimilarity between hydroxamic and sulphohydroxamic derivatives which deviate to opposite sides.

A B

The last substituent to be mentioned is the cyano group. From the pK of N-cyanobenzamide[9] we obtain $x = 2 \cdot 13$, while from cyanamide[41] $2 \cdot 45$. The difference is almost within the limits of accuracy of equation (1), considering also that the latter value[41] does not seem quite dependable. Since reliable pK values for N-cyanosulphonamides are not available (Table II), one cannot decide whether the CN substituent is well-behaved or abnormal. In Fig. 2 its point would fall below the line like those of the acyl groups and reveals thus a certain mesomeric effect. Since this deviation is opposite to that of the OR and NHR substituents, the behaviour of the cyano group is probably normal.

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