Estimation of electronic effects in aromatic systems

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A critical examination of the use of Hammett's $\sigma(X)$ values is presented. The problems due to the possible existence of two forms of benzoic acids have been discussed as well as the problems with resonance. A parameter $\sigma'(X)_m$ being valid only for *meta* substituents, is the only parameter that can be recommended for general use. For local use the Δ_B, Δ_{Ph}, and Δ_{An} values, defined in this study, are recommended.

Introduction

Electronic effects in aromatic systems are usually presented by Hammett's $\sigma(X)$ values being originally defined by eqn. (1).

$$\sigma(X) = pK_a(C_6H_5COOH) - pK_a(XC_6H_4COOH) \quad (1)$$

There are several objections for using this as a general measure for predictions of rate or equilibrium constants. The first is that it is unsuitable for the study of reactions with 2-substituents. The reason for this is that in benzoic acids the two oxygen atoms of the COOH group tend to be located in the plane of the phenyl ring. This means that 2- and 3-substituted benzoic acids may in principle exist in two different forms, *syn* and *anti*, in which the OH group is pointing from or towards the substituent in the 2-position, here termed AH and HA, see Fig 1. In this figure the five rate constants involved in the equilibrium are defined. At present, the exerimental facts available do not allow a serious discussion of the equilibrium along this kinetic line. We therefore have to base the discussion on the experimentally available pK_a values. If the protolytic constants of the pure forms are called K_{AH}, K_{HA}, and the protolytic constant observed for the mixture is K_a we can formulate the fundamental protolytic equations, eqns. (2)–(4). Combining these

$$[HA] = f \times ([A^-] \times 10^{-pH})/K_{HA} \quad (2)$$

$$[AH] = f \times ([A^-] \times 10^{-pH})/K_{AH} \quad (3)$$

$$[HA] + [AH] = f \times ([A^-] \times 10^{-pH})/K_a \quad (4)$$

three equations gives eqn. (5). This means that $pK_a \geq$ both pK_{HA}

$$1/K_{HA} + 1/K_{AH} = 1/K_a \quad (5)$$

and pK_{AH} and, if pK_{HA} is different from pK_{AH}, the value for pK_a is closer to the higher one of the two values. If the expression for [HA] is divided by that for [AH] we obtain eqn. (6). The

$$[HA]/[AH] = K_{AH}/K_{HA} \quad (6)$$

form with the highest pK_a is thus present in the highest concentration at equilibrium.

Structure–activity relations should be based on the constants of the well-defined forms HA and AH and not on the mixture. Neglecting this leads to confusion. This problem is very similar to the use of pK_a values for polybasic acids in the determination of σ values.[1]

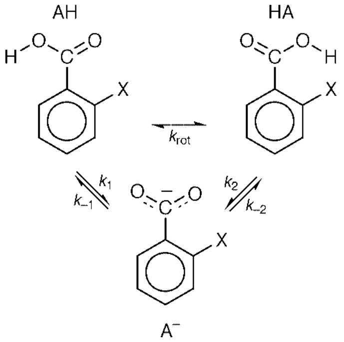

Fig. 1 The two forms of 2-substituted benzoic acids.

Instead of using pK_a values for benzoic acids as a measure of electronic effects, the pK_a values for phenols or anilines might be used for that purpose. Even phenols may, in principle, be present in two forms in the same way as benzoic acids. Inspection of molecular models indicates that the two forms should be much more readily interconverted than the corresponding benzoic acids. The difference between the two forms can therefore be expected to be low. In anilines the symmetry of the NH_2 group prevents the existence of two forms.

No objection of the kind mentioned above for the benzoic acids can thus be raised when the difference in pK_a between the parent compound and the substituted compound of anilines, Δ_{An}, is used as a measure of electronic effects. The measure of electronic effects has to separate this effect from steric effects and from resonance in order to be of general use. The problems involved using σ values obtained from pK_a of 4-substituted benzoic acids are well known and are discussed in most textbooks in physical organic chemistry. For a more thorough treatment see Hansch and Leo,[2] the classical review of Exner[3] and the statistical analysis of Sjöström and Wold.[4]

I have approached the problem differently and will argue for the use of pK_a values of anilines or preferably phenols instead of those of benzoic acids as the basis for the measurements of electronic effects. The symbols Δ_B and Δ_{Ph} have been introduced for the difference in pK_a between the parent compound and the substituted compound of benzoic acids and phenols in the same way as Δ_{An} is defined for anilines. The influence of resonance on pK_a values is seen in the difference in pK_a values between CH_3Z and C_6H_5Z. This is 0.55 for Z = COOH, about 5 for Z = OH and 6.00 for $Z = NH_3^+$. This strongly points in favor of using benzoic acids. It is, however, not as relevant to the problem and is outweighed by the stronger steric demands of the COOH group compared to the OH and NH_3^+ groups. All values here, and in the following tables unless otherwise indicated, are taken from refs. 5–7.

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Results and discussion

pK_a of methyl substituted benzoic acids, anilines and phenols

My discussion starts with methyl substituted compounds of the three different classes. The figures are given in Table 1.

The electronic effect of a methyl group is expected to increase the pK_a values of all three types of compounds. The effect is usually expected to be highest when the methyl group is in the 2-position, somewhat lower when in the 4-position and still lower when in the 3-position. This is seen for the Δ values of the phenols but not for those of the benzoic acids and the anilines. When comparing the Δ values for the different types of compounds, Table 1, one should also take into account that the electronic effect should have the same sign but be numerically 2–3 times higher for a substituent X in a phenol or an aniline than in a benzoic acid. This is obviously not the case for the Δ values which thus contain more information than the electronic effects. The dependence of the effect on the size of the substituent in the 2-position is demonstrated in Table 2. The examination of the Δ values is started with substituted anilines where only one form exists, HA ≡ AH.

The 2-methylanilinium cation has a much lower pK_a value than would be expected from the electronic effects of the 2-methyl group. The reason for this can be found in the steric interference between the H atoms on the protonated amino group and the CH_3 group. This interference is stronger for the anilinium cation than for the aniline base with the result that a proton tends to be released. This loss of a proton is facilitated by the higher resonance in the aniline than in the anilinium cation. Instead of a Δ_{An}(2-CH_3) value of at least −0.5, as expected from the electronic effect observed in the 4-position, a Δ_{An}(2-CH_3) value of 0.15 is thus obtained for the 2-CH_3 group.

2-Methylphenol may exist in two forms, one, HA, with the H atom of the OH group pointing towards the methyl group and the second, AH, with the H atom of the OH group pointing away from the methyl group. pK_{HA} and pK_{AH} are not available by measurement, unlike the pK_a of 2-$CH_3C_6H_4OH$. In form HA we might have a weak steric interference between the OH group and the CH_3 group. This interaction is much less than between the NH_3^+ group and the CH_3 group in the anilinium cation and does not exist in the anion A^- and in form AH. The steric effect in HA thus tends to release a proton. Although this loss of a proton is facilitated by an increase in the resonance between the group and the ring in going from the phenol to phenolate anion the effect can be expected to be low due to weak steric interference. This means that pK_{HA} ≅ pK_{AH}. Each of these values are, according to eqn. (1), close to pK_A(2-$CH_3C_6H_4COOH$) −0.30. This value should now be compared with the corresponding values for unsubstituted phenol. This can be considered as a mixture of two identical acids with pK_{HA} = pK_{AH} = pK_a-(C_6H_5OH) − 0.30. The effect of a 2-methyl group on the forms HA and AH is therefore equal to the value Δ_{Ph}(2-CH_3). The Δ_{Ph} values for phenols should thus be most useful in predicting the pK_a values of di- and polysubstituted phenols.

Table 1 pK_a Values of methyl substituted benzoic acids, phenols, and anilines

	Benzoic acids		Phenols		Anilines	
R	pK_a	Δ_B	pK_a	Δ_{Ph}	pK_a	Δ_{An}
H	4.204	—	9.994	—	4.60	—
2-CH_3	3.898	0.306	10.333	−0.339	4.45	0.15
3-CH_3	4.254	−0.050	10.098	−0.104	4.71	−0.11
4-CH_3	4.372	−0.168	10.276	−0.282	5.08	−0.48

The O atoms in benzoic acids are in the plane of the ring and we have an interference between a hydrogen atom of one of them with a 2-methyl group in the form HA. 2-Methylbenzoic acid will thus be present preferably in the AH form. We thus have pK_a(AH) ≅ pK_a(2-$CH_3C_6H_4COOH$). This should be compared with the pK_a value of the AH form of benzoic acid which is pK_a(C_6H_5COOH) − 0.30. We thus obtain Δ_B(AH) = 0.006 for 2-CH_3. From the Δ_B value for the 4-methyl group, for which there is no steric effect, we might expect a value Δ ≅ −0.2 if the 2-methyl group has only an electronic effect. There is, however, an additional effect. Due to interference between the methyl group and the O atoms of the COOH group forcing the oxygen atoms slightly out of the plane of the ring there is a decrease in the experimental pK_a value. From Table 2 we can see that this effect increases with an increase in the bulk of the substituent in the 2-position.

For substituents in the 3- or the 4-position we can therefore expect that, for phenols and benzoic acids, pK_{AH} ≅ pK_{HA} ≅ pK_a − 0.301. The Δ values for the 3- and 4-substituted compounds in Table 1 are thus the same as the Δ values for forms HA and AH and give rise to no problems.

Calculations of pK_a values for dimethyl substituted compounds using Δ values

In order to see how the Δ values in Table 1 can be used, the results in Table 3 demonstrate the successes and shortcomings of the additivity of Δ values in explaining pK_a values of disubstituted compounds. The calculated values (Calc.) are obtained by subtracting the sum of the Δ values for both substituents from the pK_a value of the unsubstituted compound. For the two last compounds in Table 3 we have no problem with steric effects and one can therefore expect a good additivity of the electronic effects based upon the pK_a values. This is, as seen, also the case.

In the case of the anilines we have already observed a steric effect of the 2-methyl group which decreases the pK_a value. This steric effect is not changed when adding a methyl group in the 4- or the 5-position. The additivity of the effect is shown to be good. When the additional methyl group is in the 6-position the hydrogen atoms of the anilinium cation are squeezed efficiently by the two methyl groups and are therefore forced to release a proton. The total effect is higher than the sum of the two groups as seen from the low experimental pK_a value. The effect of the two methyl groups is not sufficient to force the amino group out of the plane of the ring. Such an effect is observed if the steric effect is increased further as in 2,6-dimethyl-*N*-methylaniline for which a pK_a value as high as 6.12 is observed

Table 2 Δ Values of 2- and 4-alkyl substituted benzoic acids, phenols, and anilines

	Benzoic acids[a]		Phenols		Anilines	
R	$\Delta_B(R^2)$	$\Delta_B(R^4)$	$\Delta_{Ph}(R^2)$	$\Delta_{Ph}(R^4)$	$\Delta_{An}(R^2)$	$\Delta_{An}(R^4)$
CH_3	0.29	−0.14	−0.34	−0.28	0.15	−0.48
C_2H_5	0.41	−0.15	−0.48	−0.22	0.30	−0.40
$CH(CH_3)_2$	0.56	−0.15	−0.48	−0.25	0.18	−0.25
$C(CH_3)_3$	0.66	−0.15	−0.63	−0.40	—	−0.35

[a] Values obtained from Perrin, Demprey and Serjeant.[1]

Table 3 Use of Δ values in the calculation of pK_a values of dimethylated compounds

	Benzoic acids			Phenols			Anilines		
R	pK_a	Calc.	Diff.[a]	pK_a	Calc.	Diff.	pK_a	Calc.	Diff.
2-CH_3	3.898			10.333			4.45		
2,3-$(CH_3)_2$	3.716	3.948	0.23	10.544	10.437	−0.11	4.70	4.56	−0.14
2,4-$(CH_3)_2$	4.219	4.066	−0.15	10.595	10.615	0.02	4.85	4.93	0.08
2,5-$(CH_3)_2$	4.001	3.948	−0.05	10.404	10.437	0.03	4.55	4.56	0.01
2,6-$(CH_3)_2$	3.354	3.592	0.24	10.615	10.672	0.06	3.92	4.30	0.38
3,4-$(CH_3)_2$	4.50	4.422	−0.08	10.356	10.380	0.02	5.17	5.19	0.02
3,5-$(CH_3)_2$	4.298	4.304	0.06	10.203	10.202	−0.001	4.77	4.82	0.05

[a] Diff. = calc. − pK_a.

indicating that the resonance of the amino group and the ring is strongly diminished.

When the additional group is in the 3-position the two methyl groups are woven into each other and into the NH_3^+ group. The mobility of the groups is therefore restricted. This might affect their total effect on the pK_a value. The effect can, however, be expected to be rather low.

For the 2-substituted phenols we anticipate a low steric effect. This situation is not changed by the introduction of a methyl group in the 4-, 5-, or the 6- position. For these compounds we thus have good additivity of the effects of the methyl groups. For the 2,3-disubstituted compound we have the same type of effect as seen in 2,3-dimethylaniline and the deviation from additivity is the same.

In 2-substituted benzoic acids we have a slight steric effect due to restriction in the conjugation of the COOH group with the ring. We can thus expect a satisfactory additivity only if the group added does not affect this conjugation. This is only the case if a 5-CH_3 group, or possibly a 4-CH_3 group, is added. When a 3-CH_3 group is added the steric hindrance is increased resulting in a lower pK_a value than that calculated by strict additivity of the Δ values. When a 6-CH_3 group has been added we obtain two identical acids. This is the same situation as in unsubstituted benzoic acid and the total effect of the two CH_3 groups is equal to $4.204 - 3.354 = 0.85$. This should be compared to the effect of one 2-CH_3 group, calculated above to 0.006. The strong effect in the 2,6-dimethyl substituted benzoic acid is a result of the two CH_3 groups efficiently forcing the oxygen atoms of the carboxylic group out of the plane of the ring. When steric effects, as for the 3,4- and 3,5-dimethylbenzoic acids, are negligible the additivity of the Δ values is good.

From the different behaviour of the various types of compounds we can thus anticipate serious objections to the use of σ(2-CH_3) values obtained from benzoic acids to be an estimate of electronic effects. The errors are still higher when groups other than CH_3 are used.

Use of Δ values to calculate pK_a values for closely related compounds

It is now time to test to what extent the Δ_B(X), Δ_{Ph}(X), and Δ_{An}(X) values can be used to predict pK_a values of closely related compounds in cases when X is not CH_3. In Table 4 are summarized calculated pK_a values of substituted 2-methylbenzoic acids and 2-hydroxybenzoic acids by subtracting the Δ_B(X) values from the pK_a value of the parent compounds, 2-methylbenzoic acid or salicylic acid. The two series of compounds were selected to give information on two different effects.

In the 2-hydroxybenzoic acids we have a strong hydrogen bond between the carboxylic acid and the OH group. This tends to fix the two oxygen atoms of the carboxy group in the plane of the ring where they remain even when substituents are introduced in the 3-, 4-, or the 5-position. This situation is most similar to the situation in benzoic acid in which the two oxygen atoms of the carboxylic group are in the plane of the ring, even if the substituents are introduced in these positions. If they are introduced in the 6-position we can expect a strong interaction between the group and the oxygen atoms in the carboxy group. The effect of this interaction may be different in 2-hydroxybenzoic acids from that in benzoic acid. To support this suggestion we have an excellent fit for the 3-, 4-, and 5-substituted compounds, SD = 0.06. For the 6-substituted 2-hydroxybenzoic acids, however, the fit is not satisfactory.

In 2-methylbenzoic acids the oxygen atoms of the carboxylic group are, to some extent, forced out of the plane of the ring. This affects the resonance between the ring and the carboxy group. All groups in the 3-, 4-, and the 5-positions affect the resonance effect and thus the angle between the ring and the oxygen atoms of the carboxy group. The substituents will exert an effect in addition to that which they have in benzoic acid where the oxygen atoms are always in the plane of the ring, irrespective of the substituents in the 3-, 4-, or the 5-position. The fit of the calculation for 2-methylbenzoic acids can thus be expected to be less satisfactory than that for the salicylic acids. This is also seen in Table 4. For the 6-CH_3 substituted compound we have the additional effect that this molecule is symmetrical as discussed above.

In the case of phenols there are no problems with the loss of resonance of the OH or O^- group with the ring by steric effects. We can therefore expect that Δ_{Ph}(X) values can be used to accurately predict pK_a values of polysubstituted phenols and related compounds. In these calculations we always have to consider effects arising from hydrogen bond formations, *e.g.* between the OH group and C=O or N=O groups in the 2-position, effects of 2-substituents with free electron pairs or by restriction of resonance in for example NO_2 groups by groups in the 2-position.

The effect of a hydrogen bond between the additional substituent and the OH group is stabilizing the OH form of the phenol and thus increasing the pK_a value. The difference of the pK_a value between the 4- and the 2-substituted compound is due to this effect, but also to differences in resonance for the different positions. It is increased with an increase in the electron density of the group X. This is seen in Table 5. Only one group can be hydrogen bonded in a 2,6-disubstituted phenol.

A 2-substituent, X, with a free electron pair such as a halogen atom and an OCH_3 group decreases pK_a more than when the same group is in the 4-position.

These two effects may, to some extent, be influenced by other substituents in the ring. This is demonstrated by the values in Table 6. The agreement between found and calculated values is satisfactory for the first 21 compounds, many of these containing 2-substituents. For the rest of the compounds the calculated values are higher than the experimental values. These are either 2,6-disubstituted or 2-NO_2 substituted compounds containing an additional NO_2 group.

An example of the use of Δ_{Ph}(X) in the calculation of pK_a values in other types of compounds is given by Brändström

Table 4 Calculations of pK_a values for substituted salicylic acids and 2-methylbenzoic acids

X	H	Δ_B	2-OH	Calc.	Diff.	2-CH_3	Calc.	Diff.
H	4.204	0.00	2.97	2.97	0.00	3.898	3.90	0.00
3-Cl	3.839	0.365				3.43	3.53	−0.16
4-Cl	3.988	0.216				3.50	3.68	−0.18
5-Cl	3.899	0.31	2.65	2.67	−0.02	3.63	3.59	0.04
6-Cl	2.90	1.30	2.63	1.67[a]	0.96	2.75	2.59	0.16
3-Br	3.813	0.39	2.50	2.58	−0.08	3.36	3.51	−0.15
4-Br	3.963	0.24	2.669	2.73	−0.06	3.77	3.66	0.11
5-Br	3.813	0.39	2.627	2.58	0.05	3.58	3.51	0.07
6-Br	2.88	1.32				2.71	2.57	0.14
3-I	3.85	0.35	2.52	2.62	−0.10	3.26	3.54	−0.28
4-I	3.997	0.21	2.75	2.76	−0.01	3.79	3.69	0.10
5-I	3.85	0.35	2.619	2.62	0.00	3.62	3.54	0.08
6-I	2.93	1.27				2.70	2.62	0.08
3-NO_2	3.462	0.74	1.87	2.23	−0.36	2.98	3.16	−0.18
4-NO_2	3.426	0.78	2.23	2.19	0.04	2.95	3.12	−0.17
5-NO_2	3.462	0.74	2.12	2.23	−0.11	3.23	3.16	0.07
6-NO_2	2.21	1.99	2.24	0.98[a]	1.26	2.40	1.90[a]	0.50
3-OH	4.08	0.12	2.914	2.85	0.07	3.83	3.77	0.06
4-OH	4.53	−0.33	3.325	3.30	0.03	4.32	4.22	0.10
5-OH	4.08	0.12	2.951	2.85	0.11	3.92	3.77	0.15
6-OH	2.97	1.23	1.051	1.74[a]	−0.69	3.32	2.66[a]	0.66
3-CH_3	4.254	−0.05	3.014	3.02	−0.01	3.716	3.95	−0.23
4-CH_3	4.373	−0.17	3.172	3.14	0.03	4.219	4.07	0.15
5-CH_3	4.254	−0.05	3.03	3.02	0.01	4.001	3.95	0.05
6-CH_3	3.898	0.31	3.32	2.66[a]	0.66	3.354	3.59	−0.24
3-OCH_3	4.095	0.11				3.72	3.79	−0.07
4-OCH_3	4.496	−0.29	3.31	3.26	0.05	4.54	4.19	0.35
5-OCH_3	4.095	0.11	2.94	2.86	0.08	3.84	3.79	0.05
6-OCH_3	3.90	0.30				3.46	3.59	−0.13
3-CN	3.64	0.56				3.16	3.33	−0.17
4-CN	3.54	0.66	2.35	2.31	0.04	3.14	3.23	−0.09
5-CN	3.64	0.56	2.38	2.41	−0.03	3.31	3.33	−0.02
% Variance explained					96.7			87.3
SD of estimate					0.06			0.15

[a] Strongly deviating value not used in the calculation of SD.

Table 5 Effects on pK_a values of 2- and 4-substituents in phenols

X	pK_a(2-X)	Δ_{Ph}(2-X)	pK_a(4-X)	Δ_{Ph}(4-X)	Difference
F	8.70	1.294	9.91	0.084	1.21
Cl	8.555	1.439	9.406	0.588	0.851
Br	8.452	1.542	9.366	0.628	0.914
I	8.513	1.481	9.327	0.677	0.814
OH	9.45	0.243[a]	9.85	−0.157[a]	0.40
O^-	13.05	−3.06	11.39	−1.40	−1.66
OCH_3	9.98	0.01	10.21	−0.22	0.23
NO_2	7.230	2.764	7.156	2.838	−0.074
CHO	8.374	1.620	7.615	2.379	−0.759
$COCH_3$	10.22	−0.226	8.05	1.944	−2.17
COO^-	13.9	−3.91	9.37	0.62	−4.53

[a] Corrected for statistical factor.

et al.[7] in the calculation of pK_a values of substituted benzimidazoles.

Even in anilines the Δ_{An}(X) values can be used to calculate pK_a values of most polysubstituted anilines and related compounds. In anilines a suitable 2-substituent may form a hydrogen bond with both the NH_2 group and the NH_3^+ group. In a 2,6-disubstituted compound both groups may form hydrogen bonds. In anilines we may have problems with steric effects in 2,6-disubstituted anilines similar to those found in 2,6-dimethylaniline. A NO_2 group in the 2-position to the NH_2 group, however, fixes the oxygens of the NO_2 groups and the hydrogen atoms of the NH_2 group in the plane of the ring. This means that the additivity may be good even for many 2,6-disubstituted compounds, with at least one NO_2 group in the 2- or 6-position.

A successful calculation using 130 di- and polysubstituted anilines, varying in pK_a from −9.7 to 6 has proved these statements.[8] The mean difference between the found and calculated values for the 118 accepted compounds was −0.05 with a SD = 0.19. 26 of these compounds were 2,6-disubstituted and prediction failed for only 6 of these, 5 having a pK_a value below −4.5, thus very difficult to measure. For the other compounds prediction failed for 6 compounds. Five of these with a restricted resonance of a NO_2 or SCH_3 group, one with a NO_2 group in the 2-position with respect to an OH group. The SD accepted here is higher than that accepted for the phenols, mean −0.02 and SD = 0.08, and is due to the lower quality of the pK_a values used for the anilines compared to that of the phenols. Much of this is due to very low pK_a values and to the use of a mixture of "mixed" and thermodynamic constants for the anilines.

Table 6 Calculations for pK_a values for phenols (C_6H_3XYOH)

No.	X	Y	Δ_{Ph}(X)	Δ_{Ph}(Y)	pK_a	Calc.	Diff.
1	3-CH_3	4-Cl	−0.104	0.588	9.549	9.510	0.04
2	3-Br	4-OCH_3	0.963	−0.216	9.09	9.247	−0.16
3	3-NO_2	4-CH_3	1.639	−0.282	8.622	8.637	−0.02
4	3-NO_2	4-OCH_3	1.639	−0.216	8.64	8.571	0.07
5	3-Cl	4-Cl	0.875	0.588	8.585	8.531	0.05
6	3-Cl	5-Cl	0.875	0.875	8.185	8.244	−0.06
7	3-Br	5-Br	0.963	0.963	8.056	8.068	−0.01
8	3-I	5-I	0.961	0.961	8.103	8.072	0.03
9	3-NO_2	4-NO_2	1.639	2.838	5.42	5.517	−0.10
10	3-NO_2	5-NO_2	1.639	1.639	6.684	6.716	−0.03
11	2-CH_3	4-Cl	−0.339	0.588	9.706	9.745	−0.04
12	2-CH_3	5-NO_2	−0.339	1.639	8.592	8.694	−0.10
13	2-Br	4-OCH_3	1.542	−0.216	8.63	8.668	−0.04
14	2-NO_2	5-CH_3	2.764	−0.104	7.409	7.334	0.07
15	2-NO_2	4-CH_3	2.764	−0.282	7.597	5.512	0.09
16	2-NO_2	4-OCH_3	2.764	−0.216	7.44	7.446	−0.01
17	2-Br	4-Br	1.542	0.628	7.79	7.824	−0.03
18	2-Cl	4-CH_3	1.439	−0.282	8.74[a]	8.837	−0.10[a]
19	2-Cl	3-Cl	1.439	0.875	7.696	7.680	0.02
20	2-Cl	4-Cl	1.439	0.558	7.892	7.997	−0.11
21	2-Cl	5-Cl	1.439	0.875	7.508	7.680	−0.17
22	2-CH_3	6-Cl	−0.339	1.439[a]	8.69	8.894	−0.20[a]
23	2-Cl	4-NO_2	1.439	2.838	5.45	5.717	−0.27
24	2-Cl	6-NO_2	1.439	2.764	5.485	5.791	−0.31
25	2-Cl	6-Cl	1.439	1.439	6.786	7.116	−0.33
26	2-Br	6-Br	1.542	1.542	6.674	6.910	−0.24
27	2-NO_2	3-NO_2	2.764	1.639	4.96	5.591	−0.63
28	2-NO_2	4-NO_2	2.764	2.838	4.073	4.392	−0.32
29	2-NO_2	5-NO_2	2.764	1.639	5.21	5.591	−0.38
30	2-NO_2	6-NO_2	2.764	2.764	3.695	4.466	−0.77

[a] Measured at 20 °C.

Use of Δ_B(X) values to calculate pK_a values of phenols and anilines

We will now see to what extent Δ_B(X) can be used to calculate pK_a values of phenols and anilines. Even for substituents with no steric effects a serious objection to the use of Δ_B(X) values obtained from benzoic acids can be raised. These values are not representative for substituents that conjugate with the ring in a different way to that of COOH (or COO^-). This is a well known problem.[2–4] Examples of this can be seen in correlations of the pK_a values of phenols and anilines against Δ_B(X). The equations pK_a(XC_6H_4OH) = 9.926 − 2.36 × Δ_B(X) and pK_a-($XC_5H_4NH_3^+$) = 4.61 − 3.23 × Δ_B(X) were used in Table 7 and one observes that the fit between found and calculated values is fair for the first 29 substituents. The standard deviation of the estimate is 0.12 for the phenols and 0.13 for the anilines. Most of the substituents are located in the 3-position together with a few "well behaved" groups in the 4-position. The fair fit is not surprising since these substituents have been used in the regression analysis by which the parameters were obtained.

For phenols and anilines with a strongly conjugating substituent in the 4-position the prediction fails. All phenols and anilinium cations, 30–38, are more acidic than calculated, probably due to conjugation of the 4-substituent with the phenolate anion or the aniline. This failure is well known and has often been discussed.[2–4] For the last compounds, entries 39–43, all containing a 2-CH_3 group the prediction also fails.

A more thorough investigation will now be made. In the first 29 values for phenols we note that the two substituents causing the highest positive deviations are 3-NO_2 and 3-$COCH_3$. This is probably due to the position of one molecule of water between the COOH group and the NO_2 or C=O group, see Fig. 2. In this way a proton can be released by a concerted mechanism from the COOH group *via* a molecule of water and the NO_2 group. From the behavior of 4-substituents we can also expect that some resonance effect might be seen with halogens and alkyl groups in this position.

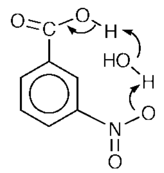

Fig. 2 The release of a proton from 3-nitrobenzoic acid by the NO_2 group using a molecule of water in a concerted reaction.

Calculation of an electronic parameter for some substituents valid for all types of compounds

We will continue this approach with values for compounds with group X which do not exert serious complication, thus 3- and 3,5-substituted compounds with no NO_2 or C=O groups. A nonlinear regression was made simultaneously using eqns. (7)–(9) to calculate σ'_m(X) values for 11 frequently used substituents

$$\mathrm{p}K_a(XC_6H_4COOH) = 4.204 - 1.00 \times \sigma'_m(X) \qquad (7)$$

$$\mathrm{p}K_a(XC_6H_4OH) = 9.994 - \sigma'_m(X) \times \rho(OH) \qquad (8)$$

$$\mathrm{p}K_a(XC_6H_4NH_3^+) = 4.63 - \sigma'_m(X) \times \rho(NH_3^+) \qquad (9)$$

together with ρ(OH) and $\rho(NH_3^+)$. The values obtained are given in Table 8. The σ'_m(X) values thus obtained are valid for all three types of compounds and are now proposed for general use as a measure of the electronic effect of these groups. They are not significantly different from the corresponding σ^0 values obtained by Sjöström and Wold. We will next try to extend this list.

The aqueous solubility of phenols is higher than for the corresponding benzoic acids and the anilines, allowing measurement of pK_a values in water for far more phenols than for the other classes of compounds. In the case of the phenols we have the additional advantage that they, in contrast to benzoic acids,

Table 7 Calculations of pK_a for phenols and anilines from pK_a(XC_6H_4COOH)

No.	X	COOH	OH	Calc.	Diff.	NH_2	Calc.	Diff.
1	H	4.204	9.994	9.926	0.07	4.63	4.61	0.02
2	3-F	3.862	9.21	9.118	0.09	3.50	3.50	0.00
3	4-F	4.153	9.91	9.805	0.10	4.65	4.45	0.20
4	3-Cl	3.899	9.119	9.065	0.05	3.46	3.43	0.03
5	4-Cl	3.988	9.406	9.416	−0.01	4.18	3.91	0.27
6	3-Br	3.813	9.031	9.003	0.03	3.58	3.35	0.23
7	4-Br	3.963	9.366	9.357	0.01	3.86	3.83	0.03
8	3-I	3.85[a]	9.033	9.090	−0.06	3.61	3.47	0.14
9	4-I	3.997	9.327	9.437	−0.11	3.78	3.94	−0.16
10	3-NO_2	3.462	8.355	8.174	0.18	2.46	2.21	0.25
11	3-OH	4.08	9.60′	9.63	−0.03	4.31	4.21	0.10
12	3-CHO	3.84	8.98	9.07	−0.09	—	3.43	—
13	3-CH_3	4.254	10.098	10.044	0.05	4.73	4.77	−0.06
14	4-CH_3	4.373	10.276	10.325	−0.05	5.08	5.16	−0.08
15	3-OCH_3	4.095	9.65	9.668	−0.02	4.23	4.26	−0.03
16	3-CN	3.64[a]	8.608	8.594	0.01	2.73	2.79	−0.06
17	3-CF_3	3.77[a]	8.95	8.901	0.05	3.20	3.21	−0.01
18	4-CF_3	3.66	8.675	8.641	0.03	2.75	2.85	−0.10
19	3-$COCH_3$	3.827	9.25	9.035	0.21	3.56	3.37	0.19
20	3-$COOC_2H_5$	3.83[a]	9.10	9.043	0.06	3.56	3.40	0.16
21	3-C_2H_5	4.27	10.069	10.082	−0.01	4.70	4.82	−0.12
22	4-C_2H_5	4.35	10.21	10.27	−0.06	5.00	5.08	−0.08
23	3,5-Cl_2	3.54	8.185	8.358	−0.17	2.37	2.47	−0.10
24	3,5-Br_2	3.42[a]	8.056	8.075	−0.02	2.36	2.08	0.28
25	3,5-I_2	3.50[a]	8.103	8.264	−0.16	2.37	2.34	0.03
26	3,5-NO_2	2.79	6.684	6.587	0.10	0.23	0.04	0.19
27	3,5-$(CH_3)_2$	4.298	10.202	10.148	0.05	4.77	4.91	−0.14
28	3,5-$(OCH_3)_2$	3.97	9.345	9.373	−0.03	3.86	3.85	0.10
29	3-SCH_3	4.05[a]	9.42	9.562	−0.14	4.00	4.11	−0.11
30	4-NO_2	3.426	7.156	8.089	−0.93[b]	1.02	2.10	−1.08[b]
31	4-OH′	4.53	10.15	10.695	−0.55[b]	5.48	5.66	−0.18
32	4-CHO	3.77	7.61	8.901	−1.30[b]	—	3.21	—
33	4-OCH_3	4.496	10.21	10.615	−0.41	5.34	5.55	−0.21
34	4-CN	3.54[a]	7.967	8.358	−0.39	1.71	2.47	−0.76[b]
35	4-$COCH_3$	3.700	8.05	8.736	−0.69[b]	2.49	2.98	−0.49[b]
36	4-$COOC_2H_5$	3.75[a]	8.50	8.854	−0.35	2.52	3.14	−0.62[b]
37	4-SCH_3	4.20[a]	9.47	9.916	−0.45	4.31	4.60	−0.29
38	4-$NHCOCH_3$	4.20[a]	9.65	9.916	−0.27	—	4.60	—
39	2-CH_3	3.898	10.333	9.199	1.13[b]	4.45	3.62	0.83[b]
40	2,3-$(CH_3)_2$	3.716	10.544	8.770	1.77[b]	4.70	3.03	1.67[b]
41	2,4-$(CH_3)_2$	4.219	10.595	9.957	0.64[b]	4.85	4.66	0.19[b]
42	2,5-$(CH_3)_2$	4.001	10.404	9.442	0.98[b]	4.55	3.95	0.60[b]
43	2,6-$(CH_3)_2$	3.354	10.615	7.915	2.70[b]	4.30	1.86	2.44[b]

[a] For this compound the pK_a value has been calculated from the σ(X) values. [b] Strongly deviating value.

Table 8 Calculation of σ'_m(X), ρ(OH), and $\rho(NH_3^+)$ from pK_a values for benzoic acids, phenols, and anilines

X	σ'_m(X)	SE[a]	COOH	Calc.	OH	Calc.	NH_3^+	Calc.
H	0	def.	4.204	4.204	9.994	9.994	4.63	4.63
3-F	0.33	0.02	3.862	3.869	9.21	9.131	3.50	3.561
3-Cl	0.35	0.01	3.839	3.852	9.119	9.087	3.46	3.507
3-Br	0.36	0.02	3.813	3.842	9.031	9.061	3.58	3.475
3-I	0.34	0.02	3.85	3.863	9.033	9.114	3.61	3.540
3-OH	0.12	0.01	4.08	4.083	9.60	9.682	4.31	4.243
3-CN	0.57	0.03	3.64	3.632	8.608	8.520	2.73	2.804
2-CF_3	0.43	0.02	3.77	3.773	8.95	8.883	3.20	3.254
3-CH_3	−0.03	0.01	4.254	4.235	10.10	10.07	4.73	4.730
3-OCH_3	0.12	0.01	4.095	4.081	9.65	9.676	4.23	4.236
3-SCH_3	0.20	0.02	4.05	4.000	9.42	9.467	4.00	3.978
3-C_2H_5	−0.01	0.01	4.27	4.213	10.07	10.02	4.60	4.659
3,5-Cl_2	0.70	—	3.54	3.500	8.185	8.180	2.37	2.384
3,5-Br_2	0.72	—	3.42	3.480	8.056	8.128	2.36	2.319
3,5-$(CH_3)_2$	−0.06	—	4.298	4.267	10.20	10.16	4.77	4.83
3,5-$(OCH_3)_2$	0.25	—	3.97	3.957	9.345	9.358	3.86	3.842
% Variance explained			96.62		99.25		99.53	
SD of estimate			0.046		0.055		0.053	

ρ(COOH) = 1.00, definition, ρ(OH) = 2.58, SD = 0.11, and $\rho(NH_3^+)$ = 3.19, SD = 0.13.

[a] SE (standard error) = SD/$\sqrt{n}$.

can be considered as existing in only one form and are less sensitive to steric effects in the 2-position than both benzoic acids and anilines. For 3-X substituents not found in Table 8 we may thus calculate $\sigma'_m(X) = [pK_a(C_6H_5OH) - pK_a(XC_6H_4OH)]/2.58$.

For NO_2 and C=O groups in the 3-position we have already suggested that a water molecule may have a special effect on the pK_a value of benzoic acids but not, however, for phenols. By the equation above we obtain $\sigma'_m(NO_2) = 0.64$, $\sigma'_m(COCH_3) = 0.29$, $\sigma'_m(COOC_2H_5) = 0.35$ and $\sigma'_m(CHO) = 0.39$. These four values are not valid for benzoic acids. The corresponding $\Delta_B(X)$ values are 0.74, 0.38, 0.37 and 0.35. Since the $\sigma'_m(X)$ values are valid for the three such different groups of compounds as benzoic acids, phenols, and anilines it is possible that they can be used as a general measure for electronic effects. No corresponding generally useful value can be obtained for substituents in the 2- or 4-positions.

The result of this discussion is that we should expect that a correlation of equilibrium and rate constants for aromatic compounds against the classical $\sigma(X)$ values can involve difficulties resulting from the inability of the $\sigma(X)$ to function as a parameter for electronic effects. In spite of that it should be possible to make good predictions of equilibrium and rate constants, even for 2-substituted compounds, using an apropriate parameter instead of $\sigma(X)$. The use of the tables and the discussions given above may be useful in this respect.

We should always remember that errors in a prediction can only be avoided by a solid knowledge of the validity of the parameter used and of special effects that may be present in the reaction under investigation.

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