Predictions of log P for aromatic compounds

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In a previous paper it has been found that Hammett's parameter $\sigma(X)_p$ is not very useful as a measure of electronic effects. The equation $\log P(XC_6H_4Y) = \log P(C_6H_6) + \pi(X) + \pi(Y) + \sigma(X) \times \rho_p(Y) + \sigma(Y) \times \rho_p(X)$ deduced for the calculation of log P values for aromatic compounds has therefore been revised. Good results are obtained when $\sigma_p(X)$ is replaced by the parameter $\sigma_p(X)_p$ specifically designed for use in distribution processes. A number of $\pi(X)$, $\pi(Y)$, and $\rho_p(Y)$ values are given which, together with the $\sigma'_m(X)$ values, can be used to calculate log P values.

Introduction

In 1982, Brändström[1] presented a method to calculate log P values for aromatic compounds by a Hammett type of equation, eqn. (1). In this equation the value $\pi(X)$ is character-

$$\log P(XC_6H_4Y) = \log P(C_6H_6) + \pi(X) + \pi(Y) + \sigma(X) \times \rho_p(Y) + \sigma(Y) \times \rho_p(X) \quad (1)$$

istic for the group X and $\pi(Y)$ for the group Y. The expression $\sigma(X) \times \rho_p(Y) + \sigma(Y) \times \rho_p(X)$ is the mutual interaction between groups X and Y. The subscript p indicates that the parameter is used in a partition process. The same type of equation was later presented by Leo.[2] In a recent paper Brändström[3] discussed the use of $\sigma(X)$ as a measure of electronic effects. There, it was found that a few objections can be raised against the general use of $\sigma(X)$ values, obtained from the difference between the pK_a value for benzoic acid and the substituted benzoic acid, as a measure of electronic effects. These objections can be avoided by the use of the somewhat modified parameter $\sigma'_m(X)$ for substituents in the *meta* position.[3] In the 4-position the corresponding $\sigma_p(X)$ values may contain a considerable quantity of resonance characteristic for the protolytic reaction of benzoic acid. The $\sigma_p(X)$ values should thus not be used in reactions with types of resonance between the groups that differ from that present in benzoic acid. This gives rise to some questions concerning the use of eqn. (1) since both 3- and 4-substituted compounds were used in the calculations, and motivated a test of the equation. The experimental values used in this calculation are taken from the compilation of Hansch, Leo, and Hoekman.[4,5]

Calculations for substituents in the *meta* position

The calculation starts with compounds of the type XC_6H_4Y with the substituents in the *meta* position containing a number of "well behaved" substituents X for which it was previously found that $\rho_p(X) = 0$ or was very small. In order to minimize the effect of erroneous experimental log P values compounds were selected where the substituent Y is a hydrophilic group. This resulted in log P values usually in the very convenient region $0.5 < \log P < 2.5$. The X groups used were F, Cl, Br, I, CH_3, CN, $COCH_3$, $COOCH_3$, NO_2, and CF_3. The Y groups were OH, NH_2, NO_2, $CONH_2$, $NHCONH_2$, $OCONHCH_3$, SO_2NH_2, COOH, CH_2COOH, OCH_2COOH, OCH_3, $COCH_3$, $CONH-NH_2$, and CH_2OH. If $\rho_p(X) = 0$, eqn. (1) can thus be written as eqn. (2).

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$$\log P(XC_6H_4Y) - \log P(C_6H_6) =$$
$$\pi(X) + \pi(Y) + \sigma'_m(X) \times \rho_p(Y) \quad \rho_p(X) = 0 \quad (2)$$

A regression of $\log P(XC_6H_4Y) - \log P(C_6H_6)$ against the 40 variables, $\sigma'_m(X)$ and the number of groups (X) and (Y) present in the molecule, should give the 40 parameters $\pi(X)$, $\pi(Y)$ and $\rho_p(Y)$.

The calculation can also be made by an iterative process in which an approximate value $\pi'(X) = \log P(C_6H_5X) - \log P(C_6H_6)$ is used, as in eqn. (3), by which a regression of log

$$\log P(XC_6H_4Y) - \log P(C_6H_6) - \pi'(X) =$$
$$\pi(Y) + \sigma'_m(X) \times \rho_p(Y) \quad (3)$$

$P(XC_6H_4Y) - \log P(C_6H_6) - \pi'(X)$ against $\sigma'_m(X)$ gives the approximate values $\pi'(Y)$ and $\rho'_p(Y)$ which then are used to calculate a better value of $\pi'(X)$ by means of eqn. (2). This value is then used in a new calculation of $\pi'(Y)$ and $\rho'_p(Y)$ and so on. The convergence is very rapid. In this way the values in Table 1 were obtained.

From the table we can see that $\rho_p(Y)$ is significantly different from 0 for all groups except NO_2 and $COCH_3$. These two groups do occur both as X and Y. For each of them we should have $\pi(X) = \pi(Y)$. This is the case for NO_2 and probably also for $COCH_3$. An attempt to use OCH_3 as an X substituent resulted in $\pi(X) \neq \pi(Y)$ as it should do since $\rho_p(X) > 0$.

We will now see what happens if both $\rho_p(X)$ and $\rho_p(Y)$ are different from 0. The values of $\pi(X)$, $\pi(Y)$, and $\rho_p(Y)$ obtained above and eqn. (1) were applied to *meta* substituted compounds. The results obtained are seen in Table 2. In this table $I_2 = \log P(X_6H_4Y) - \log P(C_6H_6) - \pi(X) - \pi(Y)$ which according to eqn. (1) should be equal to $\Sigma\sigma'_m \times \rho = \sigma'_m(X) \times \rho_p(Y) + \sigma'_m(Y) \times \rho_p(X)$. The difference between these two is given in Table 2 and is equal to the fit of the equation used.

The mean of the difference values is 0.01 with SD = 0.09 thus close to 0, as it should be. The standard deviation is of the magnitude expected for experimental values of the same compound obtained by different investigators. This means that there is nothing unexpected that occurs when calculating log P for compounds (XC_6H_4Y) where the two substituents are in the *meta* position to each other. We will now see what happens when the groups are in the *para* position to each other and we thus have the possibility of resonance.

Calculations for substituents in the *para* position

The difference, $\Delta\log P(4 - 3)$, in log P values between a 4- and a 3-substituted compound XC_6H_4Y with the same substituents X and Y should be independent of $\pi(X)$ and $\pi(Y)$ and equal to

Table 1 Calculations for $\pi(X)$, $\pi(Y)$, and $\rho(Y)$ values from log P values for (3-XC$_6$H$_4$Y) compounds with $\rho(X) = 0$

X	$\pi(X)$	SE[a]	n	Y	$\pi(Y)$	SE[a]	$\rho(Y)$	SE[a]	n
F	0.11	0.03	11	OH	−0.72	0.03	1.33	0.08	10
Cl	0.67	0.06	15	NH$_2$	−1.28	0.03	1.23	0.08	7
Br	0.82	0.04	12	CONH$_2$	−1.52	0.02	0.69	0.05	7
I	1.12	0.05	9	NHCOCH$_3$	−0.99	0.02	1.08	0.06	11
CH$_3$	0.59	0.03	14	OCONHCH$_3$	−0.96	0.03	0.66	0.08	11
CN	−0.52	0.07	10	SO$_2$NH$_2$	−1.83	0.04	0.85	0.10	8
COCH$_3$	−0.42	0.07	9	COOH	−0.29	0.04	0.38	0.11	11
COOCH$_3$	−0.01	0.08	5	CH$_2$COOH	−0.76	0.04	0.51	0.11	8
NO$_2$	−0.29	0.05	14	OCH$_2$COOH	−0.90	0.05	0.46	0.13	10
CF$_3$	0.98	0.06	6	COCH$_3$	−0.51	0.11	0.22	0.29	4
				NO$_2$	−0.27	0.03	−0.14	0.07	10
				NHCONH$_2$	−1.30	0.03	1.07	0.10	5
				CONHNH$_2$	−1.93	0.04	0.60	0.11	6
				CH$_2$OH	−1.07	0.03	0.67	0.07	4
				OCH$_3$	−0.03	0.01	0.56	0.02	5

[a] SE is the standard error, SD/$\sqrt{n}$.

Table 2 Calculations of log P for (3-XC$_6$H$_4$Y)

X	Y	log P	$\pi(Y)$	$\sigma'_m(Y)$	$\rho(Y)$	$\Sigma\sigma'_m \times \rho$	I_2	diff.
OH	3-COOH	1.50	−0.29	0.37	0.38	0.54	0.38	0.16
OH	3-CONH$_2$	0.39	−1.52	0.28	0.69	0.46	0.50	−0.04
OH	3-CH$_2$COOH	0.85	−0.76	0.13	0.46	0.23	0.20	0.03
OH	3-OCH$_2$COOH	0.76	−0.90	0.00	0.51	0.06	0.25	−0.19
OH	3-NHCOCH$_3$	0.73	−0.99	0.21	1.08	0.41	0.31	0.10
OH	3-N(CH$_3$)$_2$	1.56	−0.18	−0.16	0.52	−0.15	−0.03	−0.12
OH	3-CONHNH$_2$	−0.08	−1.93	0.28	0.60	0.44	0.44	0.00
OH	3-CH$_2$OH	0.49	−1.07	0.00	0.67	0.08	0.15	−0.07
OH	3-OH	0.80	−0.72	0.12	1.33	0.32	0.11	0.21
OH	3-NH$_2$	0.21	−1.28	0.00	1.23	0.15	0.08	0.07
OH	3-OCH$_3$	1.58	−0.03	0.12	0.56	0.23	0.20	0.03
NH$_2$	3-CONH$_2$	−0.33	−1.52	0.28	0.69	0.34	0.34	0.00
NH$_2$	3-SO$_2$NH$_2$	−0.38	−1.83	0.53	0.85	0.65	0.60	0.05
NH$_2$	3-CONHNH$_2$	−0.86	−1.93	0.28	0.60	0.34	0.22	0.12
NH$_2$	3-CH$_2$OH	−0.05	−1.07	0.00	0.67	0.00	0.17	−0.17
NH$_2$	3-OH	0.21	−0.72	0.12	1.33	0.15	0.08	0.07
NH$_2$	3-NH$_2$	−0.33	−1.28	0.00	1.23	0.00	0.10	−0.10
NH$_2$	3-OCH$_3$	0.93	−0.03	0.12	0.56	0.15	0.11	0.04
OCH$_3$	3-COOH	2.02	−0.29	0.37	0.38	0.25	0.21	0.04
OCH$_3$	3-CONH$_2$	0.84	−1.52	0.28	0.69	0.24	0.26	−0.02
OCH$_3$	3-OCONHCH$_3$	1.30	−0.96	0.39	0.66	0.30	0.16	0.14
OCH$_3$	3-SO$_2$NH$_2$	0.57	−1.823	0.53	0.85	0.40	0.29	0.11
OCH$_3$	3-CH$_2$COOH	1.50	−0.76	0.13	0.51	0.13	0.16	−0.03
OCH$_3$	3-OCH$_2$COOH	1.38	−0.90	0.00	0.46	0.06	0.18	−0.12
OCH$_3$	3-NHCOCH$_3$	1.28	−0.99	0.21	1.08	0.25	0.17	0.08
OCH$_3$	3-CONHNH$_2$	0.40	−1.93	0.28	0.60	0.23	0.23	0.00
OCH$_3$	3-OH	1.58	−0.72	0.12	1.33	0.23	0.20	0.03
OCH$_3$	3-NH$_2$	0.93	−1.28	0.00	1.23	0.15	0.11	0.04
OCH$_3$	3-OCH$_3$	2.21	−0.03	0.12	0.56	0.13	0.14	−0.01

the difference in interaction. If Y is selected to be COOH, OH, or NH$_2$ we can compare these differences with the differences $\Delta pK_a(4 - 3)$ in pK_a for the corresponding 4- and 3-substituted compounds. These are given in Table 3. We can see that the values for Δlog $P(4 - 3)$ are usually numerically low and it is in many cases doubtful whether they are significantly different from 0. They are lower than the $\Delta pK_a(4 - 3)$ values especially for the phenols and the anilines. In contrast to what is seen for the $\Delta pK_a(4 - 3)$ values it is difficult to see regularities in the Δlog $P(4 - 3)$ values, explainable by the resonance with the protolytically active groups. The reason for this is probably seen in the fact that P values can be regarded as a ratio of solubility in octan-1-ol to that in water. The dependence of these solubilities on the substituents may differ due to the different solvents, thus making the situation rather complex. The following is an attempt to solve this problem.

$\sigma_p(X)_p$ values for use in calculations of log P

The $\sigma_p(X)$ values have been used together with the $\sigma'_m(X)$ values in Hammett type correlations with reasonably good results for a great variety of reactions. We will therefore see if we can find a set of $\sigma_p(X)_p$ values that can be used to explain the variation of log P values with structure for a variety of different types of compounds. With the 4-substituted compounds we have the problem of the effect of conjugation of X with the group Y. The $\sigma_p(X)$ values contain the effect of resonance on the protolysis of benzoic acids together with the effect caused by the electronic effect of group X measured as $\sigma'_m(X)$. In the same way the corresponding value $\sigma_p(X)_p$ to be used in log P calculations contains the effect of resonance on the solvation of the compound XC$_6$H$_4$Y by water compared to that caused by octanol together with the effect caused by the electronic effect of the group X measured as $\sigma'_m(X)$. We can expect that the difference in effect of the resonance on the solvation in the water and the octanol layer is very probably less than the effect of resonance on the protolysis. This means that $\sigma_p(X)_p$ is expected to be closer to $\sigma'_m(X)$ than $\sigma_p(X)$ is to $\sigma'_m(X)$. For compounds with $\rho_p(X) = 0$ where eqn. (2) is valid we should thus obtain, eqn. (4).

$$\Delta\log P(4 - 3) = [\sigma_p(X)_p - \sigma'_m(X)] \times \rho_p(Y), \quad \rho_p(X) = 0 \quad (4)$$

Table 3 Comparison of effects of substituents in the 4- and 3-positions of XC_6H_4Y

X	Y					
	COOH		OH		NH_2	
	$\Delta pK_a(4-3)$	$\Delta \log P(4-3)$	$\Delta pK_a(4-3)$	$\Delta \log P(4-3)$	$\Delta pK_a(4-3)$	$\Delta \log P(4-3)$
F	0.29	−0.08	0.70	−0.16	1.15	−0.15
Cl	0.15	−0.03	0.29	−0.11	0.69	−0.05
Br	0.15	−0.01	0.33	−0.05	0.28	−0.05
I	0.15	−0.11	0.29	−0.02	0.17	—
CH_3	0.12	−0.10	0.18	−0.02	0.36	−0.01
OCH_3	0.40	−0.06	0.56	−0.24	1.11	0.02
CF_3	−0.11	0.15	−0.27	−0.13	−0.45	—
CN	−0.10	0.08	−0.64	−0.10	−1.02	—
$COOR^a$	−0.09	—	−0.60	0.07	−1.04	—
$COCH_3$	−0.13	0.05	−1.20	−0.04	−1.07	—
NO_2	−0.04	0.06	−1.20	−0.09	−1.45	0.02
OH	0.59	−0.09	0.50	−0.21	—	—
COOH	0.09	0.34	—	−0.09	—	—
$CONH_2$	0.03	−0.06	−0.74	−0.06	—	—

^{a} R = CH_3 or C_2H_5

Table 4 Calculations of $\sigma_p(X)_p$ values from $\Delta \log P(4-3)$ values

X	$\sigma_p(X)$	$\sigma_p(X)_p$	SE^a	n	$\sigma'_m(X)$	$\sigma_p(X)_p - \sigma'_m(X)$
$NH_2{}^b$	−0.57	−0.27	0.04	4	0.00	−0.27
OH^b	−0.38	−0.09	0.03	3	0.12	−0.21
$OCH_3{}^b$	−0.28	−0.09	0.06	4	0.12	−0.21
F	0.06	0.20	0.04	13	0.33	−0.13
Cl	0.23	0.30	0.03	13	0.35	−0.05
Br	0.23	0.35	0.03	12	0.36	−0.01
I	0.18	0.36	0.04	8	0.34	0.02
CH_3	−0.17	−0.04	0.03	13	−0.03	−0.01
CN	0.66	0.57	0.04	7	0.57	0.00
$COCH_3$	0.50	0.31	0.04	7	0.29	0.02
$COOCH_3$	0.45	0.45	0.04	3	0.35	0.10
NO_2	0.78	0.68	0.03	11	0.64	0.04
CF_3	0.54	0.36	0.04	4	0.43	−0.07

^{a} SE is the standard error, $SD/\sqrt{n}$. ^{b} For values with these substituents see text and Table 5.

Table 5 $\Delta \log P(4-3) = \sigma'_m(X) \times \rho_p(Y) - \sigma_p(X)_p \times \rho_p(Y)$ for XC_6H_4Y

X	Y	$\log P4$	$\log P3$	$\rho_p(Y)$	$\sigma'_m(X)$	$\Delta \log P(4-3)$	calc.	diff.
OH	4-COOH	1.41	1.5	0.37	0.12	−0.09	−0.08	0.00
OH	$4\text{-}CONH_2$	0.33	0.39	0.56	0.12	−0.06	−0.12	0.08
OH	$4\text{-}CH_2COOH$	0.75	0.85	0.45	0.12	−0.10	−0.09	0.01
OH	$4\text{-}CH_2OH$	0.25	0.49	0.59	0.12	−0.24	−0.12	−0.09
NH_2	$4\text{-}CONH_2$	−0.44	−0.33	0.56	0.00	−0.11	−0.15	0.04
NH_2	$4\text{-}SO_2NH_2$	−0.62	−0.38	0.78	0.00	−0.24	−0.21	−0.03
NH_2	$4\text{-}CH_2OH$	−0.22	−0.05	0.59	0.00	−0.17	−0.16	−0.01
OCH_3	4-COOH	1.96	2.02	0.37	0.12	−0.06	−0.08	−0.02
OCH_3	$4\text{-}CONH_2$	0.86	0.84	0.56	0.12	0.02	−0.06	0.08
OCH_3	$4\text{-}SO_2NH_2$	0.47	0.57	0.78	0.12	−0.10	−0.08	−0.02
OCH_3	$4\text{-}CH_2COOH$	1.42	1.50	0.45	0.12	−0.08	−0.04	−0.04

This allows a simple calculation of $\sigma_p(X)_p$ from $\sigma'_m(X)$, $\rho_p(Y)$ and $\Delta \log P(4-3)$. This can, for instance, be performed by a nonlinear regression of $\Delta \log P(4-3)$ against $\sigma'_m(X)$ and $\rho_p(Y)$. The results using the same selection of substituents as in Table 1 are seen in Table 4. We can see that the difference $\sigma_p(X)_p - \sigma'_m(X)$, as expected, is usually low and not significantly different from 0. The value for the groups $COOCH_3$ and CF_3 are very uncertain mainly due to the low number of experimental values. The value for Cl, $\sigma_p(Cl)_p - \sigma'_m(Cl) = -0.05$, is questionable but the value for the F group, $\sigma_p(F)_p - \sigma'_m(F) = -0.13$, is significantly different from 0. The same is also valid for the groups NH_2, OH, and OCH_3, see below. All these substituents have p-electrons which can conjugate with a substituent in the 4-position, especially if this is an electron deficient group.

From the numerous $\sigma_p(X) - \sigma_m(X)$ values available from the protolysis of benzoic acids we can see that these values are <0 for compounds with electron releasing substituents. The values of the different groups decrease in the order F −0.28, >OH −0.51, >NH_2 −0.57; Cl −0.14, >F −0.28, >OCH_3 −0.39 and SH −0.10, >OH −0.51. The effect is decreased by the introduction of an electron attracting group on the O or N atom. We thus have $OCOCH_3$ −0.08, >OH −0.51 and $NHCOCH_3$ −0.21 > NH_2 −0.57. The resonance of the group with the COOH group is also strongly diminished by the introduction of a CH_2 group and we have CH_2OH 0.00, CH_2NH_2 −0.08.

For electron attracting groups $\sigma_p(X) - \sigma_m(X)$ is >0 but a strongly attracting group is needed to have a significant effect on $\Delta pK_a(4-3)$. For the group SO_2NH_2 it is 0.11 and for $CONH_2$ it is 0.03.

Since the resonance effect is less pronounced for the differ-

Table 6 $\Delta \log P(4-3)$ for XC_6H_4Y compared with different types of interaction

X	Y	$\Delta \log P(4-3)$	$\Delta\sigma(X) \times \rho_p(Y)$	$\Delta\sigma(Y) \times \rho_p(X)$	Sum
OH	OH	-0.21	-0.30	-0.30	-0.60
OH	OCH_3	-0.11	-0.12	-0.26	-0.38
F	OH	-0.16	-0.16	0.00	-0.16
F	NH_2	-0.15	-0.14	0.00	-0.14
OCH_3	OCH_3	-0.18	-0.10	-0.10	-0.20

ence in solvation than it is for the protolysis of benzoic acids we can expect to use $\sigma_p(X)_p = \sigma'_m(X)$ for most groups except for F, OH, OCH_3, NH_2, $NHCH_3$, $N(CH_3)_2$, and $NHCOCH_3$. Since all these groups except F have values $\rho_p(X) > 0$ we have to make a new calculation to obtain correct values for them. This was therefore performed using OH, NH_2, and OCH_3 as X. For the rest of the groups we do not have enough data to make a calculation. Since in this case $\rho_p(X) > 0$ we have to use eqn. (1) in the calculation. We thus obtain eqn. (5) and for compounds with $\sigma_p(Y)_p = \sigma'_m(Y)$ this can be rearranged to eqn. (6).

$$\Delta \log P(4-3) =$$
$$[\sigma_p(Y)_p - \sigma'_m(Y)] \times \rho_p(X) + [\sigma_p(X)_p - \sigma'_m(X)] \times \rho_p(Y) \quad (5)$$

$$\Delta \log P(4-3) + \sigma'_m(X) \times \rho_p(Y) =$$
$$\sigma_p(X)_p \times \rho_p(Y) \quad \sigma_p(Y)_p = \sigma'_m(Y) \quad (6)$$

A regression of $\Delta \log P(4-3) + \sigma'_m(X) \times \rho_p(Y)$ against $\rho_p(Y)$ should thus give $\sigma_p(X)_p$. The results are seen in Table 5 and at the top of Table 4.

We obtain $\sigma_p(OH)_p = -0.09$, SD $= 0.04$, $\sigma_p(NH_2)_p = -0.27$, SD $= 0.03$, and $\sigma_p(OCH_3)_p = -0.09$, SD $= 0.06$. A calculation using these values is given in Table 5.

The standard deviation of the estimates of $\Delta \log P(4-3)$ is 0.06 which is of the magnitude expected for the corresponding experimental values.

Both $\sigma_p(X)_p \neq \sigma_m(X)$ and $\sigma_p(Y)_p \neq \sigma_m(Y)$ will now be examined. We should observe that, when we have a resonance in which X is acting as an electron releasing group and gives electrons to Y, this prevents a simultaneous resonance in which Y is acting as an electron releasing group giving electrons to X. This means that in the calculations of log P values for 4-substituted compounds only one of the groups can be electron releasing by

resonance. If this group is X we have to use $\sigma_p(X)_p$ in the calculation together with $\sigma'_m(Y)$. In choosing between X and Y we have to consider the solubility process for both layers. This means that we cannot make the calculation of the effect on log P before we know the rules which are valid for each layer.

The experimental data available are few for compounds of this type, in practice limited to compounds where both X and Y are selected from within the group F, OH, NH_2, and OCH_3. An additional problem is that anilines with an NH_2, OH, or OCH_3 group in the p-position are very sensitive to oxidation and correct log P values are difficult to obtain for these compounds. Only 5 acceptable $\Delta \log P(4-3)$ of this type are thus available. The results from these are given in Table 6.

The best agreement is found between $\Delta \log P(4-3)$ and $[\sigma_p(X)_p - \sigma'_m(X)] \times \rho_p(Y)$. The rules and the parameters obtained in this paper can be used to calculate log P values for a variety of compounds starting from a reference compound AX. For a compound AY this is done by adding and subtracting π values for X and Y together with differences in interactions of the group A with X and Y and that of these groups with A.

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