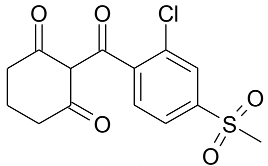
CHEM 331

Problem Set #3: Substituent Effects and LFERs

Submit answers to <u>even numbered questions only</u>. Due Monday, Mar. 21st

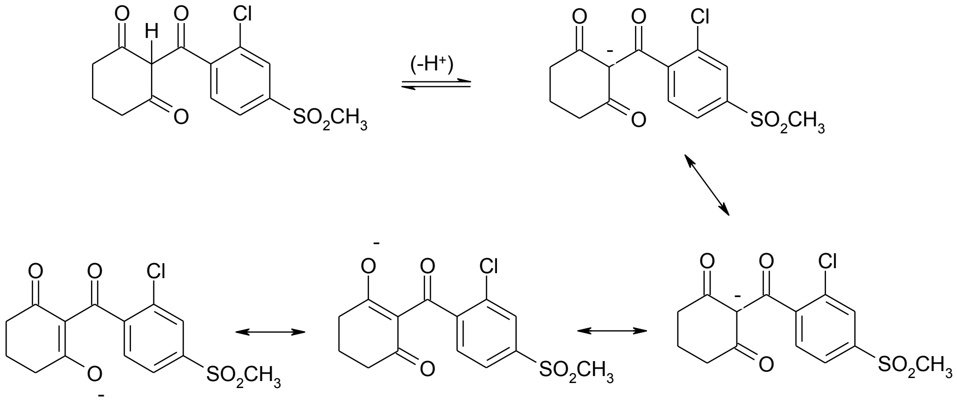
1. The structure of the herbicide *sulcotrion* has is shown below and is found to have a pK_a of 3.13. Draw the structure of the conjugate base and explain the unusual acidity of this 'carbon acid'.



sulcotrion

Solution:

The hydrogen atom α- to the three carbonyl groups is the most acidic due to the extensive resonance stabilization of the negative charge in the conjugate base (enolate ion).



There are also additional inductive and resonance stabilizing effects resulting from the ortho chlorine and para sulfone, $\sigma_p = 0.72$.

2. Answer each of the following with reference to the corresponding substituent constants considering both inductive and resonance electronic contributions (σ_I and σ_R). Illustrate your answer showing resonance structures for substituted benzoic acids, where appropriate.

a) The σ_{meta} and σ_{para} values for the $-CO_2CH_3$ group are both positive with $\sigma_{para} > \sigma_{meta}$.

b) The values of σ_{meta} for the methoxy substituent ($-OCH_3$) is positive, whereas the values for σ_{para} is negative.

c) The picryl (2,4,6-trinitrophenyl) substituent, $-C_6H_2(NO_2)_3$ is relatively large with the ortho nitro groups sterically interfering with atoms in the ortho positions on an adjacent aromatic ring. Predict the sign and relative magnitude of σ_{meta} and σ_{para} for the picryl substituent.

Solution:

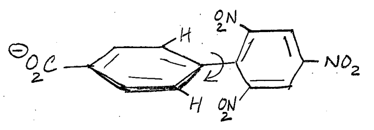
In the *meta* position, electronic effects are governed largely by inductive effects (differences in electronegativities), i.e., $\sigma_{meta} \sim \sigma_I$. In the *para* position however both inductive and resonance contributions manifest and hence $\sigma_{para} \sim \sigma_I + \sigma_R$.

a) The σ_{meta} and σ_{para} values for the $-CO_2CH_3$ group are 0.33 and 0.45, respectively. This carbomethoxy group is therefore electron withdrawing by both inductive and resonance effects. The carbonyl carbon (C=O) is bears a slightly positive charge as a result of the more electronegative oxygen atoms it is bonded to, giving rise to an inductive withdrawing effect. We can roughly say that $\sigma_I \sim 0.33$ and $\sigma_R \sim 0.12$.

Moreover, the carbonyl carbon is sp^2 hybridized and can therefore participate in resonance when bonded to an aromatic ring. The extra resonance structure in which the negative charge resides on the carbonyl oxygen contributes to the withdrawing ability of this substituent as depicted below.

b) The σ_{meta} and σ_{para} values for the $-OCH_3$ group are 0.12 and -0.27, respectively. This means that the methoxy group is electron withdrawing by induction and electron donating by resonance. In the meta position, the electronic effect is governed by the fact that the oxygen of the methoxy group bonded to an aromatic carbon is more electronegative and $\sigma_I \sim 0.12$. However, in the para position we have additional resonance effects as a result of the lone pair electrons on oxygen being donated back into the aromatic ring (depicted below). The observed σ_{para} value is the sum of both effects and is net donating. We can therefore estimate that $\sigma_R \sim -0.39$.

c) The picryl substituent is electron withdrawing due to the inductive effect of the three nitro groups pulling electron density from the aromatic ring. There is no appreciable resonance contribution when picryl is in the *para* position as can be seen by the fact that $\sigma_{meta} \sim \sigma_{para}$ (0.42). This lack of resonance contribution can be understood by considering the large steric interactions that result in a significant twist angle between the two aromatic rings. The extent of conjugation drops off steeply with the dihedral angle between adjacent p-orbitals. Hence $\sigma_R \sim 0$ in this case.



steric hinderance betw.
ortho NO_2 groups and
H's on adjacent aromatic
ring results in twisted
structure and loss of
p-orbital overlap ($\therefore \sigma_R \sim 0$)

3. Using the information in Table 1 and 2 (attached), estimate the pK_a values of the following compounds at 25°C and sketch a plot of the fractional abundance of each acid and conjugate base over a pH range of 0 – 14.

a) 3,4-dinitrophenol

b) 2,4-dichlorophenoxy acetic acid

c) the conjugate acid of para-methylaniline

Solution:

Rearranging the Hammett equation, we can estimate the pKa of acidic compounds provided we know the pKa of the parent system under the same conditions (solvent, temperature etc) and the appropriate substituent constants.

$$\log\left(\frac{K_a^{(X)}}{K_a^{(H)}}\right) = \rho \Sigma \sigma$$

$$\therefore\ pK_a(X) = pK_a(H) - \rho\ \Sigma\ \sigma_x$$

a) 3,4-dinitrophenol

pKa(phenol) = 9.92, ρ = 2.25

pKa(3,4-DNP) = 9.92 – 2.25 ((1.25) + (0.71)) = **5.49**

(note the use of σ_- for the 4-NO_2 substituent)

b) 2,4-dichlorophenoxy acetic acid

pKa (2-chlorophenoxy acetic acid) = 3.05, ρ = 0.30

pKa(2,4-DCP) = 3.05 – 0.30 (0.23)) = **2.98**

c) the conjugate acid of para-methylaniline

pKa (aniline) = 4.63, ρ = 2.89

pKa(4-MA) = 4.63 – 2.89 (-0.17) = **5.12**

4. The pK_a values of m- and p-monosubstituted benzoic acids in 50% aqueous ethanol correlate with σ, and have a ρ value of 1.60. The pK_a of benzoic acid in this system is 5.71. The pK_a values of some 4-X-3,5-dimethylbenzoic acids in this solvent system are given below. Use these results to examine and comment on the applicability of additivity of σ values.

X	$N(CH_3)_2$	NH_2	Cl	Br	CN	$COOCH_3$	NO_2
pK_a	6.23	6.88	5.59	5.55	4.90	5.44	4.91

Solution:

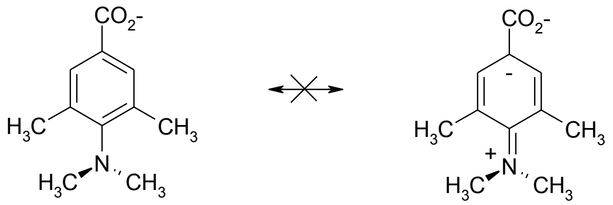
We can calculate the pK_a for each of the trisubstituted benzoic acids using the Hammett equation and a ρ value of 1.60, a $pK_a(H) = 5.71$ and the sum of the three substituent constants. In so doing, we are making the assumption that each substituent will have the same electronic effects in 3,4,5-trisubstituted benzoic acids as they would if they were present by themselves. In general, this will be true provided that there are not overriding factors that influence their degree of contribution. Since in the present case, we are looking at the effect of placing a group in the 4-position between two other substituents, we should consider the possibility of steric hinderence on resonance contributions.

$$\log\left(\frac{K_{(X)}}{K_{(H)}}\right) = \rho \Sigma \sigma$$

$$\therefore\ pK_a = 5.71 - 1.60(\sigma_x - 0.14)$$

X	**$N(CH_3)_2$**	**NH_2**	**Cl**	**Br**	**CN**	**CO_2CH_3**	**NO_2**
Expt'l pKa	6.23	6.88	5.59	5.55	4.90	5.44	4.91
Calc pKa	7.26	6.99	5.57	5.57	4.88	5.21	4.69
Difference	1.03	0.11	0.02	0.02	0.02	0.23	0.22

Although there is good agreement between the experimental pKa's and those calculated based on adding the substituent effects, there are some significant differences. In general, the agreement is best for relatively small substituents with relatively small resonance components (σ_R) such as Cl and Br. The larger groups, such as $N(CH_3)_2$, CO_2CH_3 and NO_2 show the greatest deviation. If we assume that $N(CH_3)_2$ has no resonance contribution and use the $\sigma_I \sim \sigma_{m,}$ we calculate a pKa of 6.01, which improves the agreement. Larger groups in the 4-position will experience greater steric interactions with the methyl groups and will be twisted out of the plane of the aromatic ring. This dramatically reduces the orbital overlap between 2p orbitals on the substituent with the pi-system of the aromatic and consequently reduces σ_R.

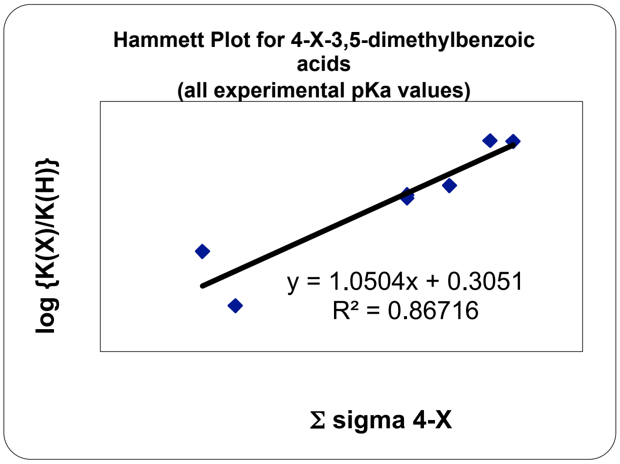


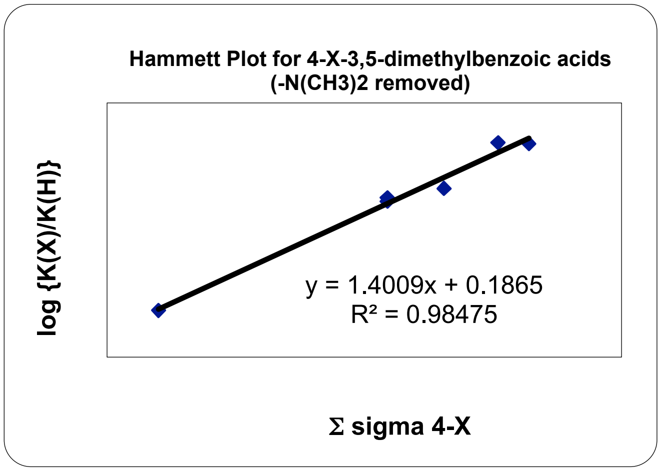
Note that the agreement is better for NH_2 than $N(CH_3)_2$ since it is smaller in size and the out of plane twist is not as dramatic such that much of it's resonance contribution is retained.

Another approach to this question involves graphing the experimental pKa values against the sum of sigma substituent constants to analyze the fit.

	σ			**exp. pKa(X)**	**log Ka(X)/Ka(H)**
	4-X	**3,5-diMe**	**Σ σ**		
N(CH3)2	-0.83	-0.14	-0.97	6.23	-0.9500
NH2	-0.66	-0.14	-0.80	6.88	-0.3000
Cl	0.23	-0.14	0.09	5.59	0.3400
Br	0.23	-0.14	0.09	5.55	0.3800
CN	0.66	-0.14	0.52	4.90	1.0300
CO2CH3	0.45	-0.14	0.31	5.44	0.4900
NO2	0.78	-0.14	0.64	4.91	1.0200

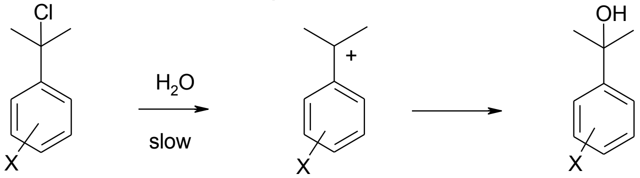
Comparing the two Hammett plots below, we see that removal of the dimethylamino substituent dramatically improves the fit as measured by the value of R^2.



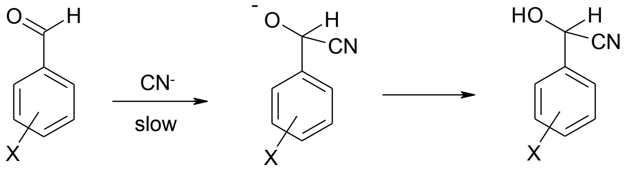


5. For each of the following mechanisms, indicate if the build up of charge at reaction centre is in direct resonance communication with substituents in the para position and specify which σ values would be used (σ, σ^+, σ^-, or $\sigma_{ortho}^{phenols}$) in obtaining the susceptibility constant. Illustrate your answer with an example.

a) hydrolysis of substituted benzyl chlorides; $\rho = -4.45$

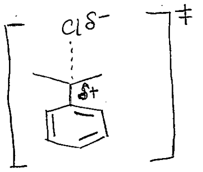


b) addition of cyanide ion to substituted benzaldehydes; $\rho = 2.55$

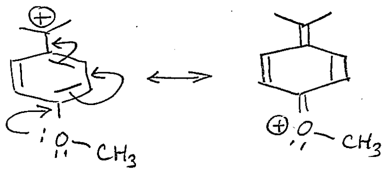


Solution:

a) The reaction constant has a large negative value consistent with a substantial decrease in electron density at the transition state, which is stabilized by electron donating groups. The magnitude of the reaction constant suggests a late transition state with a structure similar to the carbocation intermediate. Because the positive charge is located on a benzylic carbon, it can be resonance stabilized by substituents in the para positions. Therefore, σ^+ values should be used in place of σ_p for those substituents capable of electron donation by resonance. See for example, the para-methoxy substituted benzyl chloride below.

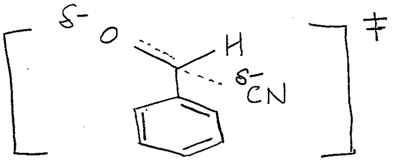


late ‡ - carbocation
almost fully formed

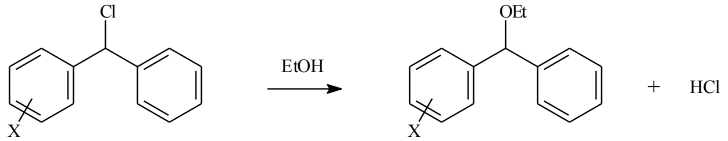


∴ use σ^+ values

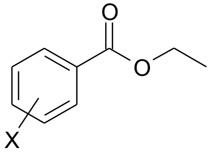
b) The reaction constant is > 0, which indicates that there is an increase in electron density in the transition state leading to the tetrahedral intermediate. The reaction constant is reasonable large suggesting a mid- to late transition state structure. Because the negative charge on the tetrahedral intermediate cannot be resonance stabilized onto an electron withdrawing group in the para position, the unmodified σ_p values should be used in this case.

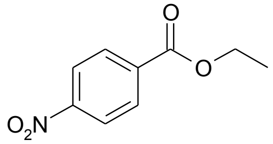


6. a) The solvolysis of substituted diphenylcarbinyl chlorides was studied in ethanol at 25°C. A plot of log *k* versus σ^+ was linear with a slope of −5.1. Suggest a mechanism consistent with this observation and provide an explanation of the ρ value in terms of the *Hammond postulate.*



b) The hydrolysis of a series of ethyl benzoates by hydroxide ion in 85% aqueous ethanol has been investigated. A Hammett plot of the second order rate constants (k_B) gave a reaction constant ρ = 2.56. Calculate how much faster ethyl 4-nitrobenzoate will undergo base catalyzed hydrolysis compared to ethyl benzoate under similar conditions.

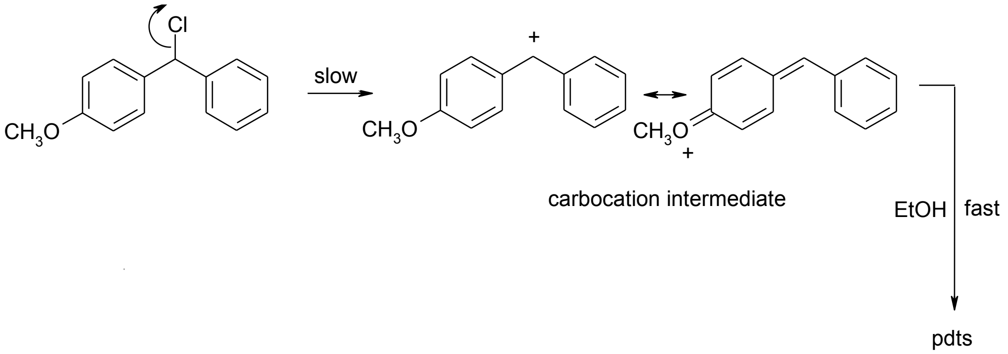


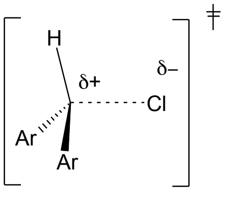


Solution:

The Hammond postulate states that the structure of the transition state will be closest to the chemical species in an elementary process to which it is closest in energy.

a) This is a nucleophilic substitution reaction in which ethanol is acting as a nucleophile and displacing the chloride leaving group. The large negative ρ value (-5.51) suggests a significant decrease in electron density (build up of positive charge) at the reaction centre of the transition state. The correlation with σ^+ further indicates that the developing positive charge is in direct conjugation with substituents in the *para* position. This is consistent with an S_N1 type reaction mechanism in which we have a late transition state that both structurally and energetically resembles the carbocation intermediate (Hammond postulate).





'late' transition state

b)

$$\log\left\{\frac{k_B(NO_2)}{k_B(H)}\right\} = \rho\Sigma\sigma_i = 2.56(0.78) = 2.00$$

Therefore, $k_B(NO_2)/k_B(H) = 10^{2.00} = 100$.

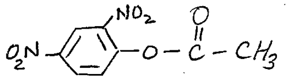
In other words, the ethyl p-nitrobenzoate reacts 100. times faster than ethyl benzoate under base enhanced hydrolysis.

7. The neutral hydrolysis of 2,4-dinitrophenyl acetate (2,4-DNPA) has a measured pseudo first order rate constant of 4.4 x 10^{-5} s^{-1} at 22.5 °C.

a) If the reaction constant for a series of substituted phenyl acetates is determined to be $\rho = 0.87$, what is rate constant for the neutral hydrolysis of the unsubstituted phenyl acetate at this temperature.

b) Suggest a substituted phenyl acetate that will have a hydrolysis half-life greater than one week.

Solution:



a) $k_N = 4.4 \text{ x } 10^{-5} \text{ s}^{-1}$, $\rho = 0.87$

$$\log\left(\frac{k_N^{(X)}}{k_N^{(H)}}\right) = \rho\,\Sigma\,\sigma$$

$\therefore \log k_N^{(H)} = \log k_N^{(X)} - \rho\,\Sigma\,\sigma = \log(4.4 \text{ x } 10^{-5} \text{ s}^{-1}) - 0.87\,(0.78 + 1.24) = -4.36 - 1.76 = -6.12$

Therefore, $k_N^{(H)} = 10^{-6.12} = 7.6 \text{ x } 10^{-7} \text{ s}^{-1}$

b) For first order processes, $t_{1/2} = \ln 2/k$, where k is a first order or pseudo first order rate constant.

So if $t_{1/2}$ = 1 week = 6.05 x 10^5 s

Therefore,

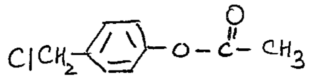
$$k < \frac{\ln 2}{6.05x10^5\ s} = \frac{0.693}{6.05x10^5\ s} = 1.1x10^{-6}\ s^{-1}$$

And since,

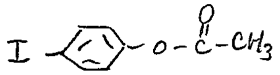
$$\log\left(\frac{k_N^{(X)}}{k_N^{(H)}}\right) = 0.87\,\Sigma\,\sigma$$

$\Sigma\,\sigma = \log(k^X/k^H)/0.87 = 0.18$

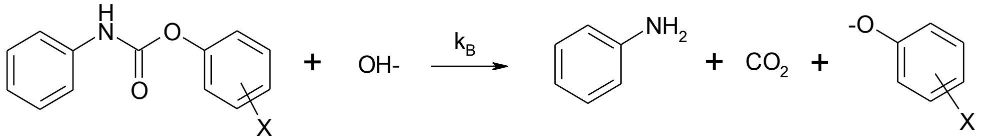
and possible substituents include chloromethyl ($-CH_2Cl$) and iodo (-I)



or



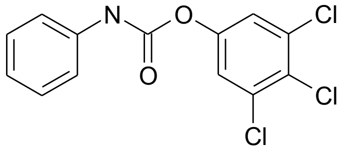
8. The base catalyzed hydrolysis of phenyl N-phenyl carbamates occurs by the elimination of PhO$^-$ group as the rate determining step. Estimate the second order rate constant, k_B for 3,4,5-trichlorophenyl N-phenyl carbamate at 25^{o}C using the k_B values given in the Table below for other substituted phenyl N-phenyl carbamates and the Hammett relation.



X	k_B (M^{-1} s^{-1})	X	k_B (M^{-1} s^{-1})
p-CH_3	3.0 x 10^1	*m*-Cl	1.8 x 10^3
p-OCH_3	2.5 x 10^1	*m*-NO_2	1.3 x 10^4
p-Cl	4.2 x 10^2	*p*-NO_2	2.7 x 10^5

Solution:

In this question, we want to estimate the second order rate constant (k_B) for hydrolysis of the trichlorocarbamate compound below from the given data. We approach this problem by constructing a Hammett plot to determine the reaction constant (ρ) and then the Hammett equation to calculate the rate constant assuming the substituent constants are additive (which seems to be a good assumption in this case, see question 4 above).



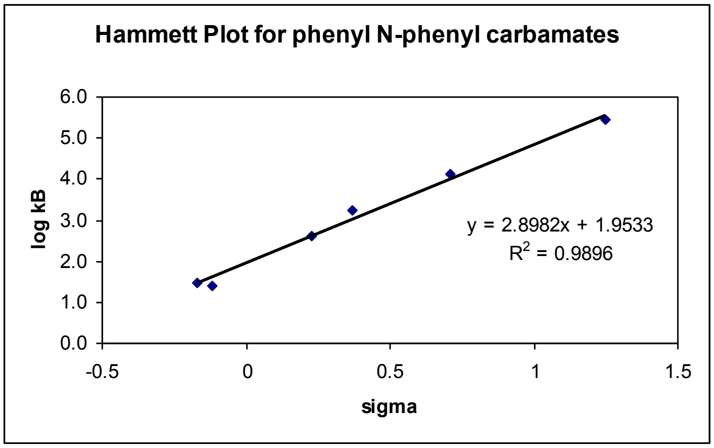
$$\log\left(\frac{k_B^{(X)}}{k_B^{(H)}}\right) = \rho\Sigma\sigma$$

$$\therefore \log k_B^{(X)} = \rho\,\Sigma\,\sigma + \log k_B^{(H)}$$

So a plot of log log $k_B^{(X)}$ versus σ, will yield a slope of ρ and an y-intercept = log $k_B^{(H)}$.
Recognizing that the substituents are on a phenoxy group with a developing negative charge which can be delocalized onto *para*-substituents, we will use σ- values where applicable (i.e., for p-OCH_3 and p-NO_2).

	σ/σ –	**k_B (M^{-1} s^{-1})**	**log k_B**
p-CH3	-0.17	30	1.48
p-OCH3	**-0.12**	25	1.40
p-Cl	0.23	420	2.62
m-Cl	0.37	1800	3.26
m-NO2	0.71	13000	4.11
p-NO2	**1.25**	270000	5.43

From the plot we see that ρ= 2.90 and the Σ σ (3,4,5-trichloro) = (2(0.37) + (0.23)) = 0.97.



So, log k_B(H) = 1.95

and

$\rho\ \Sigma\ \sigma = 2.90\ (0.97) = 2.81$

Therefore log k_B(3,4,5-TCP) = 4.76

and

k_B(3,4,5-TCP) = 5.79 x 10^4 M^{-1} s^{-1}

Table 1: Hammett constants for some common substituents

Substituent	σ_{meta}	σ_{para}	σ-	σ^+	$\sigma_o^{phenols}$
CH_3	-0.07	-0.17		-0.31	-0.13
Ph (C_6H_5)	0.06	0.01			
Cl	0.37	0.23		0.11	0.68
Br	0.39	0.23	0.26	0.15	0.70
I	0.35	0.18		0.13	0.63
OH	0.10	-0.37		-0.92	
OCH_3	0.12	-0.27	-0.12	-0.78	0.0
NO_2	0.71	0.78	1.25	0.79	1.24
CN	0.56	0.66	0.89	0.66	
CO_2CH_3	0.33	0.45	0.66		
$OCOCH_3$	0.36	0.31			
NH_2	-0.16	-0.66		-1.3	
$N(CH_3)_2$	-0.15	-0.83			

Note: σ**-** and σ^+ apply to *para* substituted groups only

Table 2: Reaction and acidity constants for aromatic acids in water at 25°C

Acid	ρ	pK_{aH}
Benzoic acid	1.00	4.19
Phenol	2.25	9.92
Phenoxy acetic acid	0.30	3.17
2-chlorophenoxy acetic acid	0.30	3.05
Conjugate acid of aniline	2.89	4.63