CHEM 331

Problem Set #3: Substitutent Effects and LFERs

Solutions

1. a) Interpret the following σ values in terms of the electronic character of each group. Discuss the inductive and resonance effects of each (σ_I and σ_R) using benzoic acid derivatives as examples, showing resonance where appropriate.

Substituent	σ_{meta}	σ_{para}
$-NH_2$	-0.16	-0.66
$-COCH_3$	0.38	0.50
-Cl	0.37	0.23

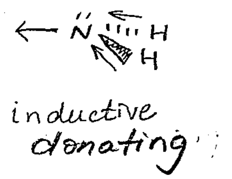
b) The picryl (2,4,6-trinitrophenyl) substituent, $C_6H_2(NO_2)_3$ has values of σ_{meta} 0.43, σ_{para} 0.41. What conclusion may be drawn regarding the resonance effect of this substituent and the configuration of the two aromatic rings in 4-(2,4,6-trinitrophenyl)benzoic acid?

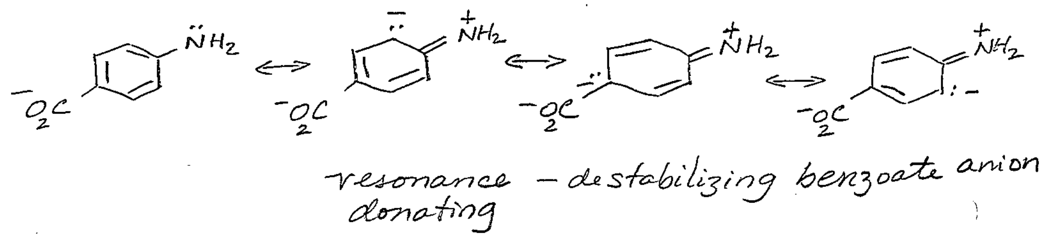
Solution:

a) 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 $\sigma_{para} \sim \sigma_I + \sigma_R$.

$-NH_2$

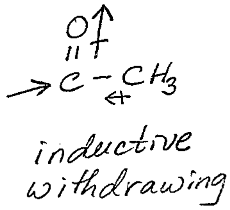
Since $\sigma_m = -0.16$ and $\sigma_p = -0.66$, the amino group is an electron donating group in both the *meta* and *para* positions. The nitrogen (EN = 3.0) is bonded to two hydrogen atoms, which are less electronegative (EN = 2.1). The net result is that the $-NH_2$ group is an electron donating by induction, $\sigma_m \sim \sigma_I \sim -0.16$. In the *para* position, the $-NH_2$ group is a powerful electron donor to the aromatic ring via resonance contributions involving the lone pair on nitrogen (i.e., $\sigma_R \sim \sigma_p - \sigma_m \sim -0.50$). Hence, NH_2 is electron donating by both inductive and resonance effects.

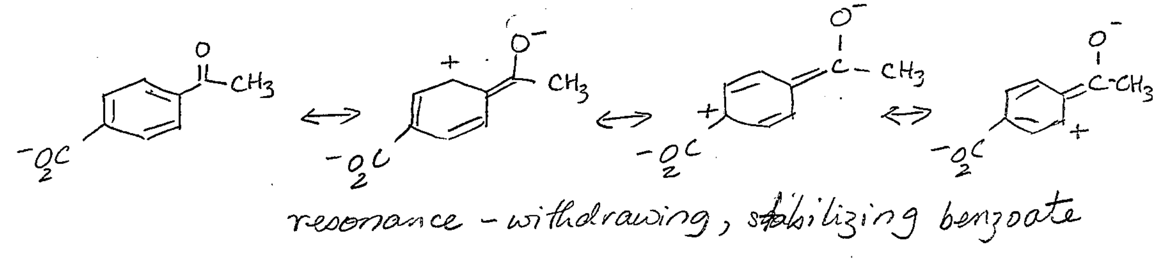




$-COCH_3$

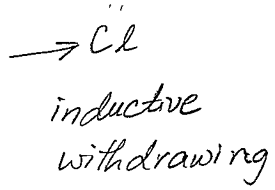
Since $\sigma_m = 0.38$ and $\sigma_p = 0.50$, a carboxymethyl group is a net electron withdrawing group (EWG) in both positions. The carbonyl carbon bears a partial positive charge due to the inductive electron withdrawing effect of the oxygen. This in turn has an inductive withdrawing effect on the aromatic ring. In the *para* position, we can write a resonance structure that places a positive charge on the aromatic ring adjacent to the reactive centre. Hence, this group is withdrawing by both inductive and resonance effects, i.e., $\sigma_I \sim \sigma_m \sim 0.38$ and $\sigma_R \sim \sigma_p - \sigma_m \sim 0.12$.

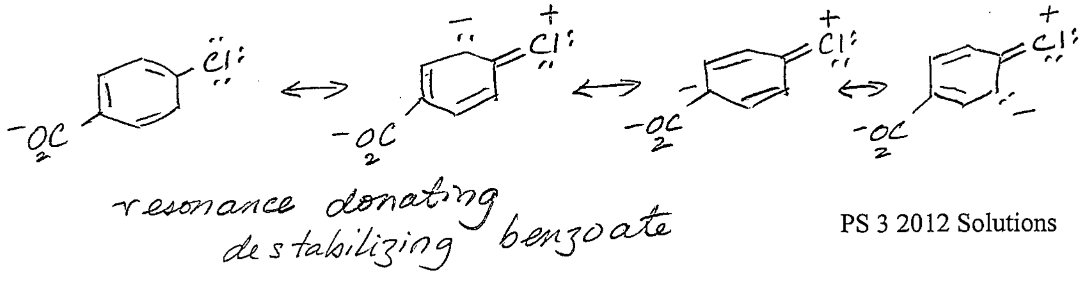




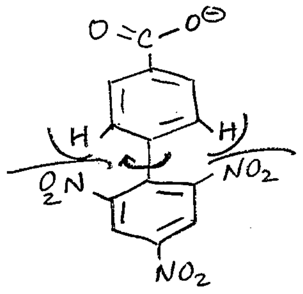
-Cl

Since $\sigma_m = 0.37$ and $\sigma_p = 0.23$, a chlorine atom is a net electron withdrawing group (EWG) in both positions. However, since $\sigma_p < \sigma_m$, it is donating electron density to the aromatic ring via resonance (i.e., $\sigma_I > 0$ whereas $\sigma_R < 0$). Hence, $\sigma_I \sim \sigma_m \sim 0.37$ and $\sigma_R \sim \sigma_p - \sigma_m \sim -0.14$.

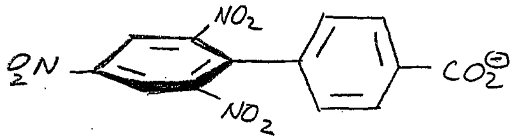




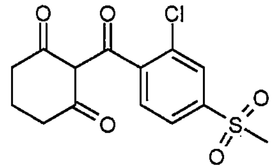
b) The picryl substituent is electron withdrawing due to the inductive effect of the three nitro groups pulling electron density from the aromatic ring. There is no appreciable resonance contribution when picryl is in the *para* position as can be seen by the fact that $\sigma_{meta} \sim \sigma_{para}$ (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 rather steeply with the dihedral angle between adjacent p-orbitals. Hence $\sigma_R \sim 0$ in this case.



steric interactions result in twist in biphenyl C-C bond ∴ removing conjugation between aromatic rings



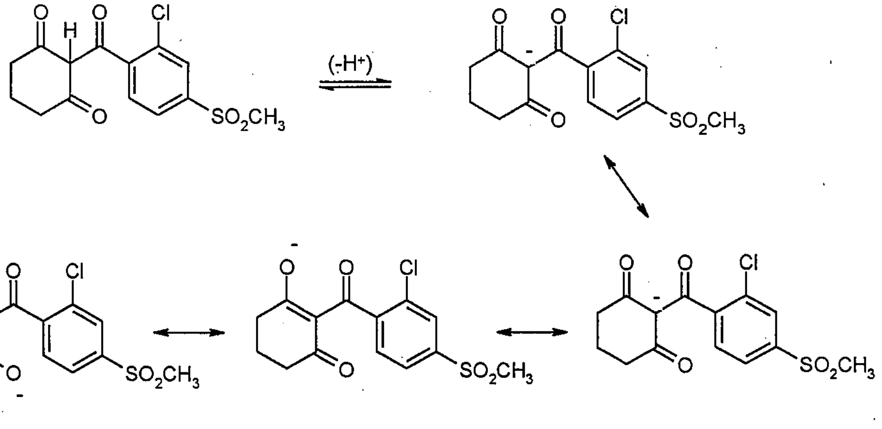
2. The structure of the herbicide *sulcotrion* is shown below and is found to have a pK_a of 3.13. Identify the acidic proton and explain the unusual acidity.



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, $\sigma_p = 0.72$.

3. a) Estimate the pK_a values of 4-methyl-2,5-dinitrophenol and 3,4,5-trimethylaniline and calculate the fractional abundance of the conjugate base of each at pH 7.70 at 25.0 °C (see Tables 1 and 2).
b) Use Excel to plot the fractional abundance of the neutral and ionized forms of ortho-phthalic acid over a pH range of 2 – 12 at 25°C ($\text{pK}_{a1} = 2.89$ and $\text{pK}_{a2} = 5.51$).

Solution:
a) 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.

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

$$\therefore\ \text{pK}_a(\text{X}) = \text{pK}_a(\text{H}) - \rho\ \Sigma\ \sigma_X$$

4-methyl-2,5-dinitrophenol; pKa(phenol) = 9.92, $\rho = 2.25$
pKa(4-MDNP) = 9.92 – 2.25 ((1.24) + (-0.17) + (0.71)) = **5.92**

3,4,5-trimethylaniline; pKa (aniline) = 4.63, $\rho = 2.89$
pKa(3,4,5-TMA) = 4.63 – 2.89 (2(-0.07) + (-0.17)) = **5.53**

Knowing the pKa of each acid we can calculate the fractional abundance of the conjugate base as follows;

$$f_{A-} = \frac{[A^-]}{[HA]+[A^-]}$$

Since ,

$\text{HA} \;====\; \text{H}^+ + \text{A}^-$

$$K_a = \frac{[H^+][A^-]}{[HA]} \quad \therefore\ [\text{HA}] = \frac{[\text{H}^+][\text{A}^-]}{\text{K}_a}$$

So substituting this into the fractional abundance expression above yields;

$$f_{A-} = \frac{[A^-]}{[HA]+[A^-]} = \frac{1}{\frac{[H^+]}{K_a}+1} = \frac{K_a}{[H^+]+K_a}$$

At pH 7.70, $[\text{H}^+] = 2.0 \times 10^{-8}$ M

So $f_{(\text{4-MDNPhenolate})}$ = **0.986 (98.6%)**
and
So $f_{(\text{3,4,5-TMA})}$ = **0.993 (99.3%)**

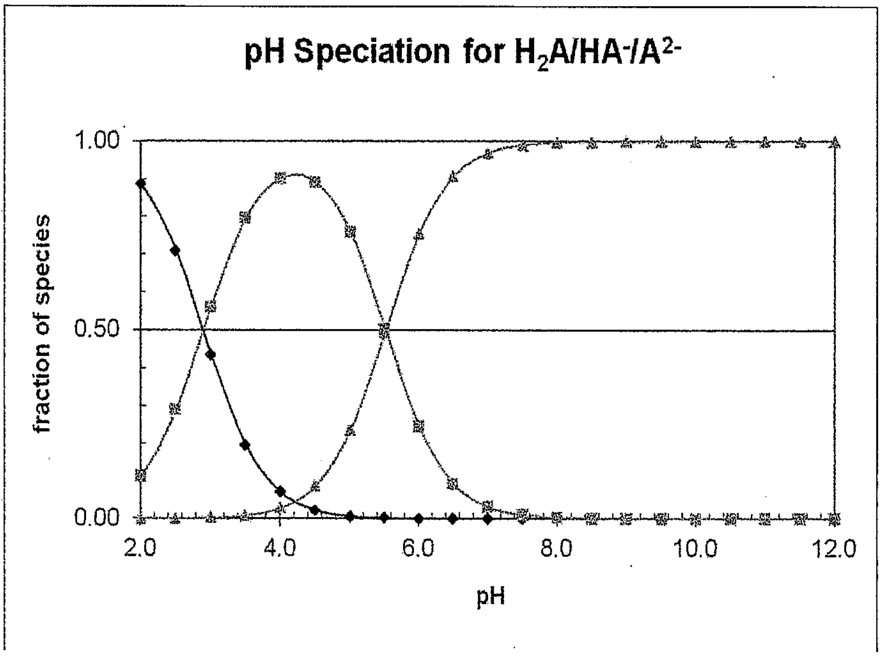
b) A similar approach for a diprotic acid yields expressions for the $f_{(H2A)}$, $f_{(HA-)}$ and $f_{(A2-)}$.

$$f_{H2A} = \frac{[H_2A]}{[H_2A]+[HA^-]+[A^{2-}]} = \frac{[H^+]^2}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}}$$

$$f_{A-} = \frac{[HA^-]}{[H_2A]+[HA^-]+[A^{2-}]} = \frac{[H^+]K_{a1}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}}$$

$$f_{A2-} = \frac{[A^{2-}]}{[H_2A]+[HA^-]+[A^{2-}]} = \frac{K_{a1}K_{a2}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}}$$

Using Excel to carry out repetitive calculations over a series of pH's ranging from pH = 2 to 12, and plotting the results yields the following. *ortho*-phthalic acid is diprotic and thus will have three chemical forms. The predominate form/s will depend on the pH, with the acidic form at low pH ($< pK_{a1}$) and the dibasic form at high pH ($> pK_{a2}$). Note, although the pH = pK_a when the fractional abundance of the acidic and basic forms are equal, this will only be true for polyprotic acids when the pK_as are well separated.



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 medium are shown 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

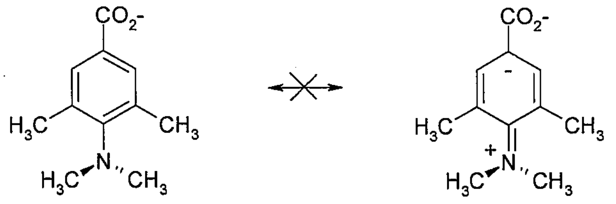
Solution:
We can calculate the pK_a for each of the trisubstituted benzoic acids using the Hammett equation and a ρ value of 1.60, a $pK_a(H) = 5.71$ and the sum of the three substituent constants. In so doing, we are making the assumption that each substituent will have the same electronic effects in 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	$\mathbf{N(CH_3)_2}$	$\mathbf{NH_2}$	**Cl**	**Br**	**CN**	$\mathbf{CO_2CH_3}$	$\mathbf{NO_2}$
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.~~08~~2	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.

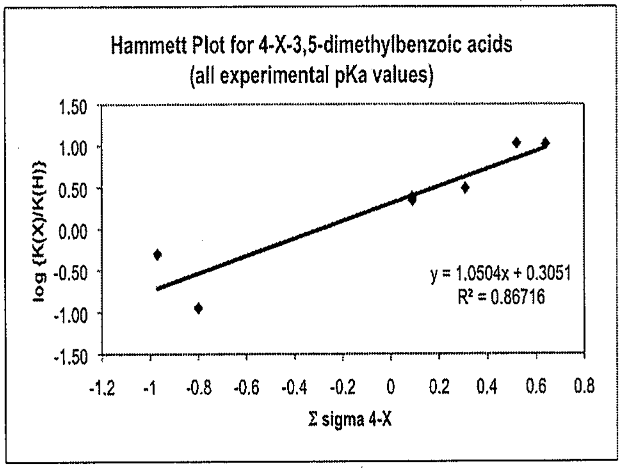


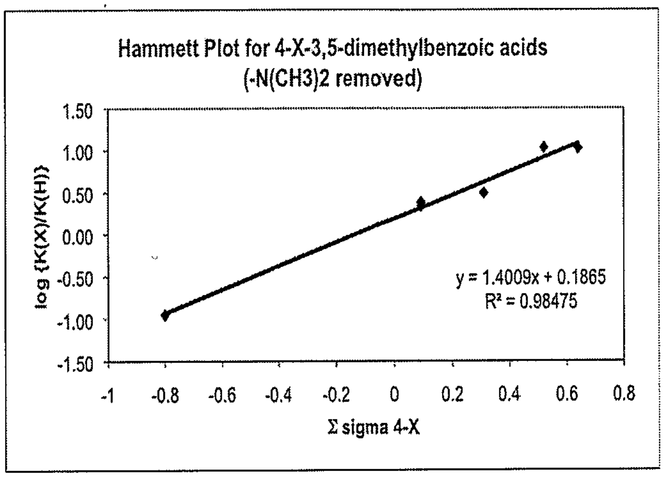
Note that the agreement is better for NH_2 than $N(CH_3)_2$ since it is smaller in size and the out of plane twist is not as dramatic such that much of it's resonance contribution is retained.

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.



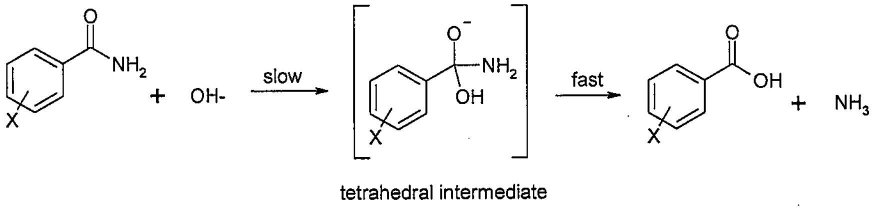


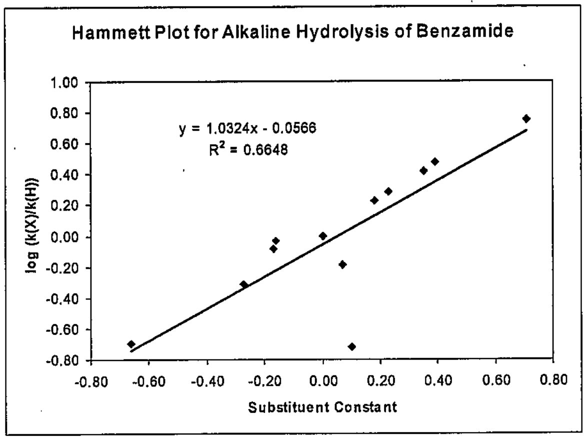
5. The relative rates of alkaline hydrolysis of substituted benzamides in water at 100°C are as follows below. Demonstrate the applicability of the Hammett equation to this reaction, calculate the ρ value, and comment on any deviations from the correlation.

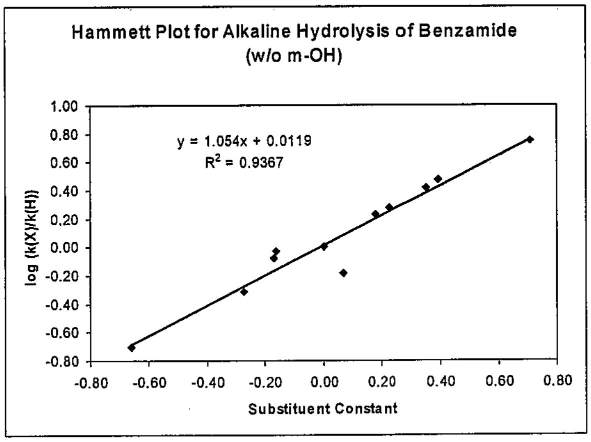
Substituent	Relative Rate	Substituent	Relative Rate	Substituent	Relative Rate
m-I	2.60	*m*-NO_2	5.60	*p*-OCH_3	0.49
p-I	1.69	H	1.00	*m*-NH_2	0.93
m-Br	2.97	*m*-CH_3	0.83	*p*-NH_2	0.20
p-Br	1.91	*p*-CH_3	0.65	*m*-OH	0.19

Solution:

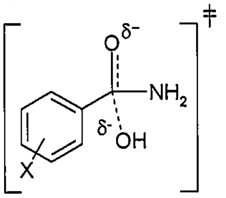
For the alkaline hydrolysis of substituted benzamides, the rate of reaction is proportional to the rate constant and the reactant concentrations. When a series of reactions are carried out under identical conditions (reactant concentration, temperature etc) the relative rates can be used as a measure of the relative rate constants (i.e., k(X)/k(H)). Thus, we can obtain the Hammett plot by graphing log (relative rate) vs σ to obtain the reaction constant (ρ) as the slope.





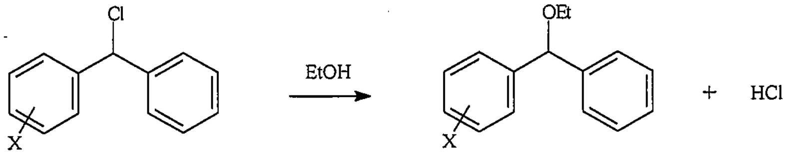


From the Hammett plots above, the reaction constant is determined to be ρ = 1.05. Since the reaction rate is faster in the presence of EWGs (e.g., -NO_2), we can deduce that this reaction involves the build up of electron density at the reaction centre of the transition state. This is consistent with the formation of the negatively charged tetrahedral intermediate depicted in the scheme above.



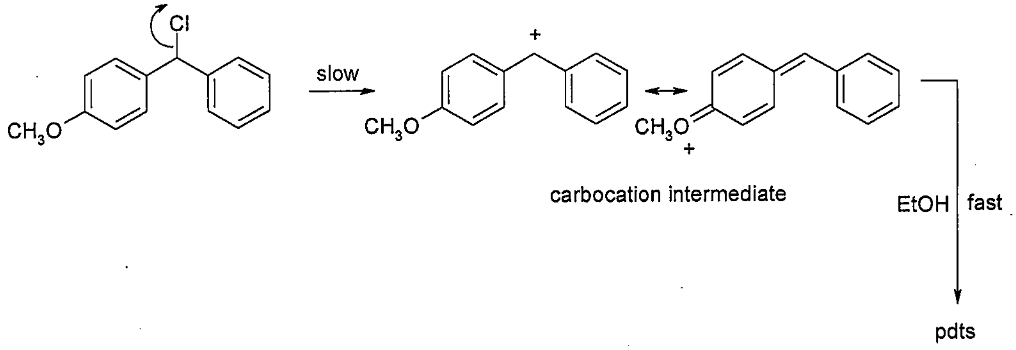
The one compound that does not seem to follow the trend is *meta*-hydroxybenzamide, which apparently reacts much slower than one would expect based on the value of the substituent constant ($\sigma_m = 0.10$). A possible explanation for this is the deprotonation of the OH substituent in alkaline solution (pK_a ~ 10). In the deprotonated form the $-O^-$ substituent is a much more powerful electron donor via induction, which would have the effect of slowing the reaction down considerably.

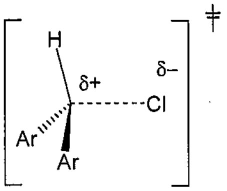
6. The solvolysis of substituted diphenylcarbinyl chlorides was studied in ethanol at 25°C. A plot of log *k* versus σ^+, displayed a linear correlation with a slope of -5.1. Suggest a mechanism that is consistent with this observation and provide an explanation of the sign and magnitude of the ρ value.



Solution:

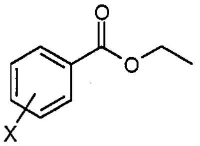
This is a nucleophilic substitution reaction in which ethanol is acting as a nucleophile and displacing the chloride leaving group. The large negative ρ value (-5.51) suggests a significant decrease in electron density (build up of positive charge) at the reaction centre of the transition state. The 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).

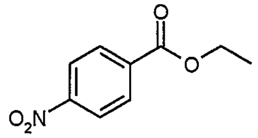




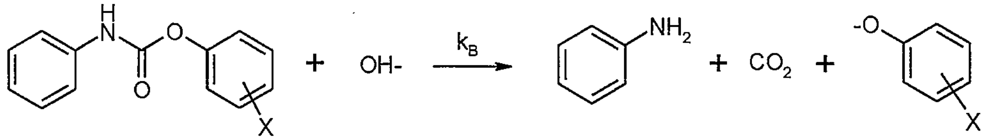
'late' transition state

7. a) 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 $\rho = 2.56$. Calculate how much faster ethyl 4-nitrobenzoate will undergo base catalyzed hydrolysis compared to ethyl benzoate under similar conditions.





b) The base enhanced 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°C using the k_B values given in the Table below for other substituted phenyl N-phenyl carbamates and the Hammett relation.



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

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:

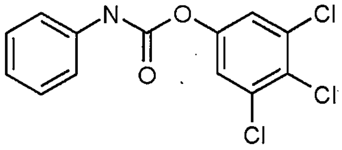
a)

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

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.

b) 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).



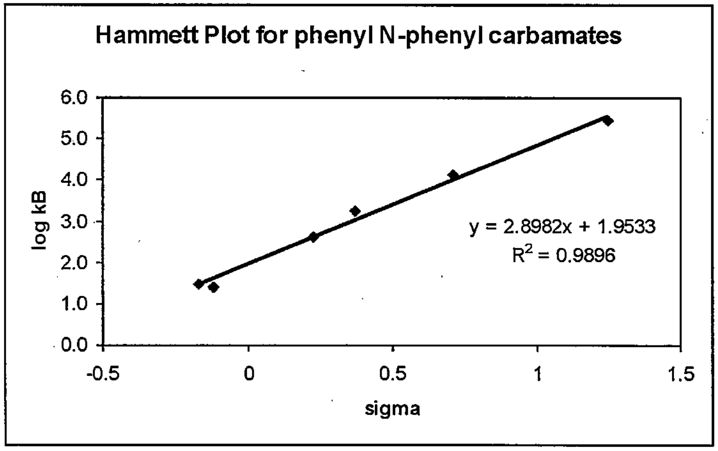
$$\log\left(\frac{k_B{}^{(X)}}{k_B{}^{(H)}}\right) = \rho \Sigma \sigma$$

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

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.



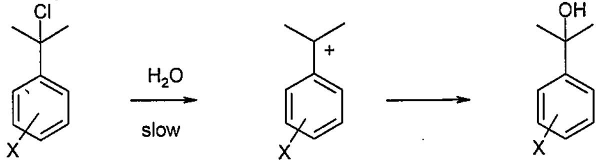
So, log k_B(H) = 1.95
and
ρ Σ σ = 2.90 (0.97) = 2.81
Therefore log k_B(3,4,5-TCP) = 4.76
and
k_B(3,4,5-TCP) = 5.79 x 10^4 M^{-1} s^{-1}

8. For the following mechanisms:

a) Explain the value of the reaction (susceptibility) constant in terms of the Hammond postulate.

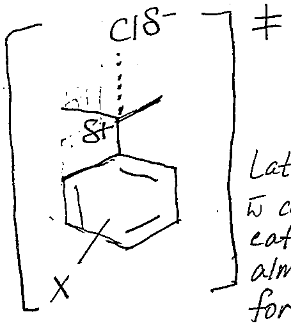
b) Specify which σ values are used (σ, σ^+, σ^-, or $\sigma_{\text{ortho}}^{\text{phenols}}$) in obtaining the susceptibility constant and indicate if the reaction centre is in direct resonance with the substituents. Illustrate with an example.

Hydrolysis of substituted benzyl chlorides; $\rho = -4.45$

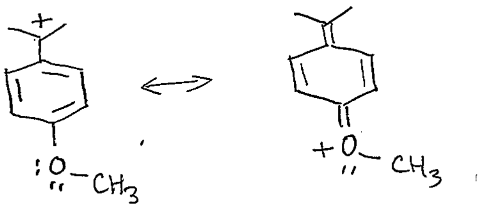


Solution:
The Hammond postulate states that the structure of the transition state will be closest to the chemical species in an elementary process to which it is closest in energy.

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.

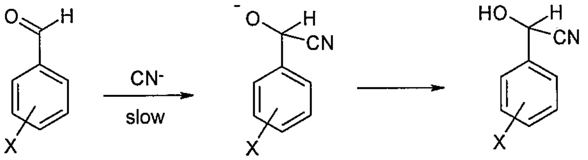


Late TS
w carbo-
cation
almost
formed

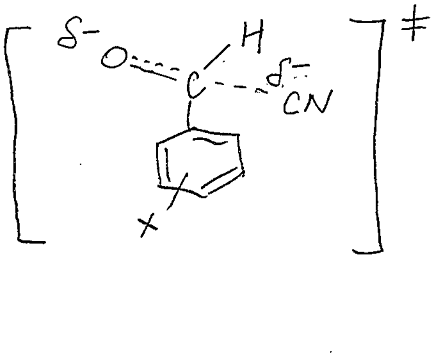


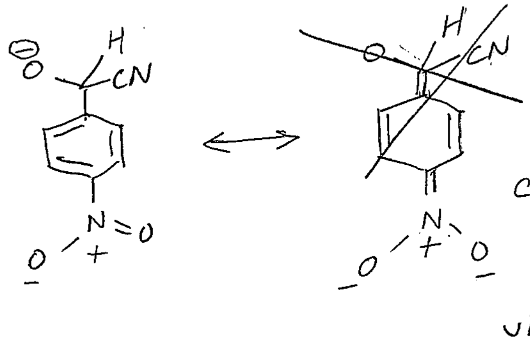
∴ use σ^+ for para-OCH_3

Addition of cyanide ion to substituted benzaldehydes; $\rho = 2.55$



Solution:
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.





cannot move negative charge onto $-NO_2$ via resonance