CHEM 331
Problem Set #3: Substituent Effects and LFERs

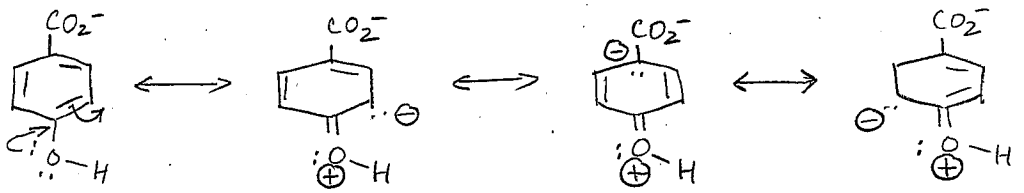
1. Consider the following substituent constants (σ values) and answer each of the following in terms of the inductive and resonance electronic character of each group (σ_I and σ_R). Illustrate your answer showing resonance structures for substituted benzoic acids, where appropriate.

Substituent	σ_{meta}	σ_{para}
-OH	0.13	-0.38
$-COCH_3$	0.38	0.50
$-C_6H_2(NO_2)_3$	0.43	0.41

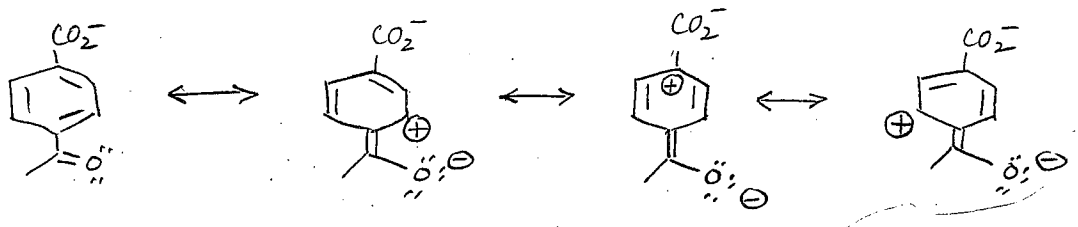
a) Why is σ_{meta} for the hydroxyl group (–OH) positive, whereas the value for σ_{para} is negative?
b) Why is the acetyl group ($-COCH_3$) a more electron withdrawing in the para vs meta position?
c) Why does the picryl substituent - $C_6H_2(NO_2)_3$ have nearly the same electron withdrawing ability in both the meta and para position?

Solution:

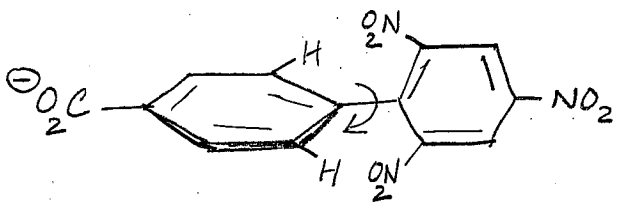
a) In the meta position, a substituent will only exhibit inductive electronic effects, whereas in the para position, both inductive and resonance effects can manifest themselves. Since oxygen is more electronegative than carbon, the –OH group is electron withdrawing by induction (hence, $\sigma_{meta} > 0$). However, the lone pair electrons on the hydroxyl group can be donated back into the benzene ring through resonance. In the para position, this resonance effect is greater than the withdrawing ability by induction and hence $\sigma_{para} < 0$. We can say therefore that $\sigma_I \sim 0.13$ and $\sigma_R \sim -0.51$.



b) The acetyl group is electron withdrawing by both inductive and resonance effects as depicted below. We can say therefore that $\sigma_I \sim 0.38$ and $\sigma_R \sim 0.12$.



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 rather 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 ($\therefore \sigma_R \sim 0$)

2. Using the information in Table 1 and 2 (attached), estimate the pK_a values of the following compounds at 25°C and use Excel to plot the fractional abundance of each acid and conjugate base over a pH range of 2 – 12.

a) 4-nitrophenol (4-NP)
b) the conjugate acid of 4-methyloxyaniline (4-MA)
c) 2,4-dinitrophenoxy acetic acid (2,4-DNPA)

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) 4-nitrophenol; pKa(phenol) = 9.92, ρ = 2.25
pKa(4-NP) = 9.92 – 2.25 (1.25) = **7.09**

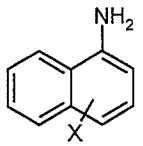
b) 4-methyoxyaniline; pKa (aniline) = 4.63, ρ = 2.89
pKa(4-MA) = 4.63 – 2.89 (-0.27)) = **5.41**

c) 2,4-dinitrophenoxy acetic acid; pKa (phenoxy acetic acid) = 3.17, ρ = 0.30
pKa(2,4-DNPA) ~ 3.17 – (0.30 (1.24) + (0.78)) = **2.5**

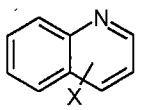
3. The pK_a's and reaction constants (susceptibility factors) ρ for the acid dissociation of substituted 1-naphthylamines and quinolines are given below.

a) Explain why the quinoline is much more susceptible to electronic substituent effects than 1-naphthylamine.

b) Predict the fraction of each compound present in the protonated form at pH = 6.00



1-naphthylamine
$pK_a = 3.85$
$\rho = 2.81$

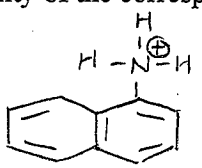


quinoline
$pK_a = 4.88$
$\rho = 5.90$

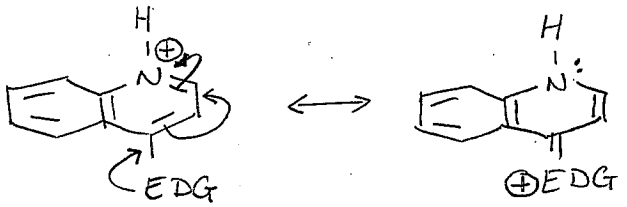
Solution:

a) Both compounds experience electronic substituent effects with a positive ρ value indicating that the parent acids become more acidic in the presence of electron withdrawing groups. To understand why $\rho > 0$, we need to remember that as the acid deprotonates, there is an increase in electron density at the reaction centre.

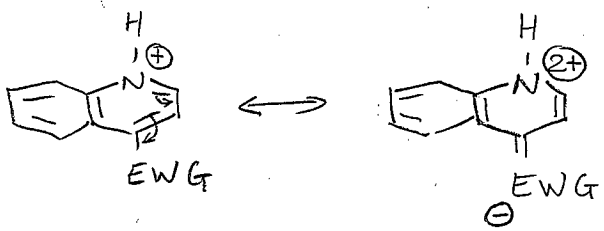
The protonated quinolones are much more susceptible to these electronic effects than the corresponding 1-naphthylamines. The difference is due to the greater electronic communication (both inductive and resonance) between the reaction centre and the substituents. Perhaps the best way to understand this is to consider the factors that stabilize/destabilize the protonated forms. Substituents that destabilize the acidic forms will have an acid strengthening effect. (Note that this is analogous to the arguments that we used to understand the acid strengthening effects of EWGs on benzoic acids by considering their influence on the stability of the corresponding conjugate base).



positive charge is isolated on nitrogen and cannot be stabilized by resonance contributions from substituents on aromatic ring. Inductive effects are still present but further away from reactive centre than for quinolines.



EDG stabilize the protonated form of quinoline
∴ weakens acid strength



EWG destabilize the protonated form of quinoline
∴ strengthens acid
(i.e. lower pKa)

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

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

Since ,

HA ==== H^+ + A^-

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

So substituting this into the fractional abundance expression above yields;

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

At pH 6.00, $[H^+] = 1.0 \times 10^{-8}$ M

So,

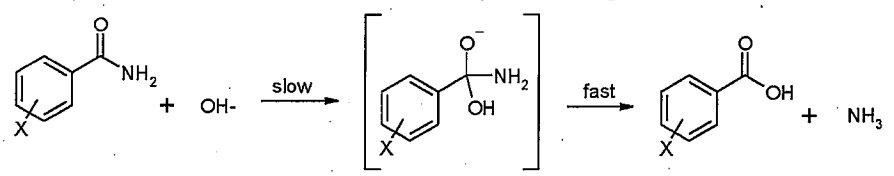
$f_{(1\text{-naphthylamineH+})} = \mathbf{7.1 \times 10^{-5}\ (0.0071\%)}$
and
$f_{(quinolineH+)} = \mathbf{7.6 \times 10^{-4}\ (0.076\%)}$

4. 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.

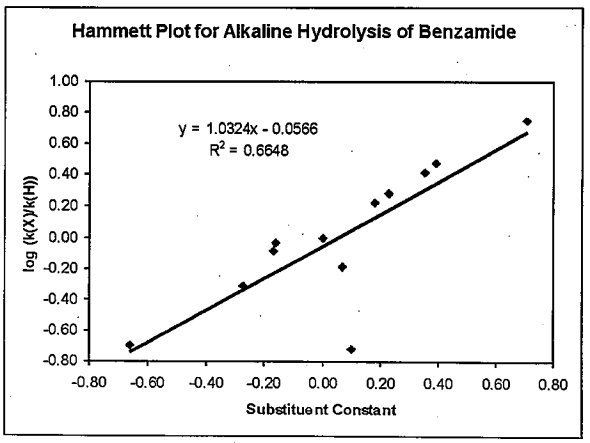
Substituent	Relative Rate	Substituent	Relative Rate	Substituent	Relative Rate
m-I	2.60	*m*-NO_2	5.60	*p*-OCH_3	0.49
p-I	1.69	H	1.00	*m*-NH_2	0.93
m-Br	2.97	*m*-CH_3	0.83	*p*-NH_2	0.20
p-Br	1.91	*p*-CH_3	0.65	*m*-OH	0.19

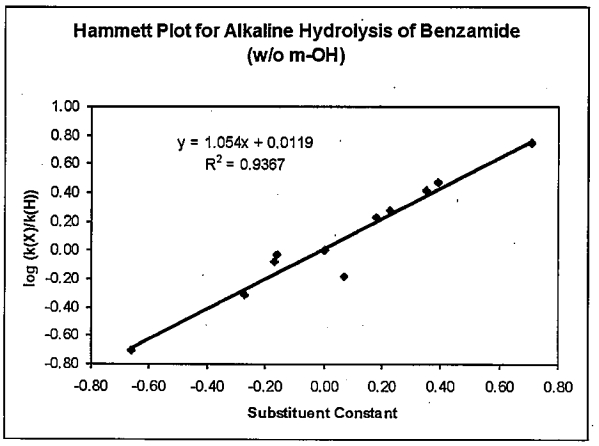
Solution:

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.

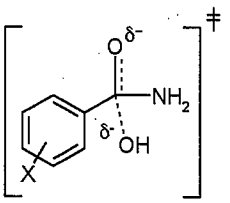


tetrahedral intermediate





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 (σ_m = 0.10). A possible explanation for this is the deprotonation of the OH substituent in alkaline solution ($pK_a \sim 10$). 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.

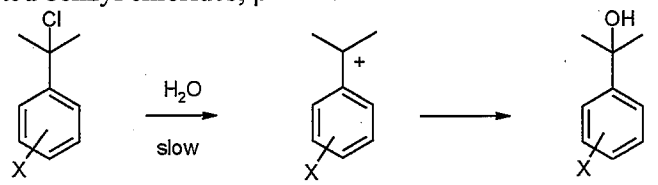
5. For the following mechanisms:

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 $\sigma_{ortho}^{phenols}$) in obtaining the susceptibility constant and indicate if the reaction centre is in direct resonance with the substituents. Illustrate with an example.

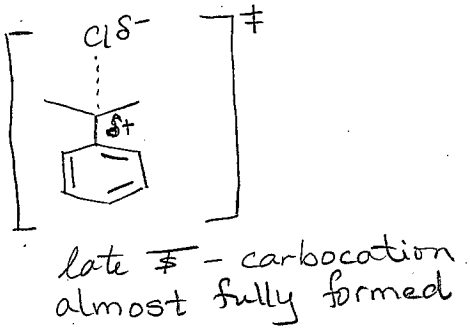
Solution:

i) hydrolysis of substituted benzyl chlorides; ρ = –4.45

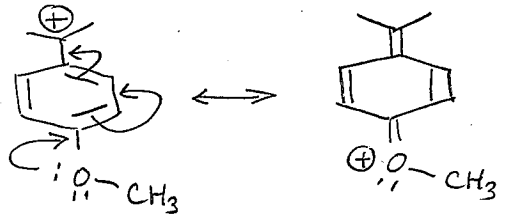


a) The reaction constant has a large negative value consistent with substantial decrease in electron density at the transition state (i.e., the transition state is stabilized by electron donating groups). The magnitude of the reaction constant suggests a late transition state with a structure similar to the carbocation intermediate.

b) Because the positive charge is located on a benzylic carbon, it can be resonance stabilized by substituents in the para position. Therefore, σ^+ values should be used in place of σ_{para} for those substituents capable of electron donation by resonance. See for example, the para-methoxy substituted benzylchloride shown below.

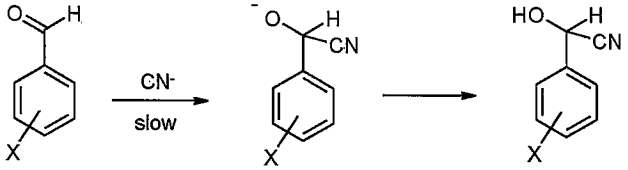


late ‡ - carbocation almost fully formed



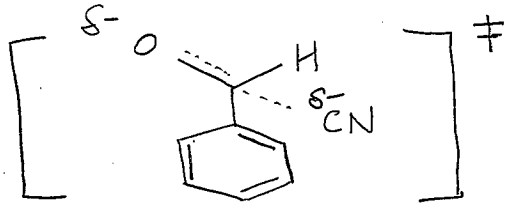
∴ use σ^+ values

ii) addition of cyanide ion to substituted benzaldehydes; ρ = 2.55



a) The reaction constant is positive indicating that there is an increase in electron density in the transition state leading to the tetrahedral intermediate. The reaction constant is reasonably large, suggesting a mid-to late transition state structure.

b) Because the negative charge on the tetrahedral intermediate cannot be resonance stabilized onto an electron withdrawing group in the para position, the unmodified σ_{para} values should be used in this case.



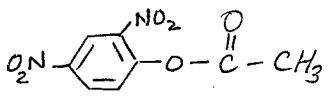
6. The neutral hydrolysis of 2,4-dinitrophenyl acetate (2,4-DNPA) has a measured pseudo first order rate constant of $4.4 \times 10^{-5}\ s^{-1}$ at 22.5 °C.

a) If the reaction constant for a series of substituted phenyl acetates is determined to be 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) $k_N = 4.4 \times 10^{-5}\ s^{-1}$, $\rho = 0.87$



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

$$\log k^{(X)} = \rho \Sigma\sigma + \log k^{(H)}$$

$$\therefore \log k^{(H)} = \log k^{(X)} - \rho \Sigma\sigma$$

$$= \log(4.4 \times 10^{-5}\ s^{-1}) - 0.87\,(0.78 + 1.24)$$

$$= -4.36 - 1.76$$

$$= -6.12$$

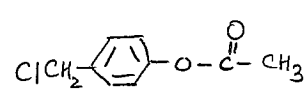
$$\therefore k^{(H)} = 10^{-6.12} = 7.6 \times 10^{-7}\ s^{-1}$$

b) $t_{1/2} = \frac{\ln 2}{k}$ $\qquad t_{1/2} = 1\ week = 6.05 \times 10^5\ s$

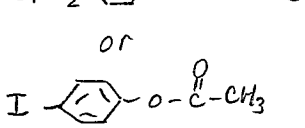
$$\therefore k < \frac{\ln 2}{6.05 \times 10^5\ s} = 1.1 \times 10^{-6}\ s^{-1}$$

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

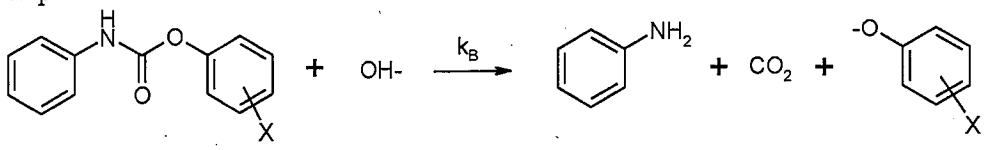
$$\therefore \Sigma\sigma = \frac{\log\left(\frac{k^{(X)}}{k^{(H)}}\right)}{0.87} = 0.18$$

$\therefore$ 

or



7. The base catalyzed hydrolysis of phenyl N-phenyl carbamates occurs by the elimination of PhO^- group as the rate determining step.



a) Determine the reaction constant (ρ) for this reaction using the using the second order rate constant (k_B) values given in the Table below for other substituted phenyl N-phenyl carbamates.
b) Calculate the second order rate constant for 3-trifloromethylphenyl N-phenyl carbamate.

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

Solution:
a) Rearranging the Hammett equation

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

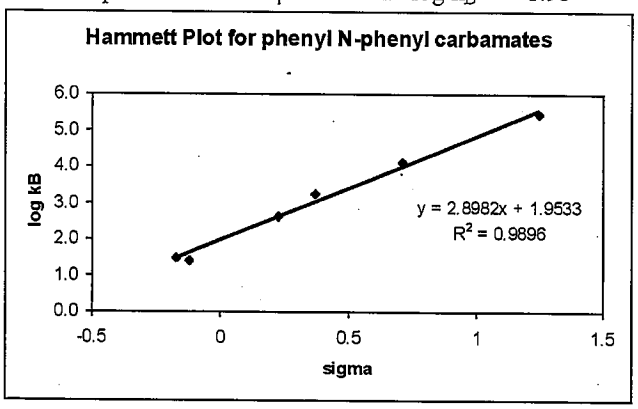
$$\therefore \log k_B^{(X)} = \rho \Sigma \sigma + \log k_B^{(H)}$$

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 log $k_B^{(H)}$ = 1.95



b) In this question, we want to estimate the second order rate constant (k_B) for hydrolysis of the trifluoromethylphenyl carbamate from the given data. Using the meta substituent constant for $-CF_3$ of 0.44 (textbook, p263), we get
log $k_B(CF_3)$ = ρ Σ σ + log $k_B^{(H)}$ = 2.90 (0.44) + 1.95 = 3.23
and hence
$k_B(CF_3) = 1.68 \times 10^3$ M^{-1} s^{-1}

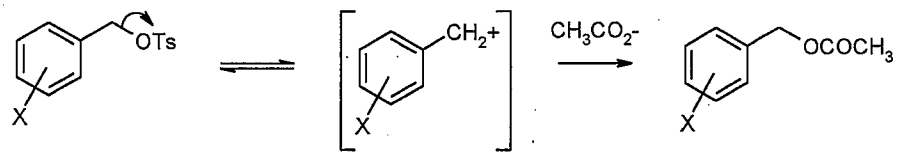
8. The acetolysis of substituted benzyl tosylates shown below proceeds via a substitution reaction. The Hammett plot for the rate constants of a series of substituents shows two linear regions, one for EDGs and another for EWGs. Hence there are two reaction (susceptibility) constants (ρ), shown on the figure below.

a) Why are the modified σ^+ values are used instead of σ

b) Explain the magnitude and sign of each of the two reaction constants and provide mechanism/s consistent with these observations.

Solution:

This is a substitution reaction in which –OTs is the leaving group and the acetate ion is the incoming nucleophile. There appears to be two linear regions in the Hammett plot with different slopes (i.e., differing susceptibilities to substituent effects). For a series of electron donating groups ($\sigma/\sigma+ < 0$), the value of $\rho = -5.58$ suggests a large decrease in the electron density at the reaction centre (build up of positive charge). This is consistent with the formation of a carbocation-like transition state, such as one encountered in an S_N1 type mechanism.



benzylic cation

Note the direct resonance capability of benzylic cation with substituents, hence the use of σ+ (where applicable).

As the substituents become increasingly electron withdrawing ($\sigma+ > 0$), the reaction constant seems to shift to a new value of -2.81. Although this again indicates a decrease in electron density at the reaction centre, it is not nearly as sensitive to electronic substituent effects. This is consistent with a change in mechanism, which occurs as substituents become increasingly withdrawing, they slow the S_N1 mechanism (by destabilizing the carbocation intermediate) to the point to where the S_N2 reaction predominates.