

CHEM 331

Problem Set #3: Substituent Effects and LFERs

Hand in all worked solutions in a neat and organized format. Not all questions will be graded.

Due: Friday, Mar 16th.

1. Consider the following σ values in terms of the electronic character of each group 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 phenols, where appropriate.

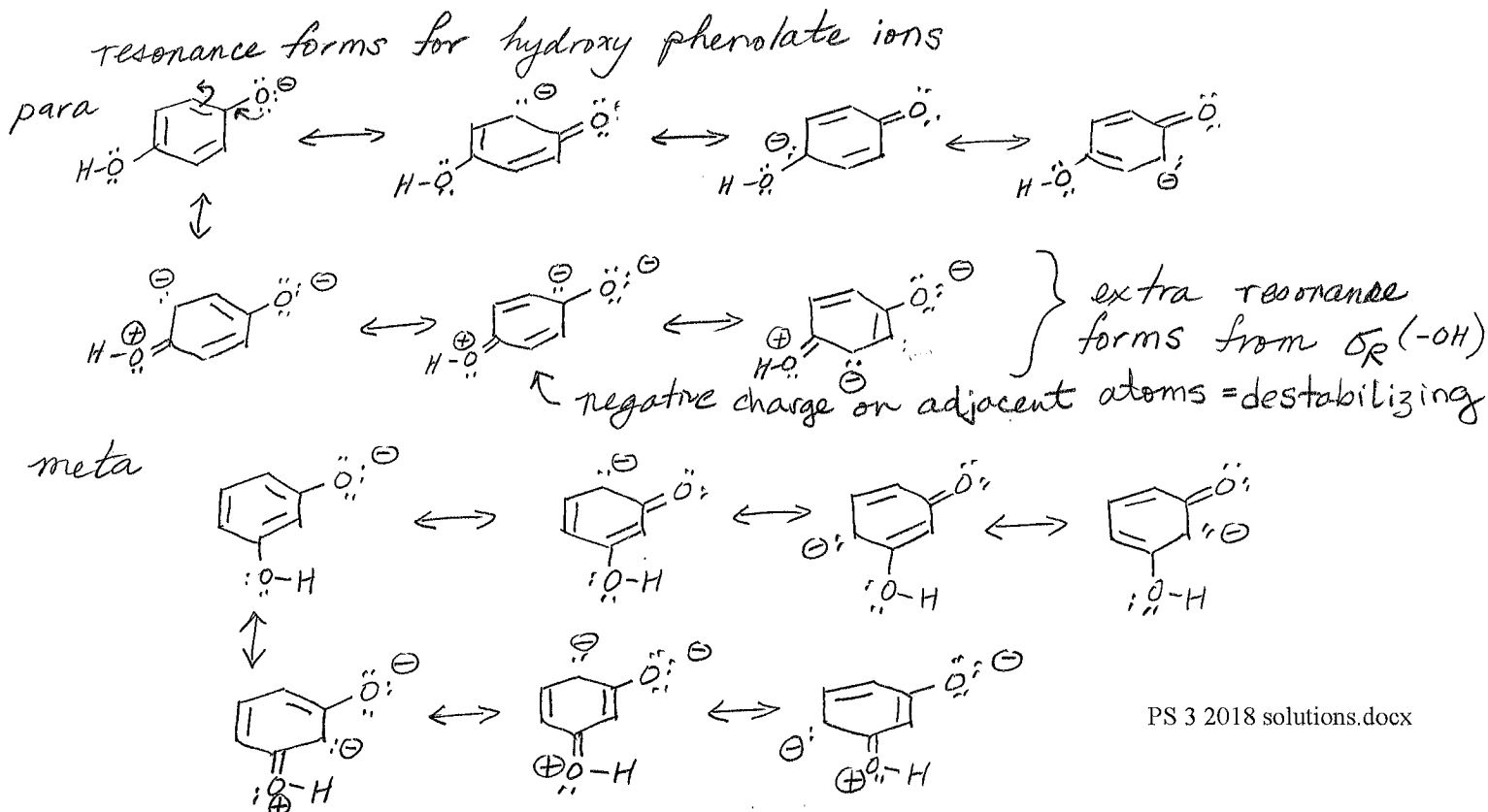
Substituent	σ_{meta}	σ_{para}	σ^-
-OH	0.13	-0.38	
-COCH ₃	0.38	0.50	0.82
-Cl	0.37	0.23	
-SO ₂ CH ₃	0.68	0.72	

- Why is σ_{meta} for the hydroxyl group (-OH) positive, whereas the value for σ_{para} is negative?
- Why is the modified σ^- value for the acetyl group (-COCH₃) more positive than either σ_{meta} or σ_{para} ?
- Why is a chloro substituent (-Cl) less electron withdrawing in the para position than the meta position?
- Why is the methyl sulfonyl group (-SO₂CH₃) a more electron withdrawing in the para than the meta position?

Solution:

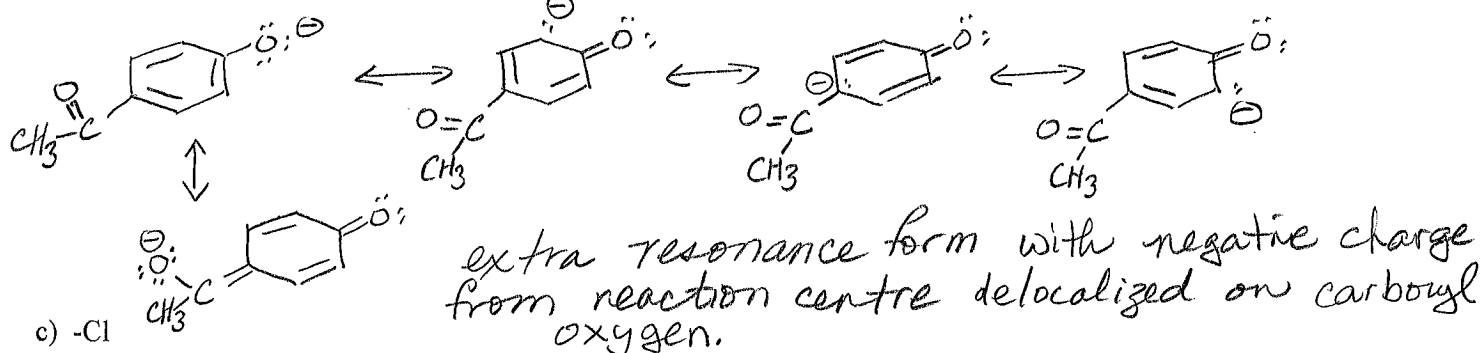
Recall, a $\sigma > 0$, corresponds to an electron withdrawing group (i.e., acid strengthening effect on benzoic acid). Furthermore, in the *meta* position, electronic effects are governed largely by inductive effects (differences in electronegativities), i.e., $\sigma_{meta} \sim \sigma_I$. However, in the *para* position both inductive and resonance contributions manifest and hence $\sigma_{para} \sim \sigma_I + \sigma_R$.

a) Since $\sigma_m = 0.13$ and $\sigma_p = -0.38$, the hydroxyl group is an electron withdrawing in the *meta* and but has a net electron donating effect in the *para* position. The oxygen is more electronegative than carbon and is therefore an EWG by induction, $\sigma_m \sim \sigma_I \sim 0.13$. In the *para* position, the -OH group is a powerful electron donor to the aromatic ring via resonance contributions involving the lone pair on oxygen (i.e., $\sigma_R \sim \sigma_p - \sigma_m \sim -0.51$). Hence, OH is electron withdrawing by inductive effectives and electron donating by resonance effects.



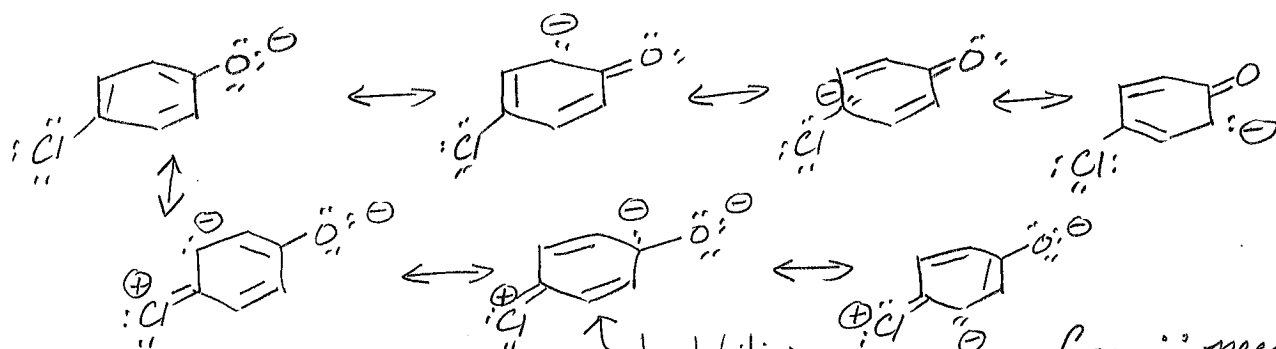
b) $-\text{COCH}_3$

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 $\sigma_R \sim \sigma_p - \sigma_m \sim 0.12$. 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 a negative charge from a conjugated reaction centre resides on the carbonyl oxygen contributes extra electron withdrawing ability of this substituent. Hence, the modified substituent constant, σ^- is greater than both σ_m and σ_p . See reaction electron density from reaction centre delocalized into the aromatic ring via resonance depicted below.



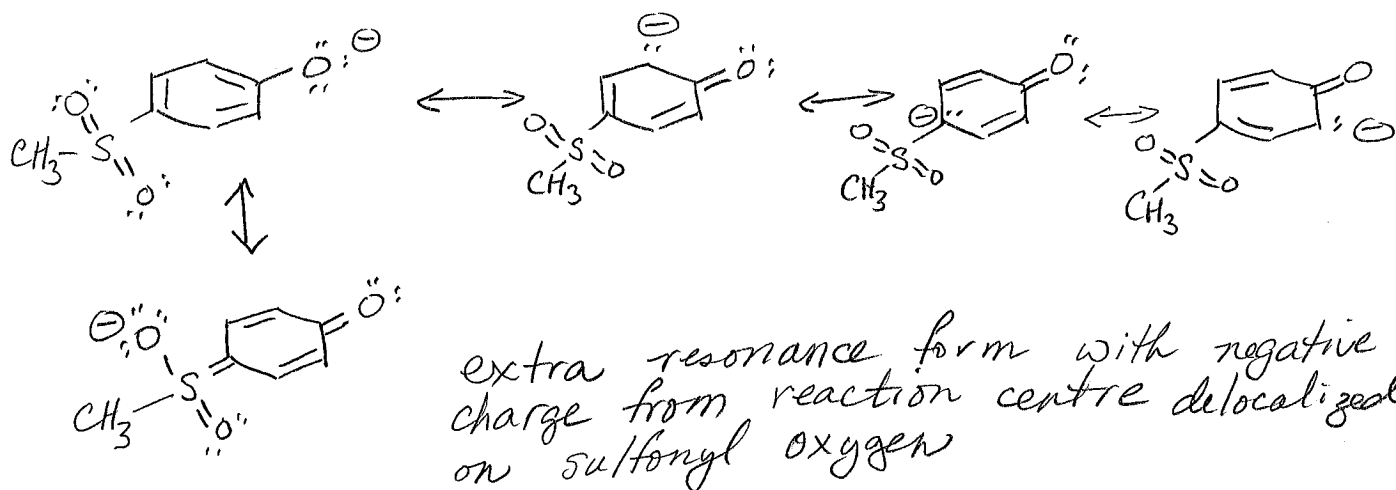
c) $-\text{Cl}$

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 $\sigma_R \sim \sigma_p - \sigma_m \sim -0.14$. This can be depicted in terms of the resonance forms for the *para* chloro substituent.



d) $-\text{SO}_2\text{CH}_3$

Since $\sigma_m = 0.68$ and $\sigma_p = 0.72$, a methyl sulfonyl group is a strong electron withdrawing group in both positions and hence withdrawing by both inductive and resonance effects. Hence, $\sigma_I \sim \sigma_m \sim 0.68$ and $\sigma_R \sim \sigma_p - \sigma_m \sim 0.04$. The resonance effects are not as pronounced as a result of the weaker orbital overlap between $2p$ orbitals on carbon and the $3p$ on sulfur, the effect is still observable as depicted below.



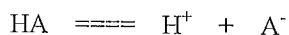
2. Derive an expression for the fractional abundance of the protonated (acidic) form of a monoprotic acid in terms of its pK_a and the pH of the solution.

Solution:

The fractional abundance of the acidic form of a monoprotic acid can be defined as;

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

Since we can write the acid dissociation as,



And the equilibrium constant is defined as,

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

Rearranging this expression to isolate $[A^-]$ yields;

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

Substituting into the fractional abundance expression gives,

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

Since, $K_a/[H^+]$ can be written as,

$$10^{\log\left(\frac{K_a}{[H^+]}\right)} = 10^{(\log K_a - \log[H^+])} = 10^{(-pK_a + pH)}$$

and the expression for fractional abundance can be written as;

$$f_{HA} = \frac{1}{1 + \frac{K_a}{[H^+]}} = \frac{1}{1 + 10^{(pH - pK_a)}}$$

3. 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).

Solution:

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

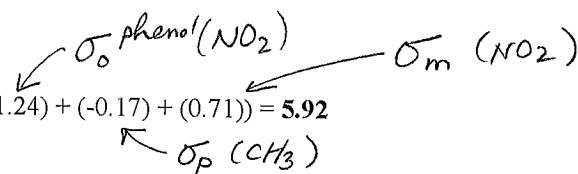
$$\log \left(\frac{K_a^{\infty}}{K_a^{(X)}} \right) = \rho \Sigma \sigma$$

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

4-methyl-2,5-dinitrophenol;

$$pK_a(\text{phenol}) = 9.92, \rho = 2.25$$

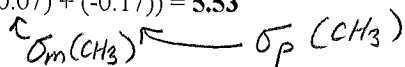
$$pK_a(4\text{-MDNP}) = 9.92 - 2.25 ((1.24) + (-0.17) + (0.71)) = 5.92$$



the conjugate acid of 3,4,5-trimethylaniline;

$$pK_a(\text{aniline}) = 4.63, \rho = 2.89$$

$$pK_a(3,4,5\text{-TMA}) = 4.63 - 2.89 (2(-0.07) + (-0.17)) = 5.53$$



At pH 7.70, $[H^+] = 2.0 \times 10^{-8} \text{ M}$ and for a monoprotic acid we can write,

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

Thus, $f_{(4\text{-MDNPhenolate})} = 0.986$ (98.6%)

and

$f_{(3,4,5\text{-TMA})} = 0.993$ (99.3%)

4. Use Excel to plot an overlay of the fractional abundance of the neutral and both ionized forms of ortho-phthalic acid over a pH range of 2 – 12 at 25°C ($pK_{a1} = 2.89$ and $pK_{a2} = 5.51$).

Solution:

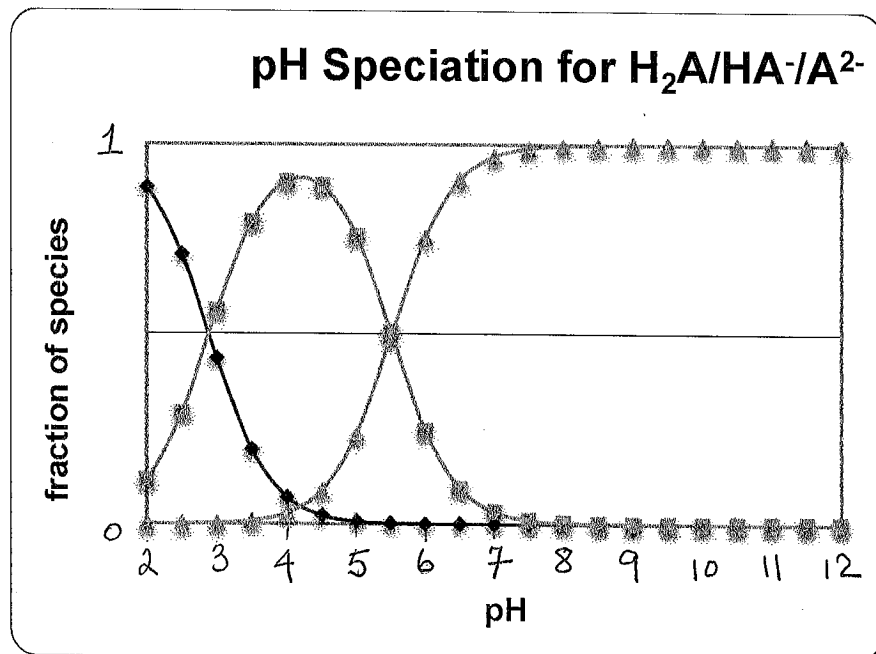
For a diprotic acid, we can write an expression for the fractional abundance of each $f_{(H_2A)}$, $f_{(HA^-)}$ and $f_{(A^{2-})}$ in terms of the acid dissociation constants as follows.

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

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

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

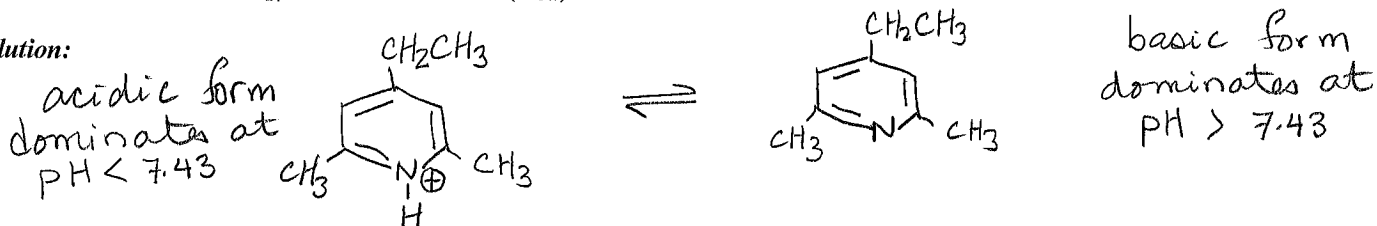
Using Excel to carry out repetitive calculations over a series of pH's ranging from pH = 2 to 12, and plotting the results yields the following. The predominate form/s will depend on the pH, with the acidic form at low pH ($< pK_{a1}$) and the dibasic form at high pH ($> pK_{a2}$). Note, although the 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_a s are well separated (e.g. $\Delta pK_a > 2$).



5. Describe the influence of changing the pH from 4 to 8 on each of the following for 4-ethyl-2,6-dimethyl pyridine ($pK_{ow} = -3.70$; $pK_a = 7.43$). Explain using chemical structures and/or mathematical expressions to illustrate your answer.

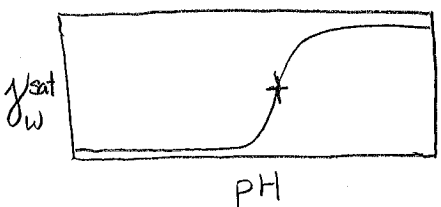
- a) aqueous activity coefficient (γ_w^{sat})
- b) air - water partition coefficient (K_{aw})
- c) octanol - water partition coefficient (K_{ow})

Solution:



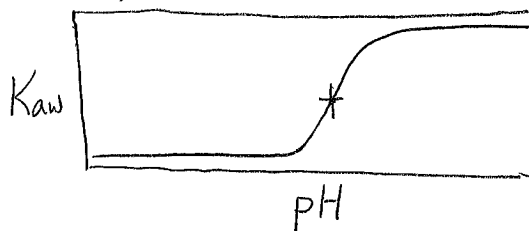
a)

γ_w^{sat} is inversely related to water solubility which will be greatly affected by pH. The protonated form will be much more water soluble and therefore have much lower γ_w^{sat} .



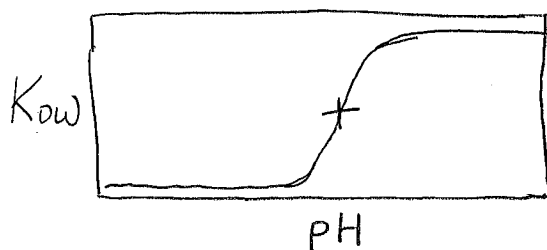
b)

K_{aw} is inversely related to water solubility $\approx P^0/c_w^{sat}$. Therefore, K_{aw} will be much lower at $pH < 7.43$.



c)

K_{ow} is inversely related to water solubility $\approx C_{oct}/c_w$. Therefore, K_{ow} will be much lower at $pH < 7.43$



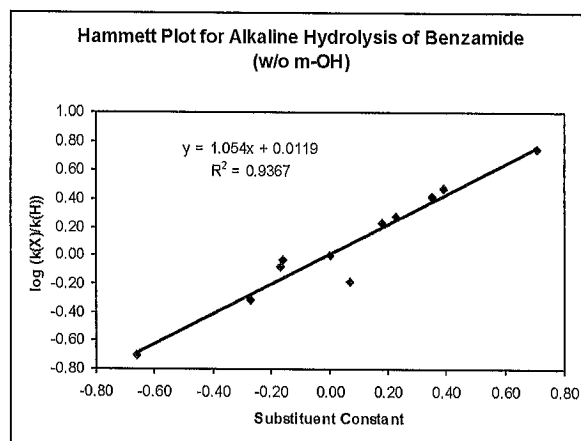
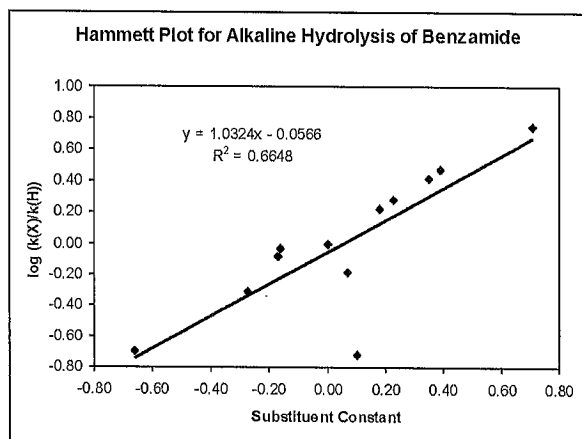
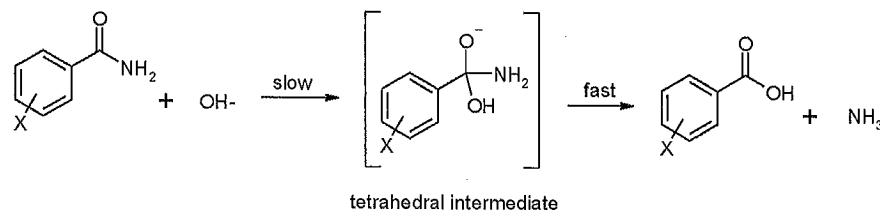
See further $D_{ow} = \alpha K_{ow}$
 ↑
 fractional abundance of neutral form

6. The relative rates of alkaline (base enhanced) 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.

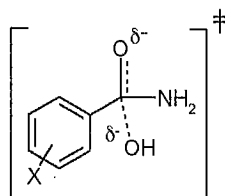
Substituent	Relative Rate	Substituent	Relative Rate	Substituent	Relative Rate
<i>m</i> -I	2.60	<i>m</i> -NO ₂	5.60	<i>p</i> -OCH ₃	0.49
<i>p</i> -I	1.69	H	1.00	<i>m</i> -NH ₂	0.93
<i>m</i> -Br	2.97	<i>m</i> -CH ₃	0.83	<i>p</i> -NH ₂	0.20
<i>p</i> -Br	1.91	<i>p</i> -CH ₃	0.65	<i>m</i> -OH	0.19

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 $\log(k(X)/k(H))$ vs σ to obtain the reaction constant (ρ) as the slope.



From the Hammett plots above, the reaction constant is determined to be $\rho = 1.05$. Since the reaction rate is faster in the presence of EWGs (e.g., -NO₂), 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 ($pK_a \sim 10$). 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.

7. The neutral hydrolysis of 4-nitrophenyl acetate (4-NPA) has a measured *pseudo* first order rate constant of $4.4 \times 10^{-5} \text{ s}^{-1}$ at room temperature and neutral pH.
- If the reaction constant for a series of substituted phenyl acetates is determined to be $\rho = 0.87$, what is the rate constant for the neutral hydrolysis of the unsubstituted phenyl acetate at this temperature?
 - Suggest a substituted phenyl acetate that will have a half life between 1 and 2 days?

Solution:

a) We can write the Hammett equation for the kinetics of this reaction using σ_p for $\text{NO}_2 = 0.78$

$$\log \left\{ \frac{k_N(\text{NO}_2)}{k_N(\text{H})} \right\} = \rho \sum \sigma_i = 0.87(0.78) = 0.68$$

Therefore, $k_N(\text{NO}_2)/k_N(\text{H}) = 10^{0.68} = 4.79$

In other words, the 4-NPA reacts 4.79 times faster than phenyl acetate under these conditions.

And the rate constant for the neutral hydrolysis of phenyl acetate is therefore,

$$k_N(\text{H}) = 9.19 \times 10^{-6} \text{ s}^{-1}$$

b) In general, the half-life is related to the first order rate constant as follows;

$$t_{1/2} = 0.693/k$$

So the half-life of 4-NPA is $1.58 \times 10^4 \text{ s} = 4.4 \text{ hr}$ and that of phenyl acetate is $7.54 \times 10^4 \text{ s} = 21 \text{ hr}$. Since we want a substituted phenyl acetate with a half-life between 24 and 48 hrs (1 - 2 days), the rate constant for neutral hydrolysis will be between 4 and $8 \times 10^{-6} \text{ s}^{-1}$. This can be achieved by adding electron donating groups to the phenyl ring of phenyl acetate.

$$\log \left\{ \frac{k_N(\text{X})}{k_N(\text{H})} \right\} = \log \left(\frac{4 \times 10^{-6} \text{ s}^{-1}}{9.19 \times 10^{-6} \text{ s}^{-1}} \right) = \rho \sum \sigma_i = 0.87 \sum \sigma_i = -0.36$$

Therefore, for a $k_N(\text{X}) = 4 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} \sim 2$ days), we need $\sum \sigma_i = -0.36/0.87 = -0.41$

$$\log \left\{ \frac{k_N(\text{X})}{k_N(\text{H})} \right\} = \log \left(\frac{8 \times 10^{-6} \text{ s}^{-1}}{9.19 \times 10^{-6} \text{ s}^{-1}} \right) = \rho \sum \sigma_i = 0.87 \sum \sigma_i = -0.06$$

And for a $k_N(\text{X}) = 8 \times 10^{-6} \text{ s}^{-1}$ ($t_{1/2} \sim 1$ days), we need $\sum \sigma_i = -0.06/0.87 = -0.07$

Hence, we are looking for a substituent or substituents with a total electron donating ability ($\sum \sigma$ between -0.07 and -0.41). There are numerous possibilities such as;

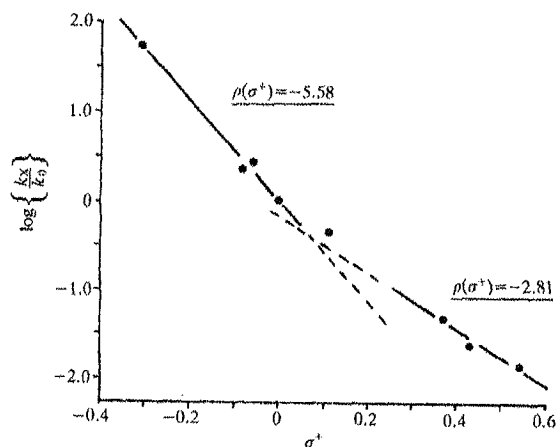
meta methyl ($\sigma_m = -0.07$)

para hydroxyl ($\sigma_p = -0.37$)

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.

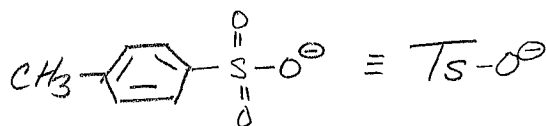


- Look up the chemical structure of a tosylate group and indicate if you think it is likely to be a relatively 'good' (i.e., stabilized) leaving group.
- Why are the modified σ^+ values used instead of σ in the Hammett plot?
- Explain the magnitude and sign of each of the two reaction constants and provide mechanism/s consistent with these observations.



Solution:

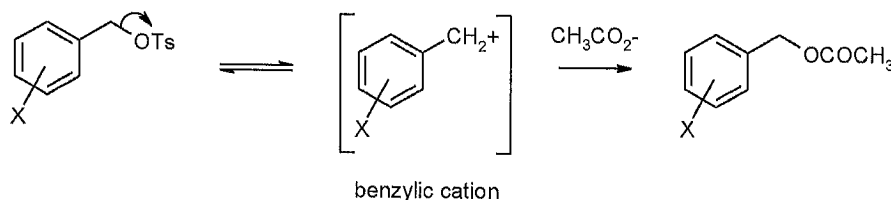
A tosylate group is a good leaving group by virtue of the formation of the resonance stabilized tosylate ion, shown below.



conjugate base of sulfonic acid \therefore stabilized anion

The modified substituent constants (σ^+) are used in this case as the developing positive charge at the reaction centre is on a benzylic carbon. This charge can be resonance stabilized on to the substituent ($-X$), where possible.

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.



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 where the S_N2 reaction predominates.

