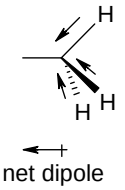
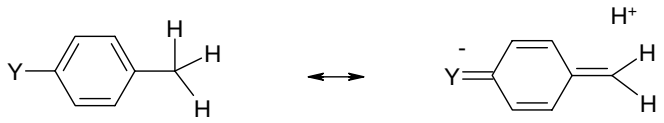
Problem Set #3 – Solutions

1. a) $-CH_3$ (methyl group)
Since carbon (EN = 2.5) is slightly more electronegative than hydrogen (EN = 2.2), there will be a small dipole moment pulling electron density away from hydrogen toward carbon. This slight build up of electron density on the carbon results in the methyl group having an electron donating effect by induction; note both σ_m and σ_p values are < 0 indicating methyl is EDG in both positions.



meta vs *para*
Since σ_p = -0.17 and σ_m = -0.07, we observe that a methyl substituent in the *para* position is more electron donating than in the *meta* position. Although there are no formal resonance contributions from the *sp*^{3} hybridized carbon atom, there is a special type of resonance contribution known as *hyper-conjugation* which results in an additional electron donation associated with the *para*-methyl group.

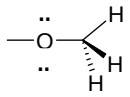


hyper-conjugation

$-CH_3$ vs $-CF_3$
Replacing hydrogen atoms with the much more electronegative fluorine atom (EN = 4.0), results in electron withdrawing character as evidenced by the positive values for the substituent constants σ_m and σ_p. Again, *hyper-conjugation* explains the additional electron withdrawing power of the *para*-trifluoromethyl group.

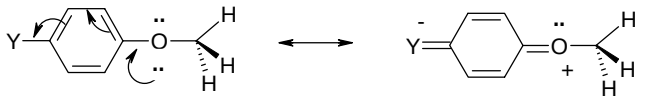
b) $-OCH_3$ (methoxy group)

The methoxy group is electron withdrawing by the inductive effect of the oxygen atom, since the electronegativity of oxygen is 2.6. This is reflected in the positive value for σ_m.



meta vs *para*

Recall that *meta* substituents only contribute inductive effects, whereas *para* substituents contribute both indictive and resonance effects. Thus, $\sigma_m \sim \sigma_I \sim 0.07$. In the *para* position, the lone pair of electrons on the oxygen can be donated back into the aryl ring by resonance giving rise to an additional resonance structure, shown below. Since $\sigma_p < 0$, the *para*-methoxy substituent is an EDG (even though the same group is an EWG in the meta position). Comparing the σ values for *meta* and *para*, we can see that the electron donating resonance effects (σ_R) dominate over the electron withdrawing inductive effect (σ_I). Since $\sigma_p \sim \sigma_I + \sigma_R$, we can estimate the $\sigma_R \sim -0.31$.



$-OCH_3$ vs $-OCF_3$

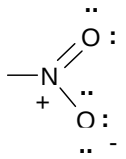
Replacing the hydrogens with fluorines results in a much more electron withdrawing substituent as can be seen by the positive values of σ_m and σ_p. Since $\sigma_p = 0.35$, we can see that in this case the inductive effect of $-OCF_3$ dominates over the resonance contribution.

$\sigma_m \sim \sigma_I \sim 0.40$

$\sigma_p \sim \sigma_I + \sigma_R, \therefore \sigma_R \sim -0.05$

c) $-NO_2$ (nitro group)

The nitro group is electron withdrawing via inductive and resonance effects as can be seen by the large positive σ values. The large inductive effect of NO_2 is the result of the formal + charge located on nitrogen. This electron deficiency withdraws electron density from the aryl ring.

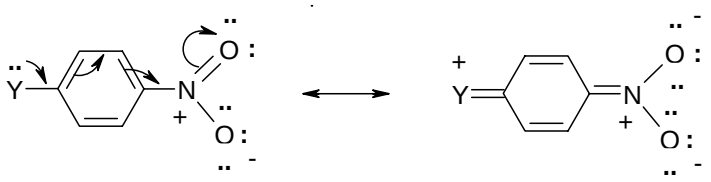


meta vs *para*

The difference in the substituent constants between *meta* and *para* positions is due to the additional resonance effect, which in this case is also electron withdrawing as can be seen in the resonance structure shown below.

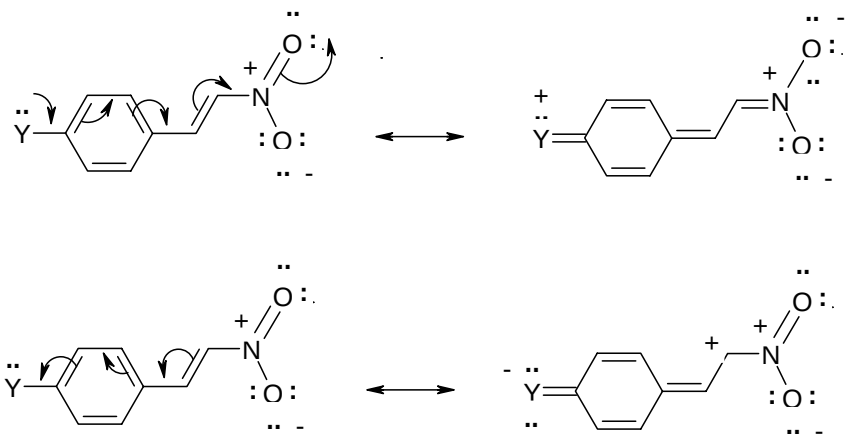
$\sigma_m \sim \sigma_I \sim 0.71$

$\sigma_p \sim \sigma_I + \sigma_R, \therefore \sigma_R \sim 0.07$



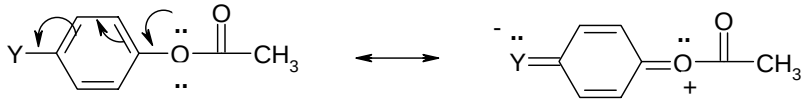
$-NO_2$ vs $-CH=CH-NO_2$

Adding an ethenyl group (-CH=CH-) between the aryl ring and the nitro group results in similar results. The substituent is still an EWG in either position ($\sigma > 0$), however the magnitude of the substituent constant is smaller since the nitro group is farther removed from the reactive centre. In the case of the *para*-$CH=CH-NO_2$ group, there is a slightly offsetting effect since the ethenyl group is electron donating by resonance.



minor

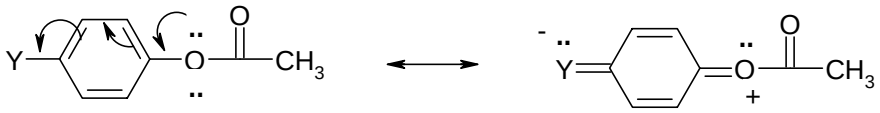
d) -$OCOCH_3$ (alkyl ester group)
Since both σ_m and σ_p are positive, this substituent is electron withdrawing due to the electronegativity of the oxygen atom.



meta vs *para*
However, in the *para* position the lone pair electrons can be donated back through resonance (shown structure below).

$$\sigma_m \sim \sigma_I \sim 0.39$$
$$\sigma_p \sim \sigma_I + \sigma_R, \therefore \sigma_R \sim -0.08$$

Note that the electron donating resonance contribution in this case is considerably less than observed for $–OCH_3$ ($\sigma_R \sim -0.31$) due the fact that the lone pair electrons on the ester are also delocalized out onto the carbonyl oxygen.



$-OCOCH_3$ vs $–NHCOCH_3$
The smaller electronegativity of nitrogen (EN = 3.0) relative to oxygen (EN = 3.5) results in smaller inductive electron withdrawing effect for the amide substituent versus the ester ($\sigma_m \sim \sigma_I \sim 0.21$). In the case of the para substituted amides, the electron withdrawing inductive effects are offset by an equal resonance electron donating effect to yield a resultant $\sigma_p = 0$. Thus, σ_R is roughly -0.21.

2. 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.

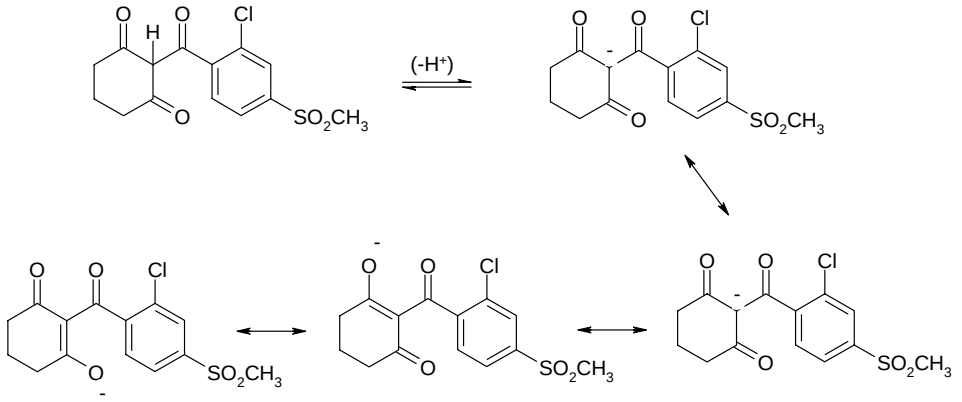
$$\log\left(\frac{K_a^{(X)}}{K_a^{(H)}}\right) = \rho \Sigma \sigma$$
$$\therefore pK_a(X) = pK_a(H) - \rho \Sigma \sigma_x$$

a) PCP; pKa(phenol) = 9.92, ρ = 2.25
pKa(PCP) = 9.92 – 2.25 (2(0.68) + 2(0.37) + (0.23)) = **4.68**

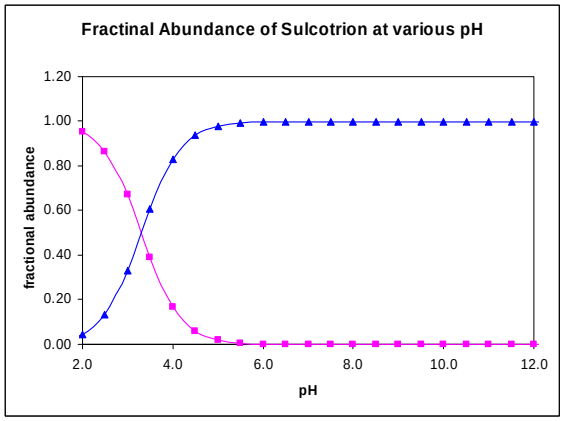
b) 3,4-DMA; pKa (aniline) = 4.63, ρ = 2.89
pKa(3,4-DMA) = 4.63 – 2.89 ((-0.07) + (-0.17)) = **5.32**

c) 2,4,5-T; pKa (2-chlorophenoxyacetic acid) = 3.05, ρ = 0.30
pKa(2,4,5-T) = 3.05 – 0.030(0.37 + 0.23) = **2.87**

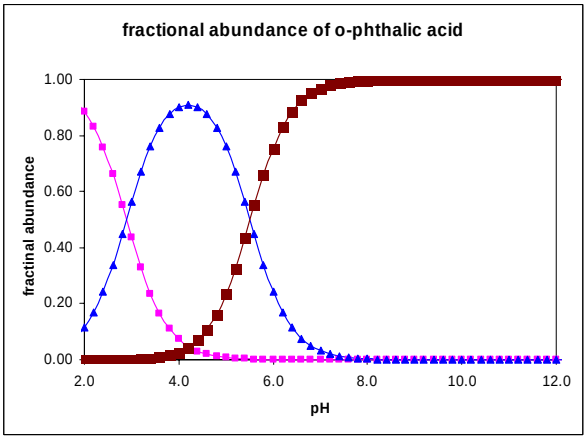
3. a) The hydrogen atom α- to the three carbonyl groups is the most acidic due to the extensive resonance stabilization of the negative charge in the conjugate base.



b) Recall, the pH = pK_a when [HA] = [A^-]. Thus, at this pH the fractional abundance of the protonated and deprotonated form is 0.5. Since the pK = 3.31, this is the pH where the fractional abundance curves 'crossover'.



c) ortho-phathalic 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}).



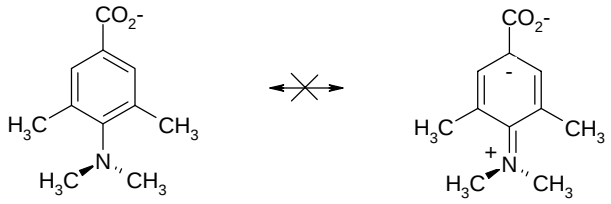
4. We can calculate the pK_a for each of the trisubstituted benzoic acids using the Hammett equation and a ρ value of 1.60, a $pK_a(H) = 5.71$ and the sum of the three substituent constants. In so doing, we are making the assumption that each substituent will have the same electronic effects in 3,4,5-trisubstituted 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 effect of steric hinderence on resonance contributions.

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

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

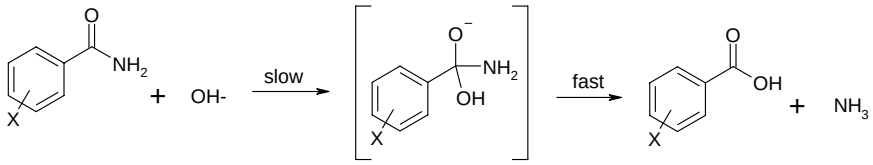
X	$N(CH_3)_2$	NH_2	Cl	Br	CN	CO_2CH_3	NO_2
Exp pKa	6.23	6.88	5.59	5.55	4.90	5.44	4.91
Calc pKa	7.26	6.99	5.57	5.57	4.88	5.21	4.69
Difference	1.03	0.11	0.02	0.02	0.08	0.23	0.22

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.

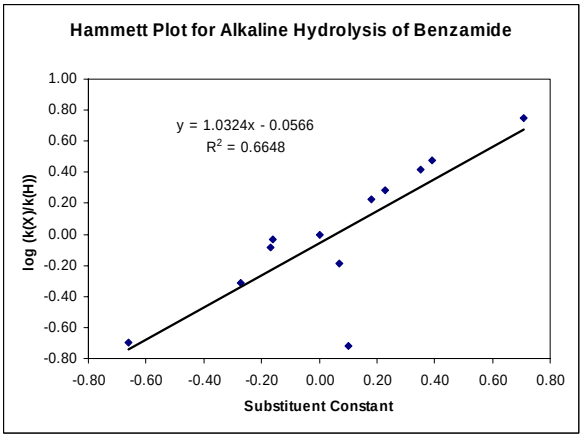


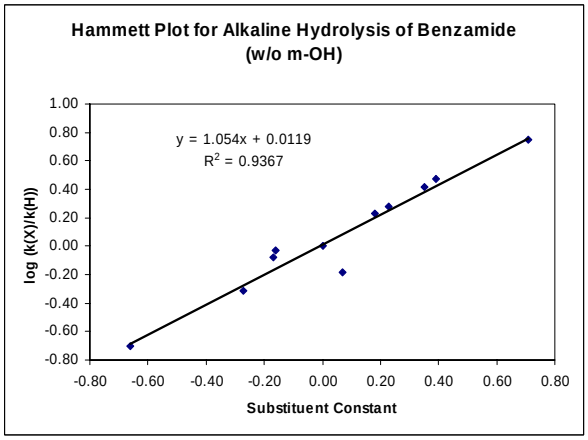
Note that the agreement is better for NH_2 than $N(CH_3)_2$ since it is smaller in size and the out of plane twist is not as dramatic such that some of it's resonance contribution is retained.

5. 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.

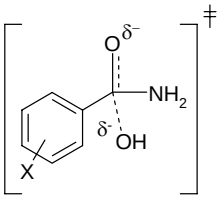


tetrahedral intermediate

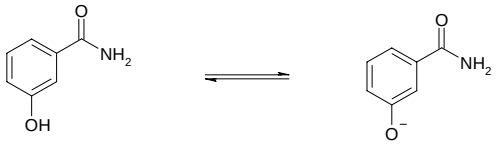




From the Hammett plots above, the reaction constant is determined to be ρ = 1.05. Since the reaction rate is faster in the presence of EWGs (e.g., -NO_2), we can deduce that this reaction involves the build up of electron density at the reaction centre of the transition state. This is consistent with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

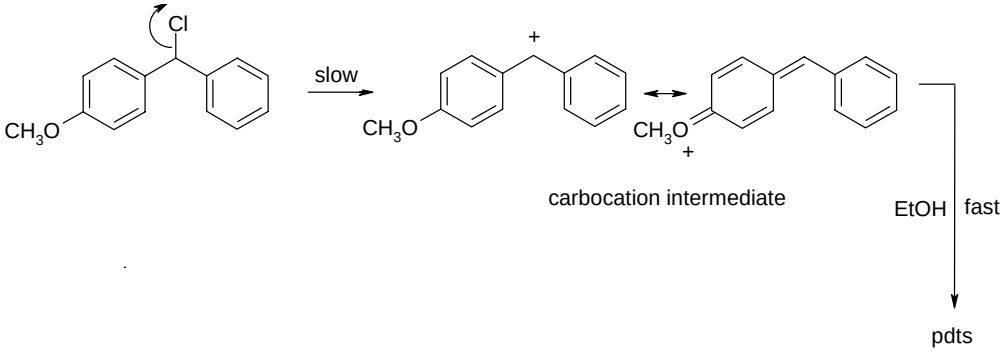


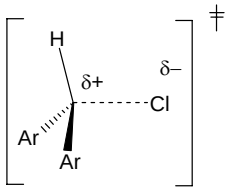
The one compound that does not seem to follow the trend is *meta*-hydroxybenzamide, which apparently reacts much slower than one would expect based on the value of the substituent constant (σ_m = 0.10). A possible explanation for this is the deprotonation of the OH substituent in alkaline solution (pK_a ~ 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.



σ_I = 0.1 $\quad$ σ_I << 0

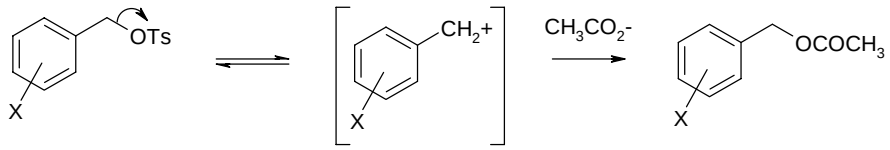
6. This is a nucleophilic substitution reaction in which ethanol is acting as a nucleophile and displacing the chloride leaving group. The large negative ρ value (-5.51) suggests a significant decrease in electron density (build up of positive charge) at the reaction centre of the transition state. The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

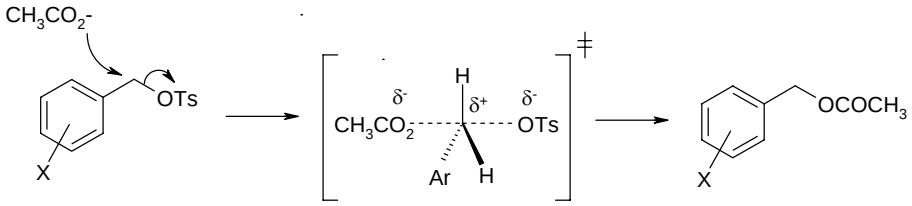
7. This is a substitution reaction in which –OTs is the leaving group and the acetate ion is the incoming nucleophile. There appears to be two linear regions in the Hammett plot with different slopes (i.e., differing susceptibilities to substituent effects). For a series of electron donating groups ($\sigma+ < 0$), 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.



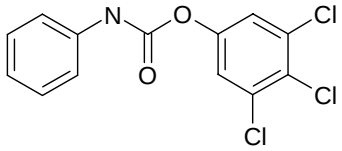
benzylic cation

Note the direct resonance capability of benzylic cation with substituents, hence the use of $\sigma+$.

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 sensentive to the 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.



8. 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).



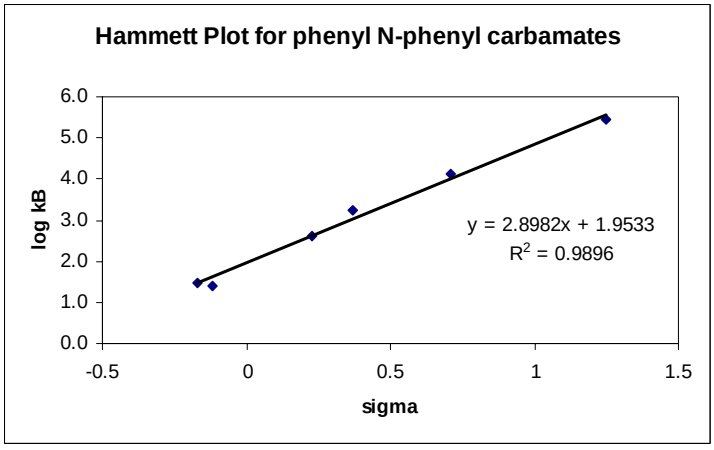
$$\log\left(\frac{k_B^{(X)}}{k_B^{(H)}}\right) = \rho \Sigma \sigma$$

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

So a plot of log log $k_B^{(X)}$ versus σ, will yield a slope of ρ and an 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.



Thus, log $k_B^{(X)}$ = 2.90 (0. 97) + 1.95 = 4.76

$\therefore$ k_B (3,4,5-trichloro) = $10^{4.76}$ = 5.8 x 10^4 M^{-1} s^{-1}