

Physical Organic Chemistry

Reading: Lecture notes – Physical Organic Chemistry
 Clayden, Greaves & Warren Edition 2 Chapters 12, & 39
 Modern Physical Organic Chemistry by Anslyn and Dougherty
 Advanced Organic Chemistry, Part A, 5th Edition by Carey and Sundberg

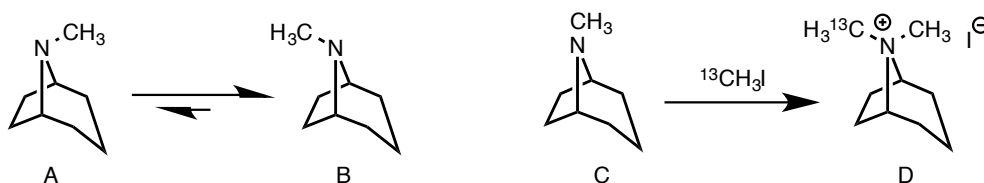
Topics for notes:

You need to be familiar with the following concepts which are useful in the determination of reaction mechanisms and will have been covered in lectures:

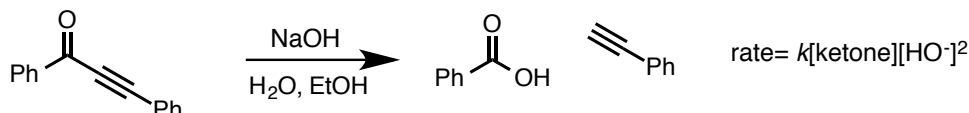
Energy diagrams; Rate Determining Step; simple kinetic expressions; the Hammond Postulate; Curtin-Hammett principle; principle of microscopic reversibility; kinetic and thermodynamic control; isotopic labeling; kinetic isotope effects; tautomerism and conformational equilibrium; solvent effects; simple linear free energy relationships; the Hammett equation; non-linear Hammett plots; specific and general acid, base and nucleophilic catalysis.

Tutorial Problems

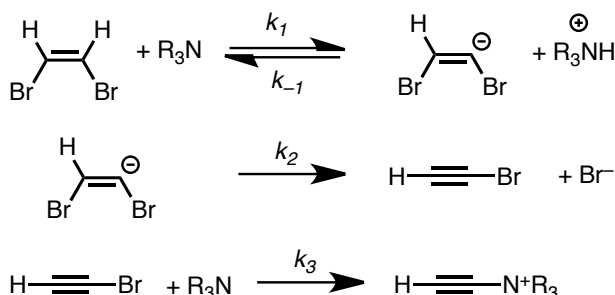
1) Conformers **A** and **B** of the amine **C** are in rapid equilibrium. Explain why conformer **B** is more stable than conformer **A** and why the diastereoselective alkylation of **C** gives the quaternary ammonium salt **D**.



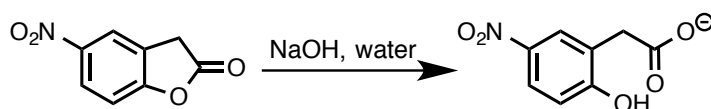
2) The reaction below shows third order kinetics, suggest a mechanism.



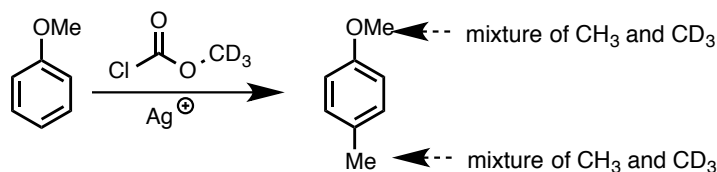
3) Write a rate law that would apply to the rate of product formation where the second step is rate-determining and the first step is in equilibrium.



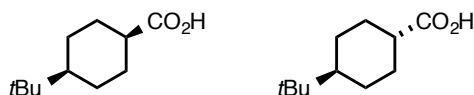
4) Hydrolysis of the lactone below could potentially proceed by (at least) three different mechanisms: i) $B_{AC}2$ (i.e. standard tetrahedral mechanism), ii) *via* an S_NAr reaction, iii) *via* formation of an enolate followed by a ketene. Draw these three possible mechanisms. How would a) deuterium labelling, b) ^{18}O labelling, help to distinguish the mechanisms.



5) Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is reisolated, at 50% reaction, its methyl group is also labelled.

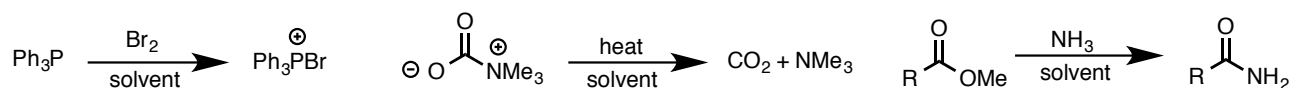


6) Predict which of the two diastereomers of the carboxylic acids shown has the lower pK_a in water.

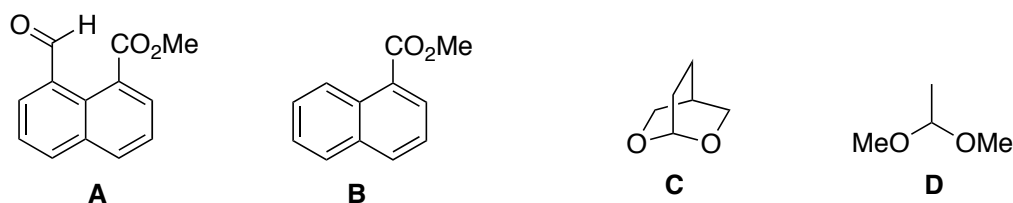


7) In water, acetic acid is about three times more acidic than the pyridinium ion (C₅H₅N⁺H). In MeOH, the relative acidities reverse. The pyridinium ion dissociates about the same amount in both solvents, but acetic acid dissociates almost 10000 times less in MeOH. Explain the reversal.

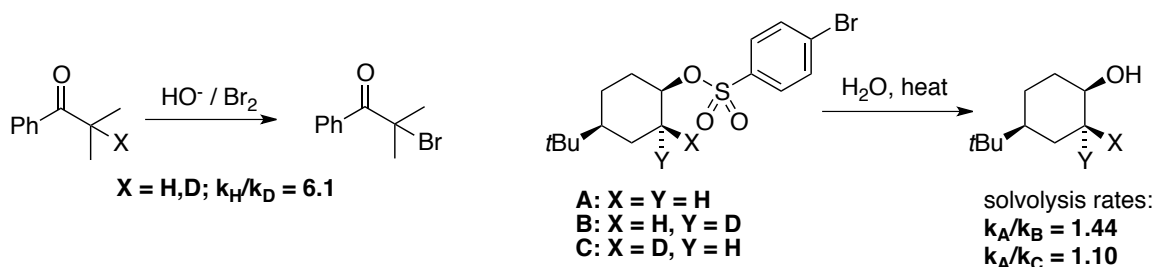
8) What would be the effect of solvent changes on these reactions? Would the reactions be accelerated or retarded by a change from a polar to a non-polar solvent?



9) Explain why compound **A** is hydrolysed in base 8300 times faster than compound **B**, and compound **C** is hydrolysed in acid 100000 times faster than compound **D**.

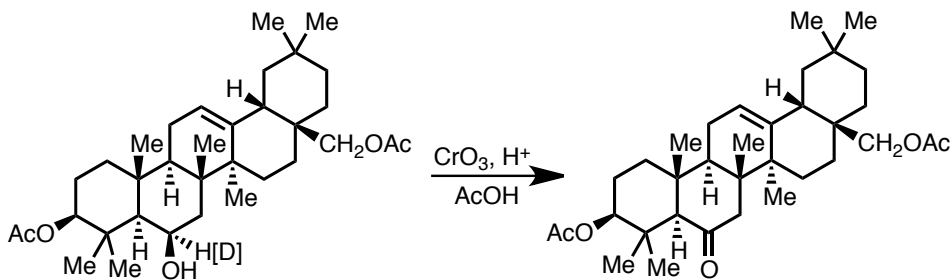


10) What do the measured kinetic isotope effects tell us about the mechanisms of the following reactions?

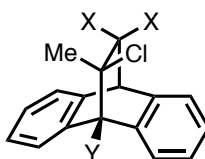


11) Suggest mechanistic interpretations for the following observations.

(a) Chromium trioxide oxidations of secondary alcohols are normally associated with a primary isotope effect of about 7.0 for CHO_H vs CDO_H. The case below is an exception having a primary isotope effect of 1.0.



(b) The rate constant for the solvolysis of X=H, Y=H is 1.14 times greater than that of the dideutero X=D, Y=H but almost identical (0.99) with that of the monodeutero X=H, Y=D.



12) The Hammett equation can be written as $\log_{10}(k_X/k_H) = \rho\sigma_X$

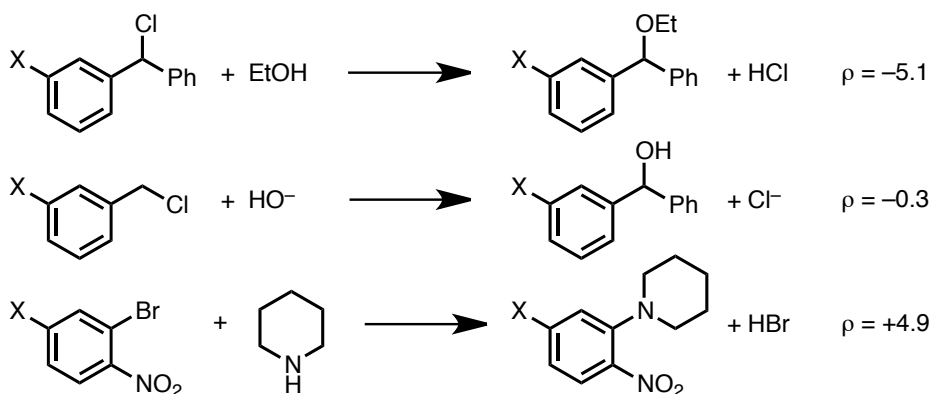
(a) How is the substituent constant σ_X defined?

(b) Put the following substituents in order of increasing σ_X value and say whether each σ_X value is positive or negative. Justify your answer.

Para-NO₂, *meta*-CH₃, *para*-NH₂, *para*-C≡N, *meta*-OMe

(c) How is the Hammett reaction constant ρ defined? Explain why the Hammett equation is called a *linear free-energy relationship*.

(d) Explain how Hammett reaction constant can be used to elucidate reaction mechanisms, using the following reactions to illustrate your answer.



(e) Why are *ortho*-substituents normally excluded from Hammett relationships?

(f) Discuss the possible causes for non-linear Hammett plots

13) Interpret as fully as possible the following data concerning the reaction of $\text{PhC}\equiv\text{CH}$ with Cl_2 .

(a) Phenyl acetylene reacts with chlorine in AcOH at 25 °C according to the rate law:

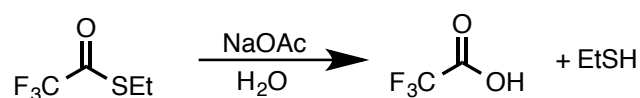
$$-d[\text{Cl}_2]/dt = k[\text{Cl}_2][\text{PhC}\equiv\text{CH}]$$

(b) The Hammett reaction constant for this reaction ρ (obtained from a series of $\text{ArC}\equiv\text{CH}$) is -4.2 , correlating better with σ^+ than σ . For comparison, the acid catalyzed hydration of $\text{ArC}\equiv\text{CH}$ to ArCOMe has a ρ value of -4.3 , also correlating better with σ^+ than σ .

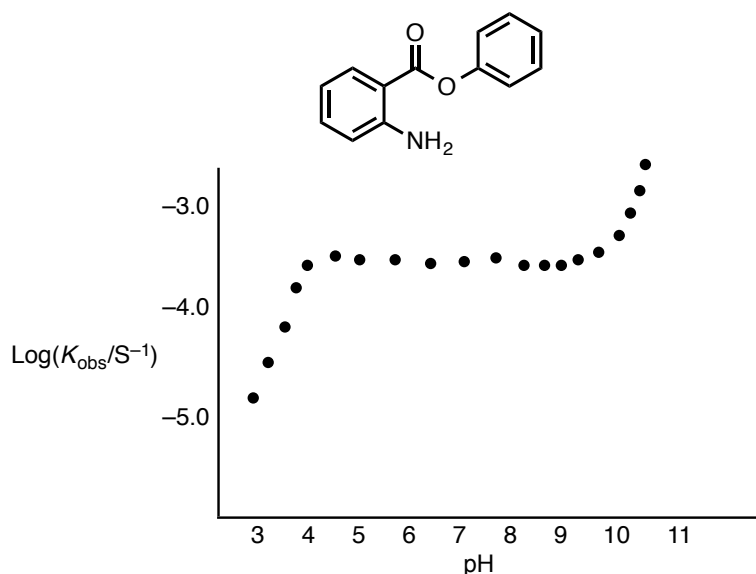
(c) Four main products are obtained: two pairs of isomers formula $\text{C}_8\text{H}_6\text{Cl}_2$ and $\text{C}_{10}\text{H}_9\text{ClO}_2$. The isomers of $\text{C}_{10}\text{H}_9\text{ClO}_2$ both yield $\text{C}_8\text{H}_7\text{ClO}$ on acidic aqueous work-up. On treatment with zinc and AcOH, this compound is converted into $\text{C}_8\text{H}_8\text{O}$, which has a ^1H NMR (CDCl_3): δ 2.60 (s, 3H), 7.2-7.7 (m, 3H), 7.8-8.3 (m, 2H); and infra-red (film): ν_{max} 1685 cm^{-1} .

(d) The two isomers of formula $\text{C}_8\text{H}_6\text{Cl}_2$ are produced in nearly equal amounts.

14) Between pH 2 and 7 the rate of hydrolysis of this ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion in the buffer solution and the reaction goes twice as fast in H_2O as in D_2O . Suggest a mechanism for the pH-independent hydrolysis. Above pH 7 the rate increases with pH. What kind of change is this?



15) What does the measured pH rate profile for hydrolysis of phenyl 2-aminobenzoate in water at 50 °C (given below) tell us about the mechanism of hydrolysis at different pH ranges? Propose relevant mechanisms.



16) The following reaction may proceed by elimination followed by conjugate addition. What experiments could you propose to support (or disprove) this mechanism?

