

Determining reaction mechanisms

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Connections

Building on:

- Mainly builds on **ch13**
- Acidity and basicity **ch8**
- Carbonyl reactions **ch6, ch12, & ch14**
- Nucleophilic substitution at saturated carbon **ch17**
- Controlling stereochemistry **ch16, ch33, & ch34**
- Eliminations **ch19**
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Arriving at:

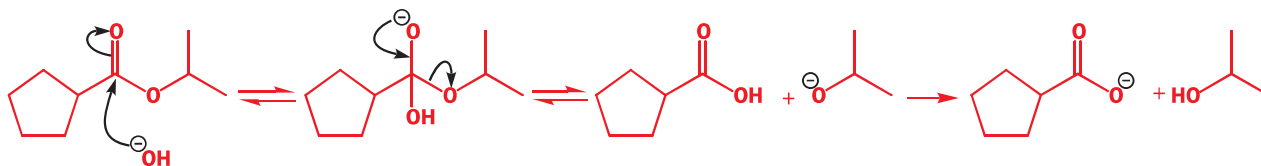
- Classes and types of mechanisms
- Importance of proposing a mechanism
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Looking forward to:

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- The chemistry of life **ch49–ch51**

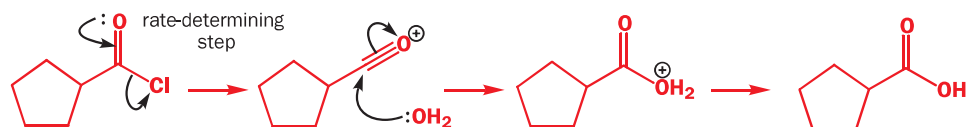
There are mechanisms and there are mechanisms

If you were asked to draw the mechanism of an ester hydrolysis in basic solution you should have no trouble in giving a good answer. It wouldn't matter if you had never seen this particular ester before or even if you knew that it had never actually been made, because you would recognize that the reaction belonged to a class of well known reactions (carbonyl substitution reactions, Chapter 12) and you would assume that the mechanism was the same as that for other ester hydrolyses. And you would be right—nucleophilic attack on the carbonyl group to form a tetrahedral intermediate is followed by loss of the alkoxide leaving group and the formation of the anion of the carboxylic acid.



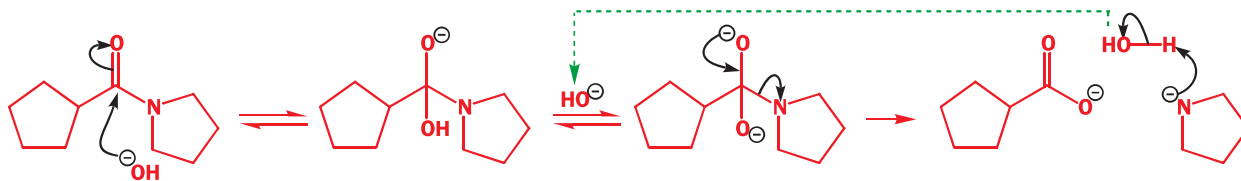
But someone at some time had to determine this mechanism in full detail. That work was done in the 1940s to 1960s and it was done so well that nobody seriously challenges it. You might also recall from Chapter 13 that, if we change the carbonyl compound to an acid chloride, the mechanism may change to an S_N1 type of reaction with an acylium ion intermediate because the leaving group is now much better: Cl^- is more stable (less basic) than RO^- . It would not be worth using hydroxide for this reaction: as the first step is the slow step, water will do just as well. Again someone had to determine this mechanism, had to show which was the slow step, and had to show that leaving group ability depended on pK_{aH} .

■ The link between leaving group ability and pK_{aH} was discussed in Chapter 12.



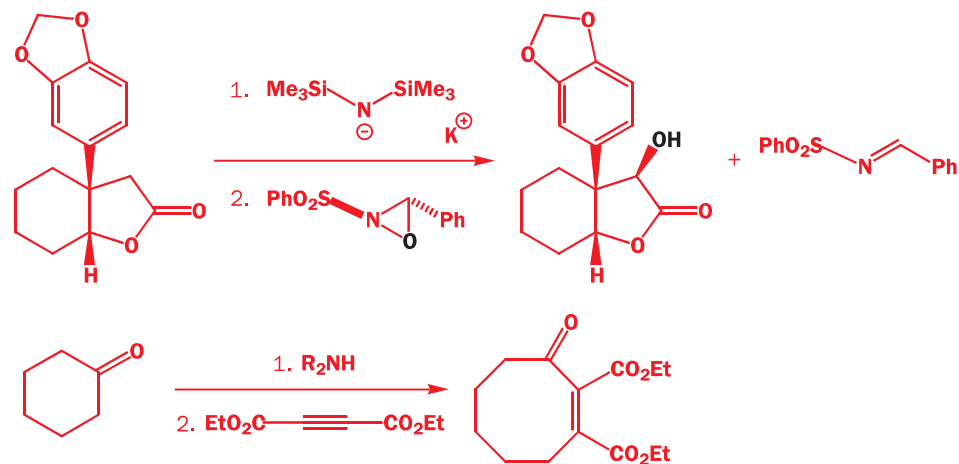
■ This chemistry was discussed in Chapter 13.

If the reaction were the hydrolysis of an amide, you might remember from Chapter 13 that third-order kinetics are often observed for the expulsion of such bad leaving groups and that this extra catalysis makes it worthwhile using concentrated base. Again, someone had to find out that: (1) the slow step is now the decomposition of the tetrahedral intermediate; (2) there are third-order kinetics involving two molecules of hydroxide; and (3) the first molecule acts as a nucleophile and the second as a base.



These reactions are versions of the same reaction. For you, writing these mechanisms chiefly means recognizing the type of reaction (nucleophilic substitution at the carbonyl group) and evaluating how good the leaving group is. For the original chemists, determining these reaction mechanisms meant: (1) determining exactly what the product is (that may sound silly, but it is a serious point); (2) discovering how many steps there are and the structures of the intermediates; (3) finding out which is the slow (rate-determining) step; and (4) finding any catalysis. This chapter describes the methods used in this kind of work.

Supposing you were asked what the mechanisms of the next two reactions might be. This is a rather different sort of problem as you probably don't recognize any of these reagents and you probably cannot fit any of the reactions into one of the classes you have seen so far. You probably don't even see at once which of the three main classes of mechanism you should use: ionic; pericyclic; or radical.

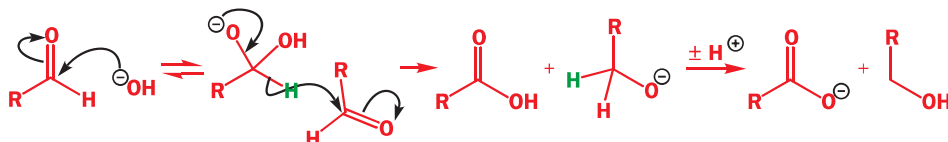


There are two types of answer to the question: 'What is the mechanism of this reaction?' You may do your best to write a mechanism based on your understanding of organic chemistry, moving the electrons from nucleophiles to electrophiles, choosing sensible intermediates, and arriving at the right products. You would not claim any authority for the result, but you would hope, as an organic chemist, to produce one or more reasonable mechanisms. This process is actually an essential preliminary to answering the question in the second way—'What is the real, experimentally verified, mechanism for the reaction?' This chapter is about the second kind of answer.

Determining reaction mechanisms—the Cannizzaro reaction

So how do we know the mechanism of a reaction? The simple answer is that we don't for certain. Organic chemists have to face situations where the structure of a compound is initially thought to be one thing but later corrected to be something different. The same is true of mechanisms. It is the nature of science that all we can do is try to account for observations by proposing theories. We then test the theory by experiment and, when the experiment does not fit the theory, we must start again with a new theory. This is exactly the case with mechanisms. When a new reaction is discovered, one or more mechanisms are proposed; evidence is then sought for and against these mechanisms until one emerges as the best choice and that remains the accepted mechanism for the reaction until fresh evidence comes along that does not fit the mechanism.

We are going to look at one reaction, the Cannizzaro reaction, and use this to introduce the different techniques used in elucidating mechanisms so that you will be able to appreciate the different information each experiment brings to light and how all the pieces fit together to leave us with a probable mechanism. Under strongly basic conditions, an aldehyde with no α hydrogens undergoes disproportionation to give half alcohol and half carboxylate. Disproportionation means one half of the sample is oxidized by the other half, which is itself reduced. In this case, half the aldehyde reduces the other half to the primary alcohol and in the process is oxidized to the carboxylic acid. Before the discovery of LiAlH_4 in 1946, this was one of the few reliable ways to reduce aldehydes and so was of some use in synthesis.



The mechanism we have drawn here is slightly different from that in Chapter 27 where we showed the dianion as an intermediate. The two reactions are related by base catalysis as we shall see. Now for some of the evidence and some of the alternative mechanisms that have been proposed for the Cannizzaro reaction. Most of these have been eliminated, leaving just the ones you have already met. Finally, we will see that even these mechanisms do not explain everything absolutely.

Proposed mechanism A—a radical mechanism

Early on it was thought that the hydrogen transfer might be taking place via a radical chain reaction. If this were the case, then the reaction should go faster if radical initiators are added and it should slow down when radical inhibitors are added. When this was tried, there was no change in the rate, so this proposed mechanism was ruled out.

Kinetic evidence for an ionic mechanism

The first piece of evidence that must be accounted for is the rate law. For the reaction of benzaldehyde with hydroxide, the reaction is first-order with respect to hydroxide ions and second-order with respect to benzaldehyde (third-order overall).

$$\text{rate} = k_3[\text{PhCHO}]^2[\text{HO}^-]$$

For some aldehydes, such as formaldehyde and furfural, the order with respect to the concentration of hydroxide varies between one and two depending on the exact conditions. In high concentrations of base it is fourth-order.

$$\text{rate} = k_4[\text{HCHO}]^2[\text{HO}^-]^2$$

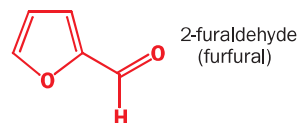
At lower concentrations of base it is a mixture of both third- and fourth-order reactions.

$$\text{rate} = k_3[\text{HCHO}]^2[\text{HO}^-] + k_4[\text{HCHO}]^2[\text{HO}^-]^2$$

Just because the overall order of reaction is third- or fourth-order, it does not mean that all the species must simultaneously collide in the rate-determining step. You saw in Chapter 13 that the rate law actually reveals all the species that are involved *up to and including* the rate-determining step.

■ The Cannizzaro reaction first appeared in Chapter 27.

■ For some examples of radical initiators, see Chapter 39. Radical inhibitors are usually stable radicals such as those on p. 000.



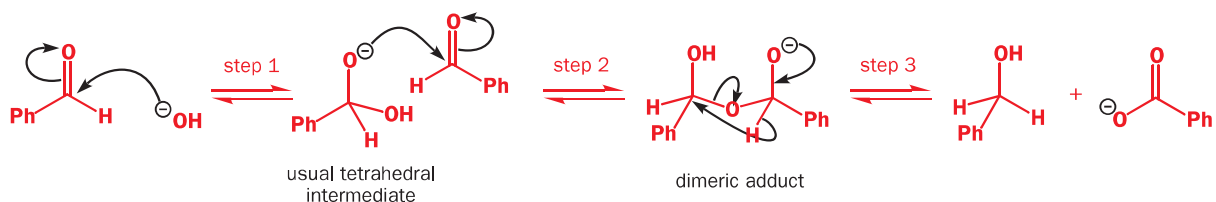
Isotopic labelling

When the reaction is carried out in D_2O instead of in H_2O it is found that there are no C–D bonds in the products. This tells us that the hydrogen must come from the aldehyde and not from the solvent.

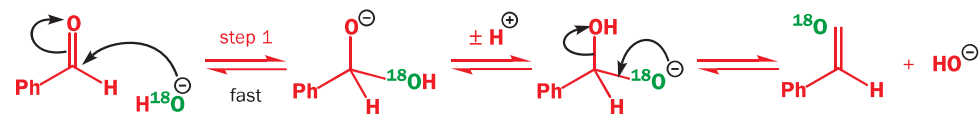


Proposed mechanism B—formation of an intermediate dimeric adduct

A possible mechanism that fits all the experimental evidence so far involves nucleophilic attack of the usual tetrahedral intermediate on another aldehyde to give an intermediate adduct. This adduct could then form the products directly by hydride transfer. You may not like the look of this last step, but the mechanism was proposed and evidence is needed to disprove it.

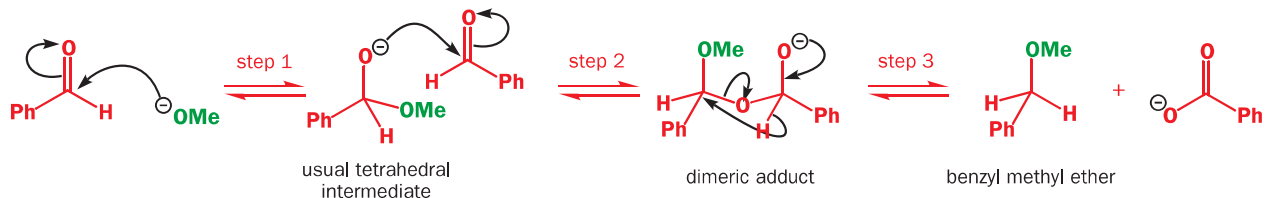


Which step would be rate-determining for this mechanism? It could not be step 1 since, if this were the case, then the rate law would be first-order with respect to the aldehyde rather than the observed second-order relationship. Also, if the reaction is carried out in water labelled with oxygen-18, the oxygen in the benzaldehyde exchanges with the ^{18}O from the solvent much faster than the Cannizzaro reaction takes place. This can only be because of a *rapid* equilibrium in step 1 and so step 1 cannot be rate-determining.



So, for mechanism B, either step 2 or step 3 could be rate-determining—either case would fit the observed rate law. Step 2 is similar to step 1; in both cases an oxyanion nucleophile attacks the aldehyde. Since the equilibrium in step 1 is very rapid, it is reasonable to suggest that the equilibrium in step 2 should also be rapid and thus that the hydride transfer in step 3 must be rate-determining. So mechanism B can fit the rate equation.

How can mechanism B be ruled out? One way is to change the attacking nucleophile. The Cannizzaro reaction works equally well if methoxide is used in a mixture of methanol and water. If mechanism B were correct, the reaction with methoxide would be as follows.



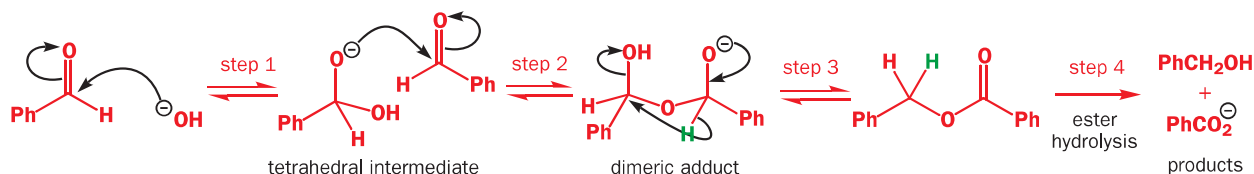
■ We shall discuss this kind of technique as well as other evidence used to evaluate an intermediate towards the end of this chapter.

One of the products would be different by this mechanism: benzyl methyl ether would be formed instead of benzyl alcohol. None is observed experimentally. Under the conditions of the experiment, benzyl methyl ether does not react to form benzyl alcohol, so it cannot be the case that the ether is formed but then reacts to form the products. Mechanism B can therefore be ruled out.

Proposed mechanism C—formation of an ester intermediate

This mechanism is like mechanism B but the hydride transfer in the adduct formed in step 2 displaces OH^- to form an ester (benzyl benzoate) that is then hydrolysed to the products. This was at

one time held to be the correct mechanism for the Cannizzaro reaction. One piece of evidence for this, and at first glance a very good one, is that by cooling the reaction mixture and avoiding excess alkali, some benzyl benzoate could be isolated during the reaction. An important point is that this does not mean that the ester *must* be an intermediate in the reaction—it might be formed at the end of the reaction, for example. However, it does mean that any mechanism we propose must be able to account for its formation. For now though we want to try and establish whether the ester is an *intermediate* rather than a by-product in the Cannizzaro reaction.



An early objection to mechanism C was that the ester would not be hydrolysed fast enough. When someone actually tried it under the conditions of the experiment, they found that benzyl benzoate is very rapidly hydrolysed (the moral here is ‘don’t just think about it, try it!’). However, just because the ester *could* be hydrolysed, it still did not show that it actually was an intermediate in the reaction. How this was eventually shown was rather clever. The argument goes like this. We can measure the rate constant for step 4 by seeing how quickly pure benzyl benzoate is hydrolysed to benzyl alcohol and benzoate under the same conditions as those of the Cannizzaro reaction. We also know how quickly these products are formed during the Cannizzaro reaction itself. Since, if this mechanism is correct, the only way the products are formed is from this intermediate, it is possible to work out how much of the intermediate ester must be present at any time to give the observed rate of formation of the products. If we can measure the amount of ester that is actually present and it is significantly less than that which we predict, then this cannot be the correct mechanism. It turned out that there was never enough ester present to account for the formation of the products in the Cannizzaro reaction and mechanism C could be ruled out.

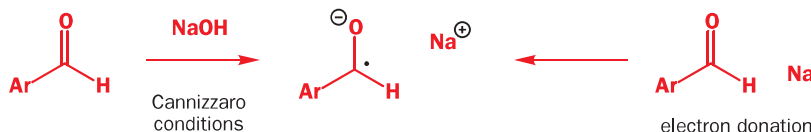
The correct mechanism for the Cannizzaro reaction

The only mechanism that has not been ruled out and that appears to fit all the evidence is the one we have already given (p. 000). The fact that the rate law for this mechanism is overall third- and sometimes fourth-order depending on the aldehyde and the conditions can be explained by the involvement of a second hydroxide ion deprotonating the tetrahedral intermediate to give a dianion. When methoxide is used in a methanol/water mix, some methyl ester is formed. This does not stay around for long—under the conditions of the experiment it is quickly hydrolysed to the carboxylate.



Even this mechanism does not quite fit all the evidence

We said earlier that we can never prove a mechanism—only disprove it. Unfortunately, just as the ‘correct’ mechanism seems to be found, there are some observations that make us doubt this mechanism. In Chapter 39 you saw how a technique called **electron spin resonance (ESR)** detects radicals and gives some information about their structure. When the Cannizzaro reaction was carried out with benzaldehyde and a number of substituted benzaldehydes in an ESR spectrometer, a radical was detected. For each aldehyde used, the ESR spectrum proved to be identical to that formed when the aldehyde was reduced using sodium metal. The radical formed was the radical anion of the aldehyde.



Our mechanism does not explain this result but small amounts of radicals are formed in many reactions in which the products are actually formed by simple ionic processes. Detection of a species in a reaction mixture does not prove that it is an intermediate. Only a few chemists believe that radicals are involved in the Cannizzaro reaction. Most believe the mechanism we have given.

Variation in the structure of the aldehyde

Before leaving the Cannizzaro reaction, look at these rates of reactions for aromatic aldehydes with different substituents in the *para* position. These aldehydes may be divided into two classes: those that react faster than unsubstituted benzaldehyde and those that react more slowly. Those that go slower all have something in common—they all have substituents on the ring that donate electrons.

We have already seen how substituents on a benzene ring affect the rate of electrophilic substitution (Chapter 22).

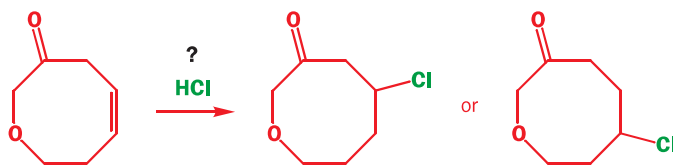
Electron-donating groups such as MeO– and Me₂N– dramatically speed up the rate at which an aromatic ring is attacked by an electrophile, whereas electron-withdrawing groups, particularly nitro groups, slow the reaction down. The Cannizzaro reaction is not taking place on the benzene ring itself, but substituents on the ring still make their presence known. The fact that the Cannizzaro reaction goes much *slower* with electron-donating groups and faster with electron-withdrawing groups tells us that, for this reaction, rather than a positive charge developing as in the case of electrophilic substitution on an aromatic ring, there must be negative charge accumulating somewhere near the ring. Our mechanism has mono- and dianion intermediates that are stabilized by electron-withdrawing groups. Later in the chapter you will see a more quantitative treatment of this variation of structure.

The rest of the chapter is devoted to discussions of the methods we have briefly surveyed for the Cannizzaro reaction with examples of the use of each method. We give examples of many different types of reaction but we cannot give every type. You may rest assured that all of the mechanisms we have so far discussed in this book have been verified (not, of course, proved) by these sorts of methods.

Be sure of the structure of the product

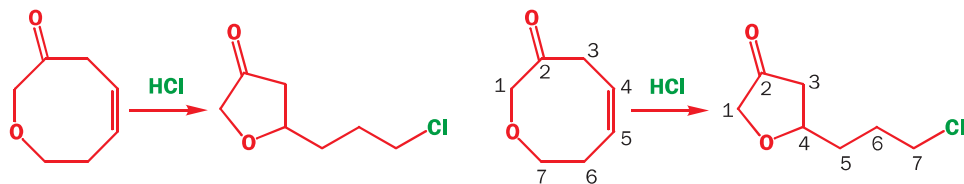
This seems a rather obvious point. However, there is a lot to be learned from the detailed structure of the product and we will discuss checking which atom goes where as well as the stereochemistry of the product. You will discover that it may be necessary to alter the structure of the starting material in subtle ways to make sure that we know exactly what happens to all its atoms by the time it reaches the product.

Suppose you are studying the addition of HCl to this alkene. You find that you get a good yield of a single adduct and you might be a bit surprised that you do not get a mixture of the two obvious adducts and wonder if there is some participation of the ether oxygen or whether perhaps the ketone enolizes during the reaction and controls the outcome.

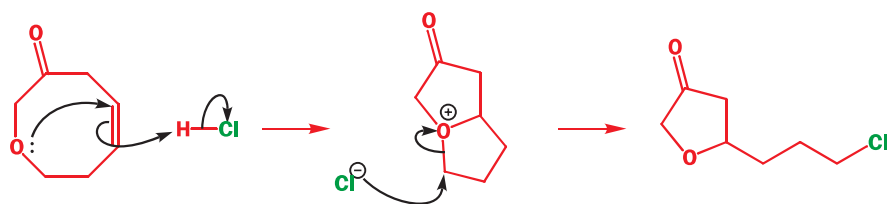


If you are cautious you might check on the structure of the product before you start a mechanistic investigation. The NMR spectrum tells you at once that the product is neither of these suggestions. It contains a (CH₂)₃Cl unit and can no longer have an eight-membered ring. A ring

contraction has given a five-membered ring and a mechanistic investigation is hardly needed. Simply knowing what the product is allows us to propose a mechanism. A rearrangement has occurred and we could use the method suggested in Chapter 37, of numbering the atoms in the starting material and finding them in the product. This is quite easy as only one numbering system makes any sense.



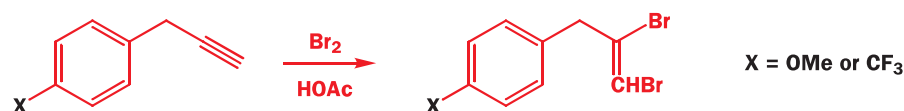
This numbering suggests that the carbon skeleton is unaffected by the reaction, that protonation has occurred at C5, that the ether oxygen has acted as an internal nucleophile across the ring at C4, and that the chloride ion has attacked C7. The mechanism is straightforward.



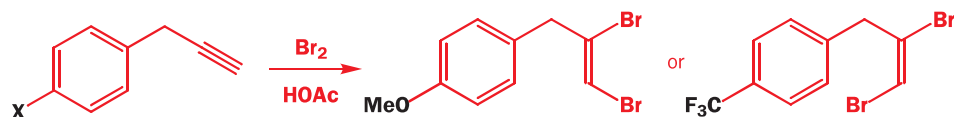
It may be disappointing to find that every step in this mechanism is well known and that the reaction is exactly what we ought to have expected with an eight-membered ring as these rings are famous for their transannular (across-ring) reactions to form 5/5 fused systems. However, it is good that a prolonged investigation is not necessary.

● Find out for sure what the structure of the product is before you start a mechanistic investigation.

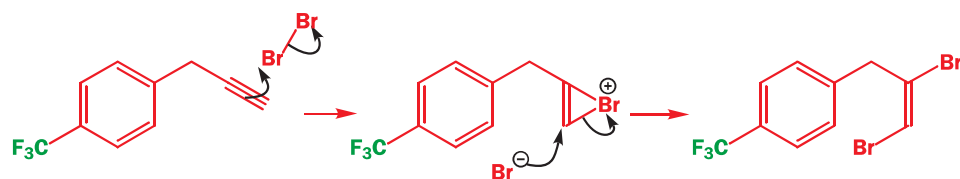
A more subtle distinction occurred in a study of the bromination of alkynes. Bromination of benzyl alkynes in acetic acid gave the products of addition of one molecule of bromine—the 1,2-dibromoalkenes. The reaction was successful with a variety of *para* substituents and there seems at first to be no special interest in the structure of the products.



Closer investigation revealed an extraordinary difference between them, not at all obvious from their NMR spectra: the compound from X = OMe was the *Z*-dibromoalkene from *cis* addition of bromine while the product from X = CF₃ was the *E*-alkene from *trans* addition. What mechanism could explain this difference?

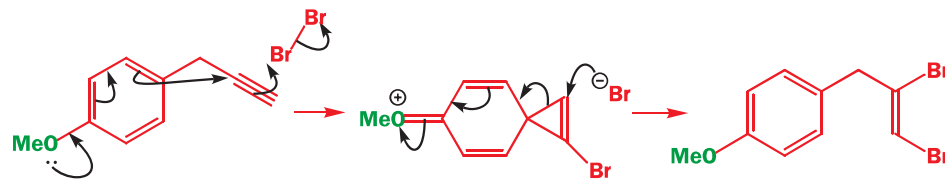


The *anti* addition is more easily explained: it is the result of formation of a bromonium ion, similar, in fact, to the normal mechanism for the bromination of alkenes. Bromine adds from one side of the alkyne and the bromide ion must necessarily form the *E*-dibromo product regardless of which atom it attacks.



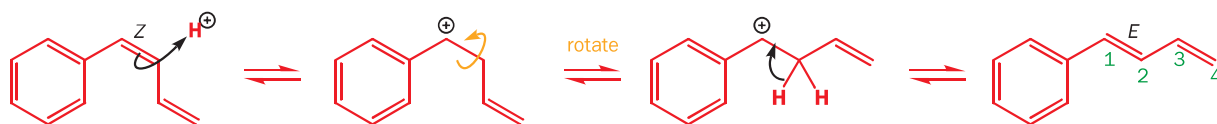
■ A similar aryl participation in saturated compounds to give a 'phenonium ion' intermediate appears in Chapter 37, p. 000.

So why does the *p*-MeO- compound behave differently? It cannot react by the same mechanism and a reasonable explanation is that the much more electron-donating ring participates in the reaction to give a carbocyclic three-membered ring intermediate that is attacked in an *anti* fashion to give the *Z*-alkene. Both intermediates are three-membered ring cations and both are attacked with inversion but the *p*-MeO- compound undergoes double inversion by participation of the ring.

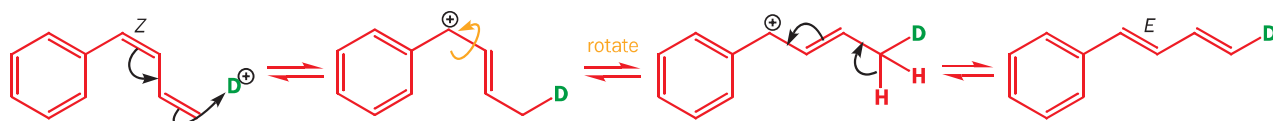


Labelling experiments reveal the fate of individual atoms

It often happens that the atoms in starting material and product cannot be correlated without some extra distinction being made by isotopic labelling. The isomerization of *Z*-1-phenylbutadiene to the *E*-diene in acid looks like a simple reaction. Protonation of the *Z*-alkene would give a stabilized secondary benzylic cation that should last long enough to rotate. Loss of the proton would then give the more stable *E*-diene.

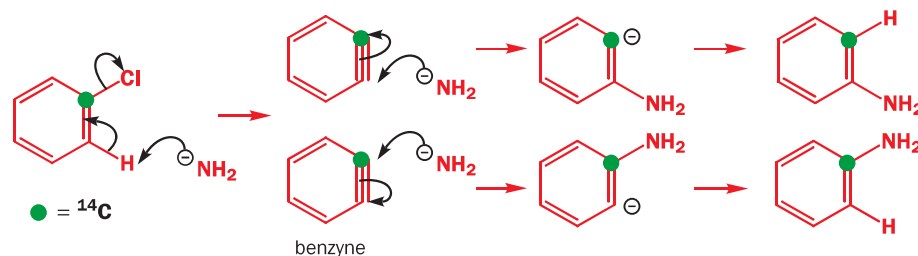


However, reaction with D^+ in D_2O reveals that this mechanism is incorrect. The product contains substantial amounts of deuterium at C4, not at C2 as predicted by the proposed mechanism. Protonation must occur at the end of the conjugated system to produce the more stable conjugated cation, which rotates about the same bond and loses H or D from C4 to give the product. More H than D will be lost, partly because there are two Hs and only one D, but also because of the kinetic isotope effect, of which more later.



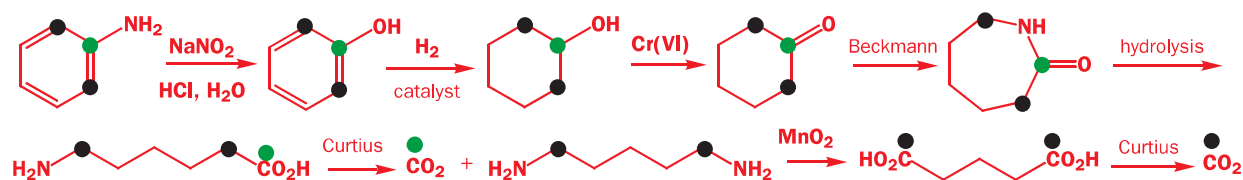
▶ Tritium and ^{14}C are β emitters—they give off electrons—having half-lives of 12 and over 5000 years, respectively. Tritium is made on a large scale by neutron irradiation of 6Li in a nuclear reactor.

■ Benzene is discussed in Chapter 23 as an intermediate in nucleophilic aromatic substitution.



The easiest labels to use for this job are D for H, ^{13}C , and ^{18}O . None of these is radioactive; all can be found by mass spectrometry, while D and ^{13}C can be found by NMR. Old work on mechanisms used radioactive tracers such as T (tritium) for H and ^{14}C . These are isotopes of hydrogen and carbon having extra neutrons. They are, of course, more dangerous to use but they can at least always be found. The real disadvantage is that, to discover exactly where they are in the product, the molecule must be degraded in a known fashion. These radioactive isotopes are not much used nowadays except in determining biological mechanisms as you will see in Chapters 49–51. The first evidence for benzene as the intermediate in the reaction of chlorobenzene with NH_2^- came from radioactive labelling.

If benzyne is an intermediate, the product should have 50% label at C1 and 50% at the two identical *ortho* carbons. The labelled aniline was degraded by the reactions shown here, which you must agree was a lot of work for the chemists concerned. Each potentially labelled carbon atom had to be isolated from any other labelled atom and the radioactivity measured. We shall follow the fate of the two labelled atoms with black and green spots. Since the two *ortho* positions are identical, we must put a green spot on both of them.

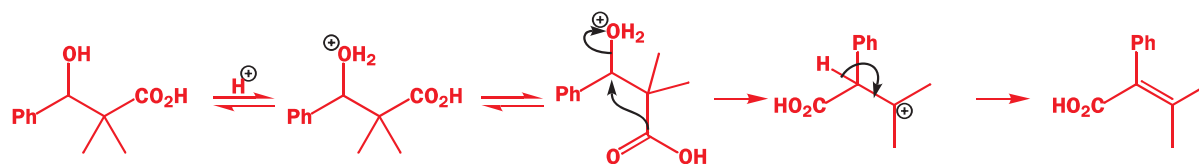


Most of these reactions are well known—the Beckmann rearrangement is described in Chapter 37 and the Curtius reaction in Chapter 40—but the oxidation of the diamine to the dicarboxylic acid is not a standard procedure and is not recommended. All the label came out in the CO₂ and almost exactly half of it was from the black and half from the green labelled carbons. This was the original evidence that convinced organic chemists in 1953 that benzyne was involved in the reaction. The evidence presented in Chapter 23 is more modern.

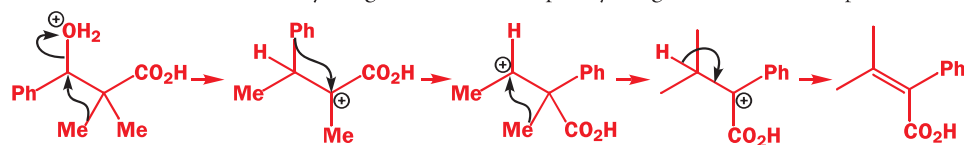
Other symmetrical intermediates originally identified by radioactive labelling include the cyclopropanone in the Favorskii rearrangement in Chapter 37, p. 000, and a spirocyclic intermediate in electrophilic substitution on an indole in Chapter 43, p. 000.

The value of double labelling experiments

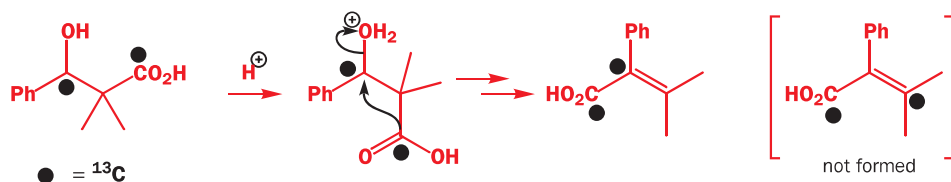
An altogether more modern approach to a labelling study was used in the surprising rearrangement of a hydroxy-acid in acidic solution. The structure of the product suggests a CO₂H migration as the most likely mechanism. This mechanism resembles closely the cationic rearrangements of Chapter 37.



Received wisdom (Chapter 37) objects that the best migrating group in cationic rearrangements is the one best able to bear a positive charge, so that the more familiar Ph and Me migrations ought to be preferred and that a more elaborate mechanism should be sought. Such a mechanism can be written: it involves two methyl migrations and one phenyl migration and is acceptable.



These mechanisms can be tested by finding out whether the CO₂H group remains attached to its original position or becomes attached to the other carbon in the skeleton of the molecule. This can be done by double labelling. If a compound is prepared with two ¹³C labels, one on the CO₂H group itself and one on the benzylic carbon, the NMR spectrum of the product will show what has happened. In fact, the two ¹³C labels end up next to each other with a coupling constant ¹J_{CC} = 71 Hz. It is the CO₂H group that has migrated.



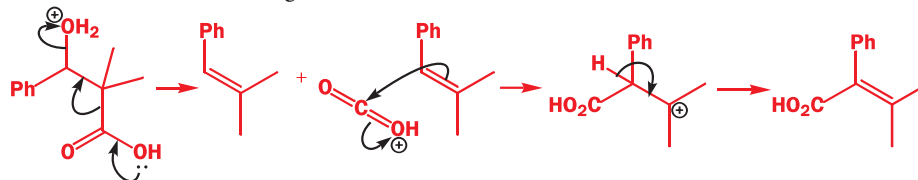
This style of double labelling with NMR active isotopes will be seen again in Chapters 49–51.

So why does the CO₂H group migrate? It does so not because it is a good migrating group but because it cannot bear to be left behind. The rearranged cation from CO₂H migration is a stable tertiary alkyl cation. The cation from Me migration is a very unstable cation with the positive charge

next to the CO₂H group. Such cations are unknown as the carbonyl group is very electron-withdrawing. Received wisdom needs to be amended.

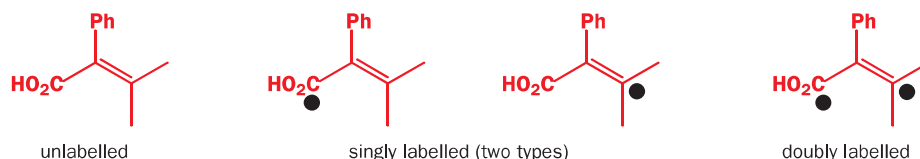
'Crossover' experiments

There is still one tiny doubt. Supposing the reaction is not intramolecular at all, but intermolecular. The CO₂H group might be lost from one molecule as protonated CO₂ and be picked up by another molecule of alkene. No migration would be involved at all.

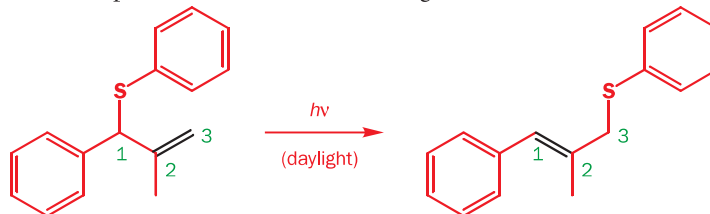


This mechanism can be checked by using a 50:50 mixture of doubly labelled and unlabelled starting material. The molecule of alkene that captures the roving protonated labelled CO₂ might happen to be labelled too but equally well it might be unlabelled. If this last mechanism is correct, we should get a mixture of unlabelled, singly labelled, and doubly labelled product in the ratio 1:2:1 as there are two types of singly labelled product. The two singly labelled compounds are called the **crossover products** and the experiment is called a **crossover experiment** as it discovers whether any parts of one molecule cross over to another.

There is an example of a crossover experiment proving that an S_N2 reaction is intermolecular in Chapter 42, p. 000.

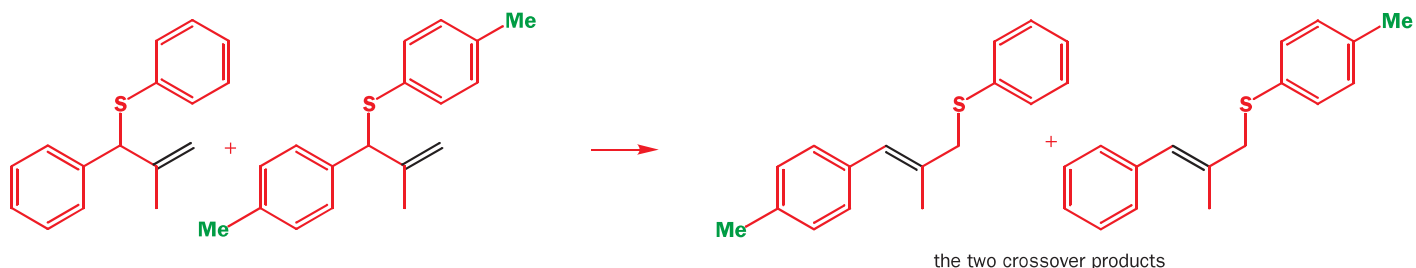


In fact, no singly labelled compounds were found: NMR analysis showed that the product consisted entirely of unlabelled or doubly labelled molecules. The CO₂H group remains attached to the same molecule (though not to the same atom) and the first mechanism is correct. Crossover experiments demand some sort of double labelling, which does not have to be isotopic. An example where crossover products are observed is the light-initiated isomerization of allylic sulfides.

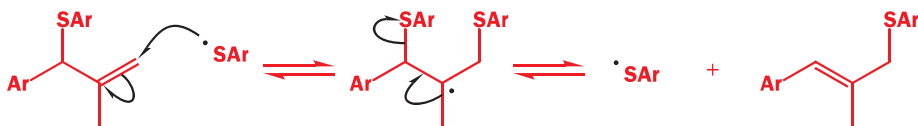


This is formally a [1,3] sigmatropic shift of sulfur (Chapter 36) but that is an unlikely mechanism and a crossover experiment was carried out in which the two molecules had either two phenyl groups or two *para*-tolyl groups.

The mixture was allowed to rearrange in daylight and the products were examined by mass spectroscopy. There was a roughly 1:2:1 mixture of products having two phenyl groups, one phenyl and one *para*-tolyl group, and two *para*-tolyl groups. The diagram shows the starting materials and the two crossover products only.



Clearly, the ArS group had become separated from the rest of the molecule and the most likely explanation was a radical chain reaction (Chapter 39) with the light producing a small amount of ArS[•] to initiate the chain. The *para*-methyl group acts as a label. The whole system is in equilibrium and the more highly substituted alkene is the product.



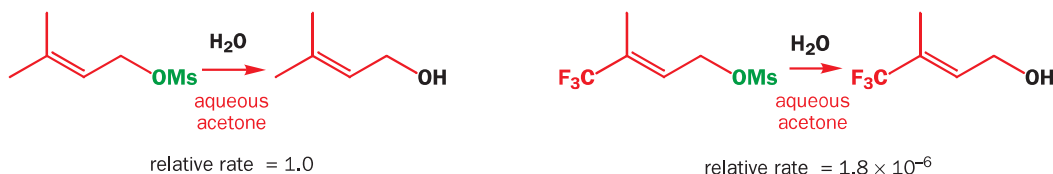
Systematic structural variation

In this last example, the hope is that the *para*-methyl group will have too weak an electronic or steric effect and in any case will be too far away to affect the outcome. It is intended to make nearly as slight a change in the structure as an isotopic label. Many structural investigations have exactly the opposite hope. Some systematic change is made in the structure of the molecule in the expectation of a predictable change in rate. A faster or slower reaction will lead to some definite conclusion about the charge distribution in the transition state.

Allylic compounds can react efficiently with nucleophiles by either the S_N1 or S_N2 mechanisms (Chapter 17) as in these two examples.



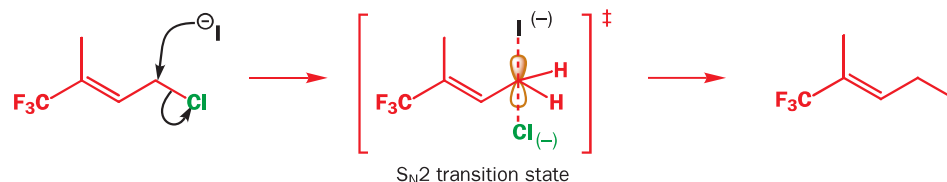
The carbon skeleton is the same in both reactions but the leaving groups and the nucleophiles are different. These reactions might both go by S_N1 or S_N2 or one might go by S_N1 and the other by S_N2. One way to find out is to make a large change in the electronic nature of the carbon skeleton and see what happens to the rate of each reaction. In these experiments one of the methyl groups was changed for a CF₃ group—exchanging a weakly electron-donating group for a strongly electron-withdrawing group. If a cation is an intermediate, as in the S_N1 reaction, the fluorinated compound will react much more slowly. Here is the result in the first case.



The fluorinated compound reacts half a million times more slowly so this looks very much like an S_N1 mechanism. The slow step in an S_N1 mechanism is the formation of a carbocation so any group that destabilizes the positive charge would have (and evidently does have) a large effect on the rate. Rate ratios of several powers of ten are worth noticing and a rate ratio of nearly 10⁻⁶ is considerable. In the second case the rate difference is much less.



A rate ratio of 11 is not worth noticing. The point is not that the fluorinated compound reacts faster but that the two compounds react at about the same rate. This strongly suggests that no charge is generated in the transition state and an S_N1 mechanism is not possible. The S_N2 mechanism makes good sense with its concerted bond formation and bond breaking requiring no charge on the carbon skeleton.

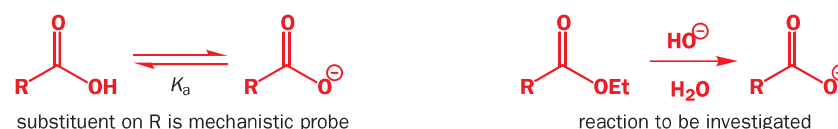


The CF_3 group works well here as a mechanistic probe because it is held well out of the way of the reaction site by a rigid π system but is connected electronically by that same allylic system. Steric effects should be minimized and electronic effects clearly seen. This approach is clearly limited by the small number of groups having properties like those of the CF_3 group and the small number of reactions having such favourable carbon skeletons. We will now present the most important serious correlation between structure and reactivity.

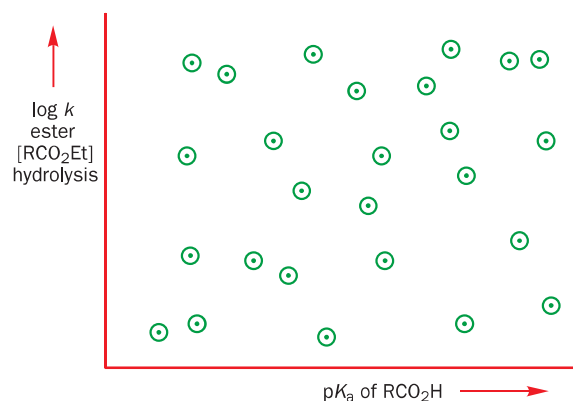
The Hammett relationship

■ Louis P. Hammett (1894–1987) invented 'physical organic chemistry' and at Columbia University in 1935 derived the Hammett σ/ρ relationship. The impact was enormous and in the 1960s chemists were still working out more such correlations.

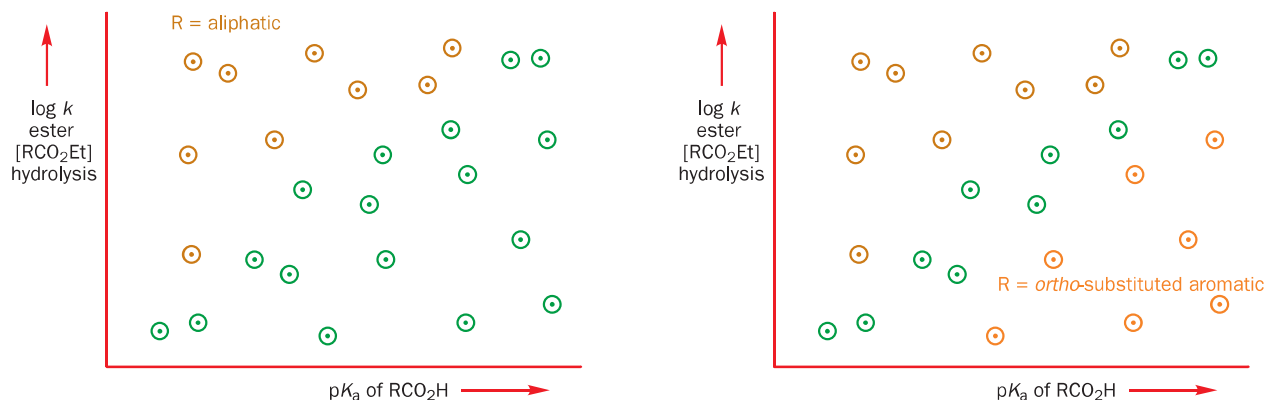
What we would ideally like to do is find a way to quantify the effects that electron-donating or -withdrawing groups have on the transition state or intermediate during the course of a reaction. This will then give us an idea of what the transition state is really like. The first question is: can we define exactly how efficient a given group is at donating or withdrawing electrons? Hammett took the arbitrary decision to use the pK_a of an acid as a guide. For example, the rate of hydrolysis of esters might well correlate with the pK_a of the corresponding acid.



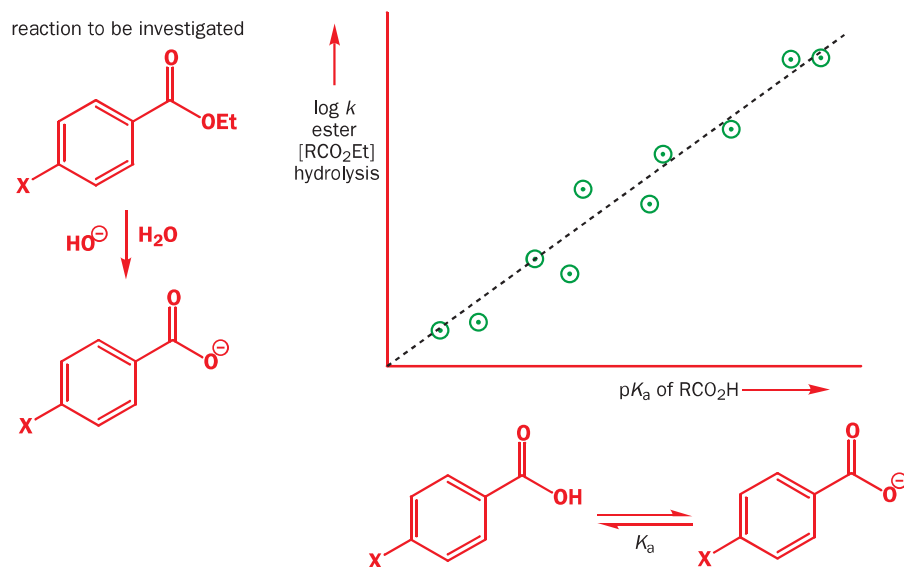
When Hammett plotted the rates of ethyl ester hydrolyses (as $\log k$ since pK_a has a log scale) against the pK_a s of the corresponding acids, the initial results were not very encouraging as there was a random scatter of points over the whole graph.



Hammett had used some aliphatic acids (substituted acetic acids) and some aromatic acids (substituted benzoic acids) and he noticed that many of the points towards the top of the graph belonged to the substituted acetic acids. Removing them (brown points) made the graph a lot better. He then noticed that the remaining aromatic compounds were in two classes: the *ortho*-substituted esters reacted more slowly than their *meta*- and *para*-isomers and came towards the bottom of the graph (orange points). Removing them made the graph quite good (remaining green points).



It was not a perfect correlation but Hammett had removed the examples where steric hindrance was important. Aliphatic compounds can adopt a variety of conformations (Chapter 18) and the substituent in some of them will interfere with the reaction. Similarly, in *ortho*-substituted aromatic compounds the nearby substituent might exert steric hindrance on the reaction. Only with *meta*- and *para*-substituted compounds was the substituent held out of the way, on a rigid framework, and in electronic communication with the reaction site through the flat but conjugated benzene ring. The diagrams show the *para* substituent.



Notice that the straight line is not perfect. This graph is an invention of the human mind. It is a correlation between things that are not directly related. If you determine a rate constant by plotting the right function of concentration against time and get an imperfect straight line, that is your fault because you haven't done your measurements carefully enough. If you make a Hammett plot and the points are not on a straight line (and they won't be) then that is *not* your fault. The points really don't fit on a perfectly straight line. As you will see soon, this does not matter. We need to look at the Hammett correlation in more detail.

The Hammett substituent constant σ

A quick glance at the pK_as of some substituted benzoic acids will show how well they correlate electron donation with pK_a. The substituents at the top of the table are electron-donating and the anions of the benzoic acids are correspondingly less stable so these are the weakest acids. At the bottom of the table we have the electron-withdrawing groups, which stabilize the anion and

▶ If you plot a graph to correlate the number of miles travelled by jumbo jet against the percentage of births outside of marriage over the twentieth century you will get a sort of straight line. This does not imply a direct causative link!

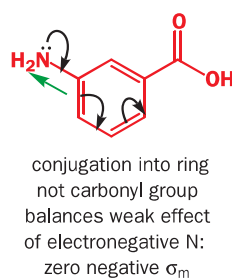
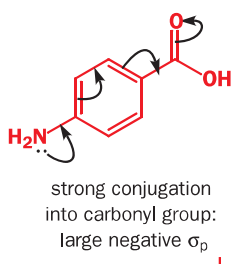
▶ You cannot push arrows from the negative charge or the carboxylate into the ring. Try it.

make the acid stronger. The whole range is not that great, only one pH unit or so, because the carboxylate anion is not conjugated with the ring.

Hammett decided not to use the pK_a s themselves for his correlation but defined a new parameter, which he called σ . This σ shows how electron-donating or -withdrawing a group is relative to H as a ratio of the $\log K_a$ s or the difference of the pK_a s between the substituent and benzoic acid itself. If the acid required to determine σ for a new substituent was not available, σ could be determined by correlation with other reactions. Here are the equations and the table of σ values for the most important substituents. A different value of σ for any given substituent was needed for the *meta* and the *para* positions and these are called σ_m and σ_p , respectively.

$$\sigma_X = \log \left(\frac{K_a(X-C_6H_4COOH)}{K_a(C_6H_5COOH)} \right) = pK_a(C_6H_5COOH) - pK_a(X-C_6H_4COOH)$$

You need a general idea as to what a σ value means. If $\sigma = 0$ the substituent has no effect: it is electronically the same as H. If σ is positive, the substituent is electron-withdrawing. This is unfortunate perhaps, but just remember that the comparison is with acid strength. Positive σ means a stronger acid so the substituent is electron-withdrawing. The more positive the charge induced on the ring by a substituent, the larger its σ value. Negative σ means weaker acid and electron donation. Inductive effects from polarization of σ bonds are greater for σ_m than for σ_p because the substituent is nearer.



Conjugation is generally more effective in the *para* position (see Chapter 22) so $\sigma_p > \sigma_m$ for conjugating substituents. Indeed, the NH_2 group has a large negative σ_p and a zero σ_m . The NH_2 group donates electrons strongly to the carbonyl group of benzoic acid from the *para* position but does not conjugate in the *meta* position where its donation happens just to balance the effect of electronegative nitrogen.

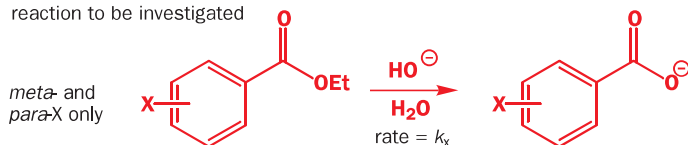
The OMe group has a negative σ_p but a positive σ_m because a weaker electron donation from the lone pairs is more important in the *para* position but the effect of very elec-

Substituent, X	pK_a of p -XC ₆ H ₄ COOH	pK_a of m -XC ₆ H ₄ COOH
NH ₂	4.82	4.20
OCH ₃	4.49	4.09
CH ₃	4.37	4.26
H	4.20	4.20
F	4.15	3.86
I	3.97	3.85
Cl	3.98	3.83
Br	3.97	3.80
CO ₂ CH ₃	3.75	3.87
COCH ₃	3.71	3.83
CN	3.53	3.58
NO ₂	3.43	3.47

Substituent, X	σ_p	σ_m	Comments
NH ₂	-0.62	0.00	groups that donate electrons have negative σ
OCH ₃	-0.29	0.11	
CH ₃	-0.17	-0.06	
H	0.00	0.00	there are no values for <i>ortho</i> substituents
F	0.05	0.34	
I	0.23	0.35	
Cl	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	0.23	0.40	
CO ₂ CH ₃	0.45	0.33	
COCH ₃	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	0.67	0.62	
NO ₂	0.77	0.73	groups that withdraw electrons have positive σ

tronegative oxygen on the σ framework of the ring in the *meta* position is more important than lone pair donation that doesn't reach the carbonyl group. You do not need to learn any σ values but you should be able to work out the sign of σ for well known substituents and estimate a rough value.

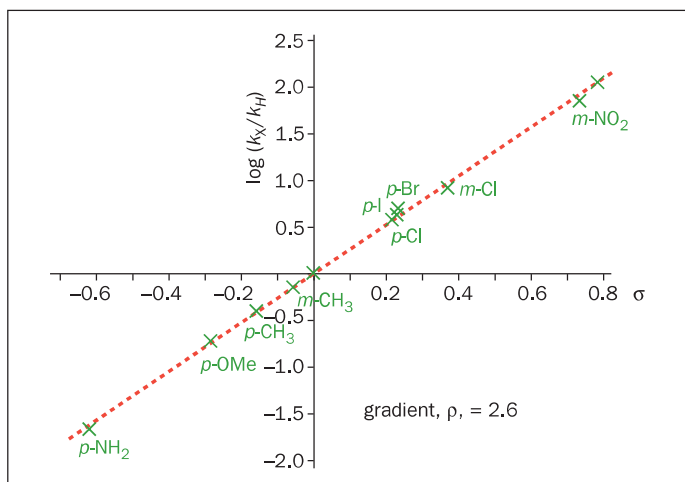
reaction to be investigated



The Hammett reaction constant ρ

Now we can return to our reaction: the alkaline hydrolysis of various *meta*- and *para*-substituted ethyl benzoates. The rate constants for this second-order reaction have been measured and shown here is a graph of $\log(k_X/k_H)$ versus σ , where k_X is the rate constant for the reaction with the substituted benzoate and k_H is that for the unsubstituted reaction ($X = H$).

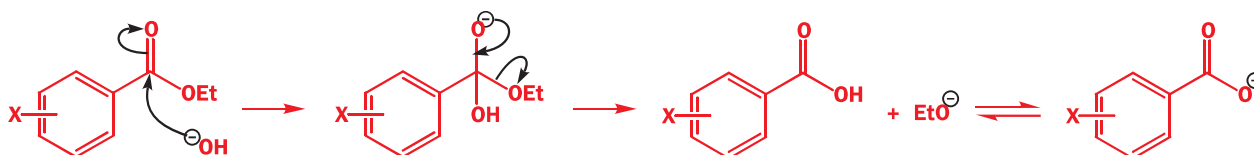
We can see straight away that there is a good correlation between how fast the reaction goes and the value of σ ; in other words, the points lie more or less on a straight line. The gradient of this best fit line, given the symbol ρ (rho), tells us how sensitive the reaction is to substituent effects in comparison with the ionization of benzoic acids. The gradient is $\rho = +2.6$. This tells us that the reaction responds to substituent effects in the same way (because it is +) as the ionization of benzoic acids but by much more ($10^{1.6}$ times more) because it is 2.6 instead of 1.0. We already know what the mechanism of this reaction is.



▶ Getting to grips with logs

A difference between two values of x log units means the values actually differ by a factor of 10^x . From the graph for the hydrolysis of ethyl benzoates we can see that the *p*-NO₂ benzoate hydrolyses some 10^2 times faster than the unsubstituted benzoate, while the *p*-NH₂ benzoate hydrolyses some 10^2 times slower.

▶ Hammett chose σ (Greek s) for *substituent* and ρ (Greek r) for *reaction*.

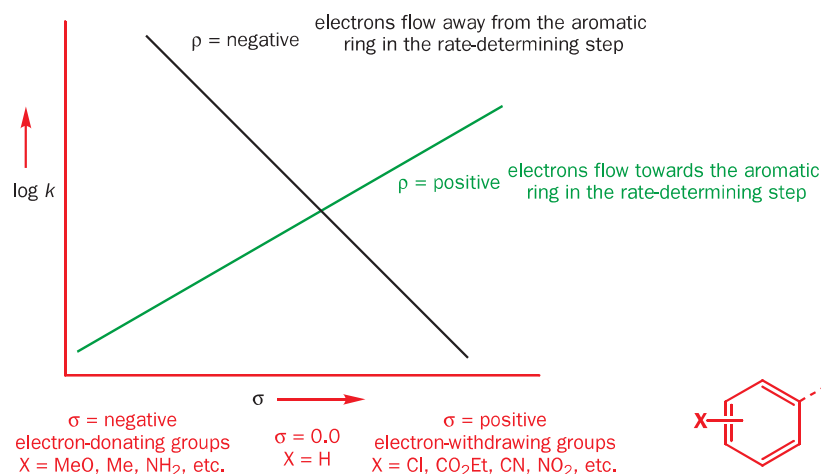


The first step is quite like the ionization of benzoic acid. A negative charge is appearing on the carbonyl oxygen atom and that negative charge will be stabilized by electron-withdrawing X groups. Provided that the first step is rate-determining, a positive ρ is fine. We cannot say much as yet about the value as we are comparing a reaction rate (for the hydrolysis) with an equilibrium position (for the ionization). It will help you a great deal if you think of *positive* ρ values as meaning an *increase* in electron density near to or on the benzene ring. They may mean the appearance of a negative charge but they may not. We need now to look at some other reactions to get a grasp of the meaning of the value of the Hammett ρ .

● The Hammett reaction constant ρ measures the *sensitivity* of the reaction to electronic effects.

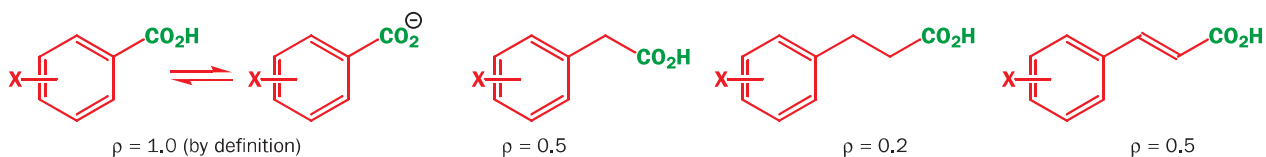
- A *positive* ρ value means *more* electrons in the transition state than in the starting material
- A *negative* ρ value means *fewer* electrons in the transition state than in the starting material

typical Hammett plots

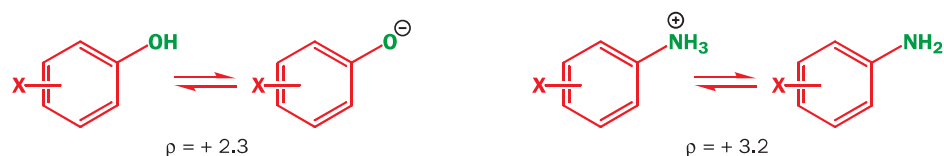


Equilibria with positive Hammett ρ values

We can compare these directly with the ionization of benzoic acids. If we simply move the carboxylic acid away from the ring, the ρ value for ionization gets less. This is just the effect of a more distant substituent. When there are two saturated carbons between the benzene ring and the carboxylic acid, there is almost no effect. When we are using the aromatic ring as a probe for a reaction mechanism, it must be placed not too far away from the reaction centre. However, if we restore electronic communications with a double bond, ρ goes back up again to a useful value.

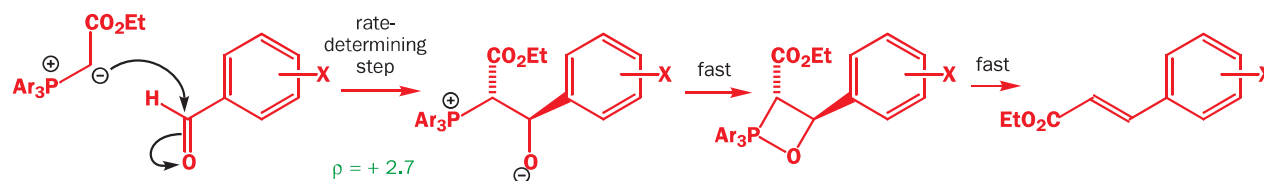


If the negative charge on the anion can actually be delocalized round the ring, as with substituted phenols, we should expect the size of ρ to increase. Both the phenol and the anion are delocalized but it is more important for the anion. The effect is larger for the ionization of anilinium salts as the acid (ArNH_3^+) does not have a delocalized lone pair but the conjugate base (ArNH_2) does.

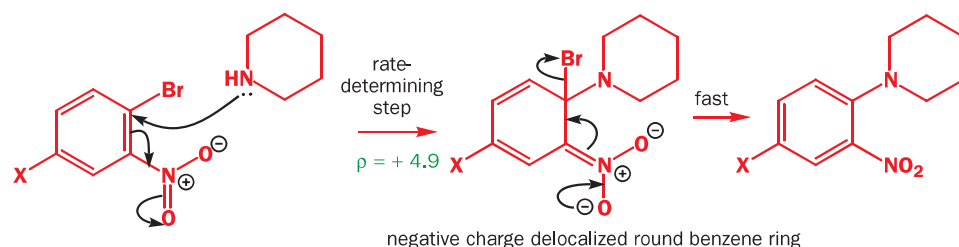


Reactions with positive Hammett ρ values

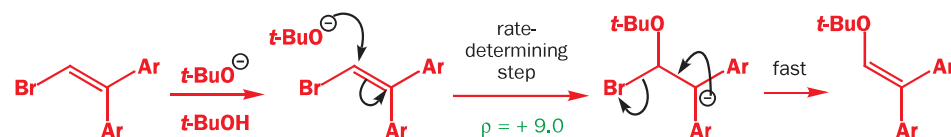
Any reaction that involves nucleophilic attack on a carbonyl group as the rate-determining step is going to have a ρ value of about 2–3, the same as for the hydrolysis of esters that we have already seen. Examples include the Wittig reaction of stabilized ylids (Chapters 14 and 31). Though there is some dispute over the exact mechanism of the Wittig reaction, the ρ value of 2.7 strongly suggests that nucleophilic attack on the aldehyde by the ylid is involved with stabilized ylids and aromatic aldehydes at least. In addition, there is a small variation of rate with the aryl group on phosphorus: if $\text{Ar} = p\text{-MeOC}_6\text{H}_4$ the reaction goes about six times faster than if $\text{Ar} = p\text{-ClC}_6\text{H}_4$. These groups are a long way from the reaction site but electron donation would be expected to accelerate the donation of electrons from the ylid.



Large positive ρ values usually indicate extra electrons in the transition state delocalized into the ring itself. A classic example is nucleophilic aromatic substitution by the addition–elimination mechanism (Chapter 23). The ρ value is +4.9, but even this large value does not mean a complete anion on the benzene ring as the nitro group, present in all cases, takes most of the negative charge. The substituent X merely helps.

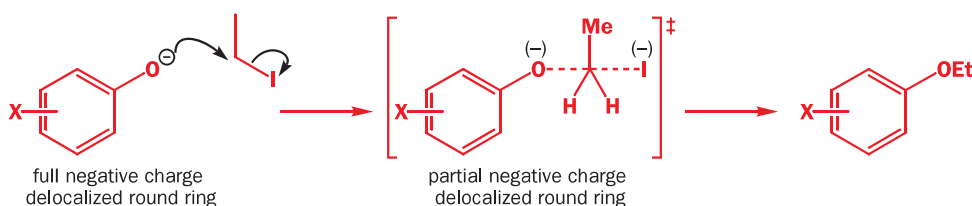


We get the full value when there are no nitro groups to take the brunt of the negative charge. This vinylic substitution (an unusual reaction!) has a ρ value of +9.0. It cannot be an S_N2 reaction or it would have a small ρ value and it cannot be an S_N1 reaction or it would have a negative ρ value (fewer electrons in the transition state). It must be an addition–elimination mechanism through a benzylic anion delocalized round both benzene rings.

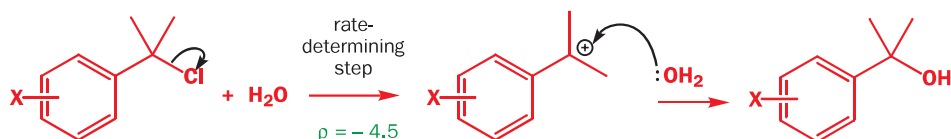


Reactions with negative Hammett ρ values

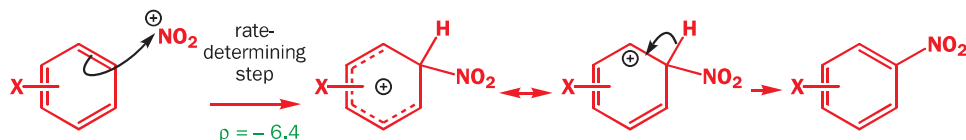
Negative ρ values mean electrons flowing away from the ring. A useful example is the S_N2 displacement of iodide from EtI by phenoxide anions. This has a ρ value of exactly -1.0 . Though the transition state has a negative charge, that charge is decreasing on the aromatic ring as the starting material approaches the transition state.



An S_N1 reaction on the carbon atom next to the ring has a large negative ρ value. In this example, a tertiary benzylic cation is the intermediate and the rate-determining step is, of course, the formation of the cation. The cation is next to the ring but delocalized round it and the ρ value is -4.5 , about the same value, though negative, as that for the nucleophilic substitution on nitrobenzenes by the addition–elimination mechanism that we saw in the last section.

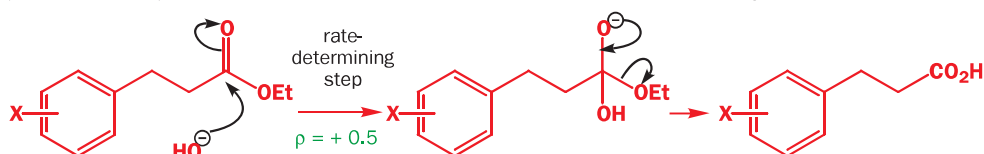


The largest negative ρ values come from electrophilic aromatic substitution (Chapter 22) where the electrons of the ring are used in the reaction leaving a positive charge on the ring itself in the intermediate. Some of this charge is already there in the transition state. Negative ρ values mean electrons flowing out of the ring. This simple nitration has $\rho = -6.4$ and ρ values for electrophilic aromatic substitution are usually in the range -5 to -9 .

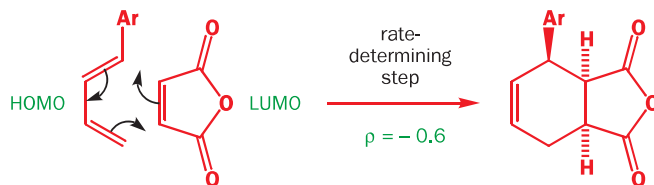


Reactions with small Hammett ρ values

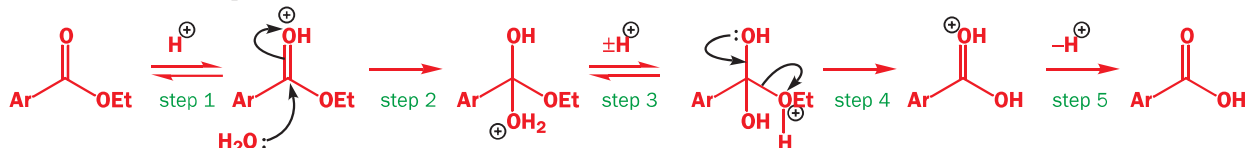
Small Hammett ρ values arise in three ways. The aromatic ring being used as a probe for the mechanism may simply be too far away for the result to be significant. This trivial case of the alkaline hydrolysis of the 3-aryl propionate ester has a ρ value of $+0.5$ and it is surprising that it is even that large.



The second case is the informative one where the reaction is not dependent on electrons flowing into or out of the ring. Pericyclic reactions are important examples and the Diels–Alder reaction of arylbutadienes with maleic anhydride shows a small negative ρ value of -0.6 . The small value is consistent with a mechanism not involving charge accumulation or dispersal but the sign is interesting. We explained this type of Diels–Alder reaction in Chapter 35 by using the HOMO of the diene and the LUMO of the dienophile. The negative sign of ρ , small though it is, supports this view.



The third case is in many ways the most interesting. We have seen that the alkaline hydrolysis of ethyl esters of benzoic acids (ArCO_2Et) has a ρ value of $+2.6$ and that this is a reasonable value for a reaction involving nucleophilic attack on a carbonyl group conjugated with the aromatic ring. The hydrolysis of the same esters in acid solution, which also involves nucleophilic attack on the same carbonyl group, has a ρ value of $+0.1$. In other words, all these esters hydrolyse at the same rate in acid solution. Neither of the previous explanations will do. We need to see the full mechanism to explain this remarkable result.

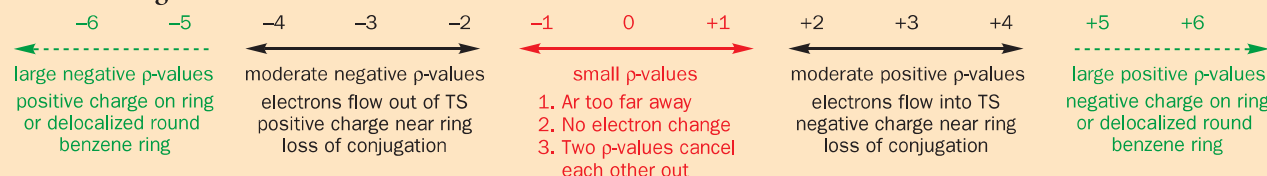


Steps 1, 3, and 5 cannot be slow as they are just proton transfers between oxygen atoms (Chapter 13). That leaves only steps 2 and 4 as possible rate-determining steps. The bimolecular addition of the weak nucleophile water to the low concentration of protonated ester (step 2) is the most attractive candidate, as step 4—the unimolecular loss of ethanol and re-formation of the carbonyl group—should be fast. What ρ value would be expected for the reaction if step 2 were the rate-determining step? It would be made up of two parts. There would be an equilibrium ρ value for the protonation and a reaction ρ value for the addition of water. Step 1 involves electrons flowing out of the molecule and step 2 involves electrons flowing in so the ρ values for these two steps would have opposite charges. We know that the ρ value for step 2 would be about $+2.5$ and a value of about -2.5 for the equilibrium protonation is reasonable. This is indeed the explanation: step 2 is the rate-deter-

mining step and the ρ values for steps 1 and 2 almost cancel each other out. All steps before the rate-determining step are present in the rate equation and also affect the Hammett ρ value.

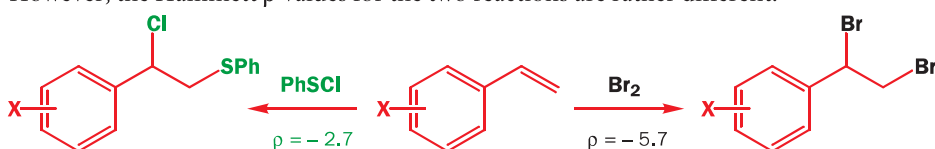
The meaning of Hammett ρ values

This then is the full picture. You should not, of course, learn these numbers but you need an idea of roughly what each group of values means. You should see now why it is unimportant whether the Hammett correlation gives a good straight line or not. We just want to know whether the Hammett correlation gives a good straight line or not. We just want to know whether ρ is + or – and whether it is, say, 3 or 6. It is meaningless to debate the significance of a ρ value of 3.4 as distinct from one of 3.8.

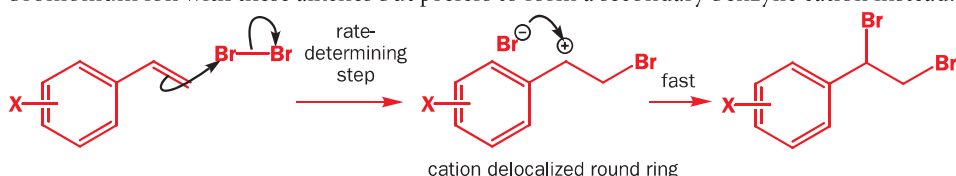


Using the Hammett ρ values to discover mechanisms

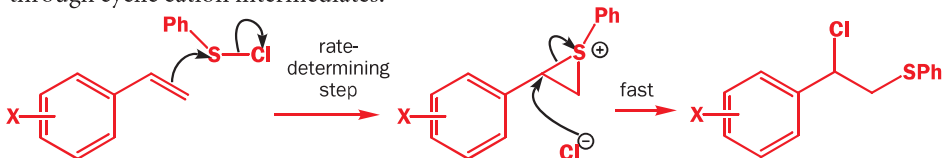
Electrophilic attack on alkenes by bromine often goes through three-membered ring cyclic bromonium ions and we can sometimes tell that this is so by studying the stereochemistry. Here are two reactions of styrenes that look very similar—a reaction with bromine and one with PhSCl. With no further information, we might be tempted to assume that they both go by the same mechanism. However, the Hammett ρ values for the two reactions are rather different.



The ρ value for bromination is definitely in the ‘large’ range and can only mean that a positive charge is formed that is delocalized round the benzene ring. Bromine evidently does not form a bromonium ion with these alkenes but prefers to form a secondary benzylic cation instead.



The sulfenylation, on the other hand, has a moderate negative ρ value. No cation is formed that is delocalized round the ring, but electrons flow out of the ring and we suspect some loss of conjugation. All this fits well with the formation of a three-membered ring intermediate. From experiments like this we learn that PhSCl is much more likely than bromine to react stereospecifically with alkenes through cyclic cation intermediates.

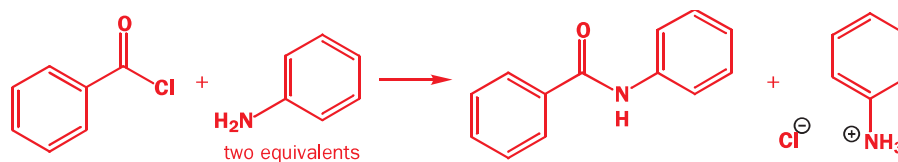


A complete picture of the transition state from Hammett plots

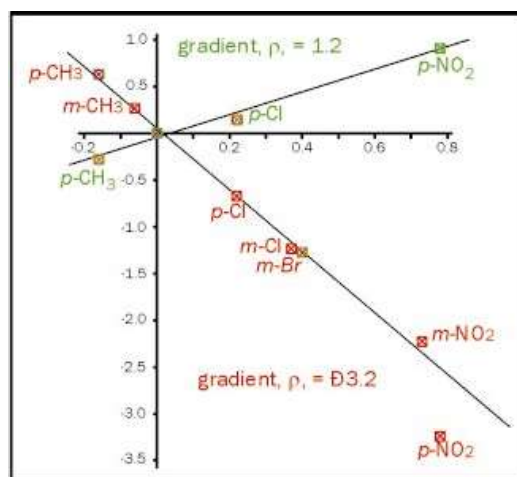
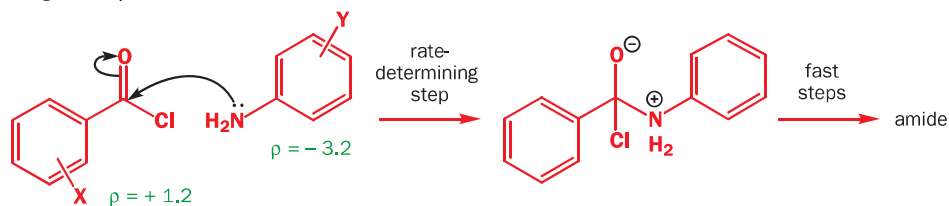
More information can be gained on the mechanism of the reaction if two separate experiments can be carried out with the mechanistic probe inserted at two different sites on the reagents. If we are studying a reaction between a nucleophile and an electrophile, it may be possible to make Hammett plots from the variation of substituents on both reagents. The acylation of amines with acid chlorides is an example.

Chapter 20 gives a full description of these mechanisms.

There is more about these sulfonyl chlorides in Chapter 46.

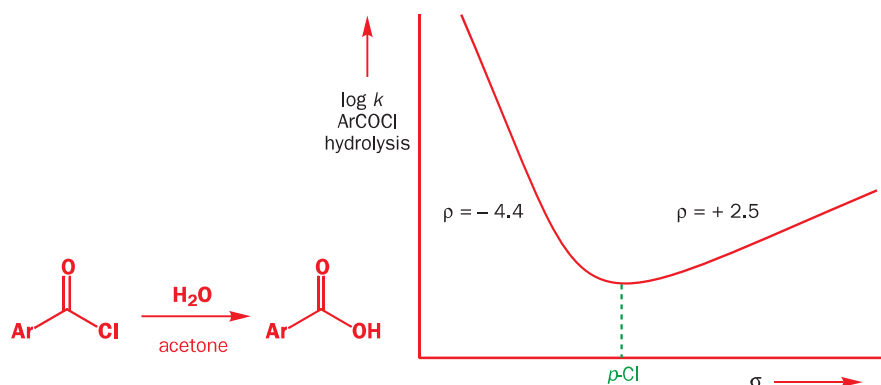


If we vary the structure of the acid chloride we get a ρ value of +1.2, suitable for nucleophilic attack on the carbonyl group. If we vary the amine we get a ρ value of -3.2 , again suitable for electrons that were conjugated round the ring moving away to form a new bond. The simple answer is correct but the rate depends on the nucleophilicity of the amine 100 times more than on the electrophilicity of the acid chloride.

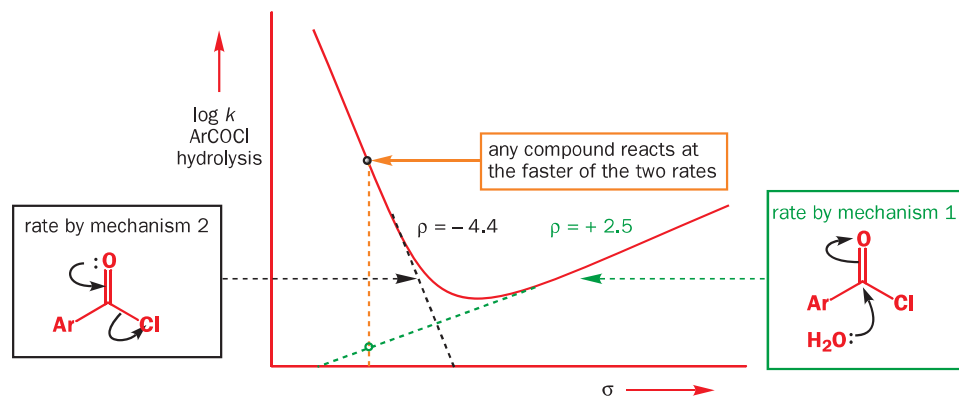


Nonlinear Hammett plots

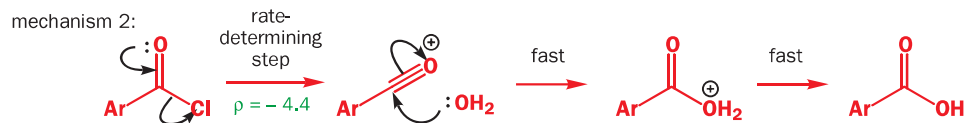
If we look at the hydrolysis of the acid chlorides of benzoic acids in aqueous acetone, we see a very odd Hammett plot indeed. You know that Hammett plots need not be perfectly linear but this one is clearly made up of two intersecting straight lines. This might look like disaster at first but, in fact, it gives us extra information. The right-hand part of the curve, for the more electron-withdrawing substituents, has a slope of +2.5: just what we should expect for rate-determining attack of water on the carbonyl group. As we go to less electron-withdrawing substituents, the rate of the reaction suddenly starts to increase as we pass the *para*-chloro compound and the left-hand part of the curve has a slope of -4.4 .



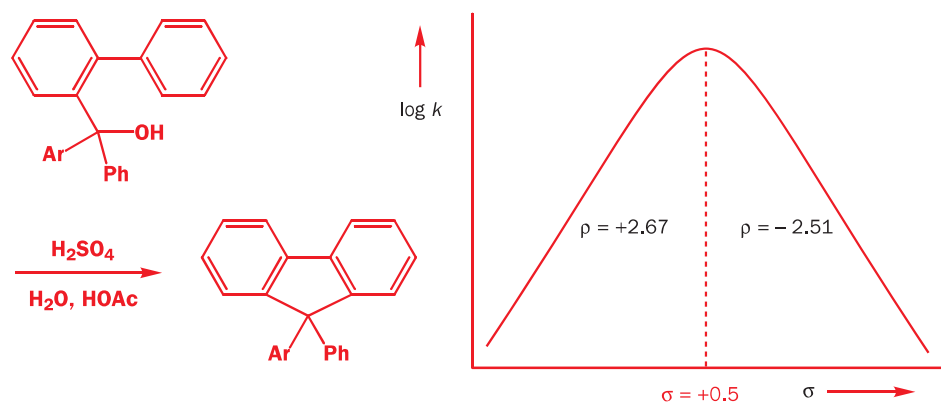
What can this mean? If the reaction becomes faster as we pass the discontinuity in the curve—and it gets faster whether we go from right to left or left to right—there must be a change in mechanism. If there is a choice between two mechanisms, the faster of the two will operate. Mechanism 1 is the rate-determining nucleophilic attack by water on the carbonyl group.



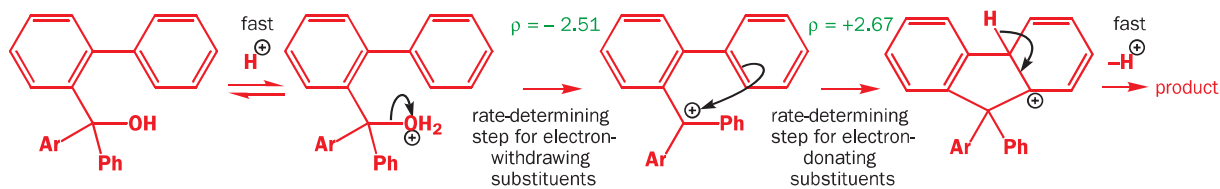
The new mechanism goes faster for more electron-donating substituents and has quite a large negative ρ value suggesting the formation of a cation in the rate-determining step. This mechanism (mechanism 2) must surely be the $\text{S}_{\text{N}}1$ -like process of preliminary formation of an acylium ion by loss of chloride ion.



When the Hammett plot bends the other way, so that the rate of the reaction decreases as it passes the discontinuity, we have a single mechanism with a change in rate-determining step. A reaction goes by the fastest possible mechanism but its rate is limited by the slowest of the steps in that mechanism. An example is the intramolecular Friedel–Crafts alkylation of a diphenyl derivative where the alkylating agent is a diarylmethanol attached to one of the benzene rings in the *ortho* position.



The carbocation intermediate in the Friedel–Crafts reaction (Chapter 22) is rather stable, being tertiary and benzylic, and the formation of the cation, normally the rate-determining step, with inevitably a negative ρ value, goes faster and faster as the electron-donating power of the substituents increases until it is faster than the cyclization which becomes the rate-determining step. The cyclization puts electrons back into the carbocation and has a positive ρ value. As the two steps have more or less the reverse electron flow to and from the same carbon atom, it is reasonable for the size of ρ to be about the same but of opposite sign.



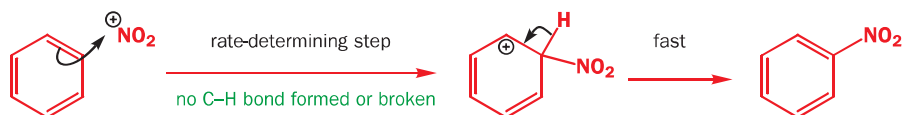
● A reaction occurs by the faster of two possible mechanisms but by the slower of two possible rate-determining steps.

We shall see more examples of Hammett ρ values used in conjunction with other evidence as the chapter develops but now it is time to look at what other evidence is available.

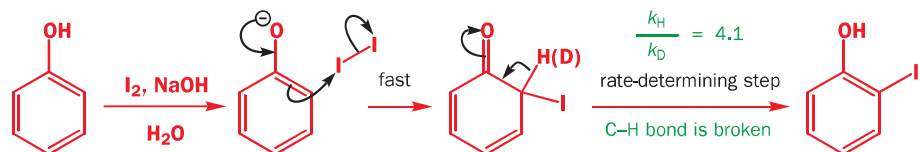
Other kinetic evidence

The kinetic deuterium isotope effect

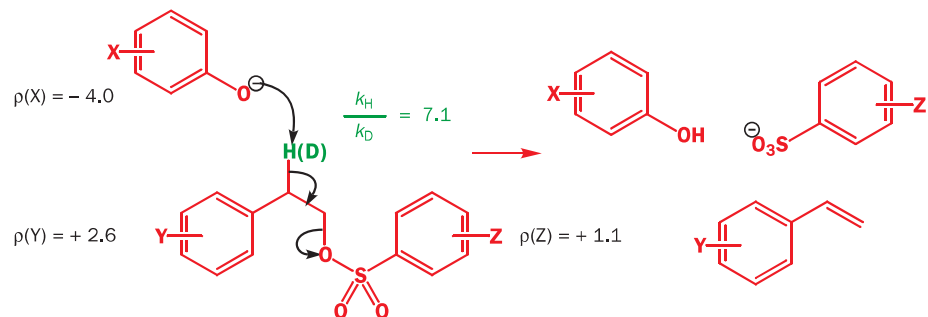
The kinetic isotope effect was introduced in Chapter 19. If a bond to deuterium is formed or broken in the rate-determining step of a reaction, the deuterated compound will react more slowly, usually by a factor of about 2–7. This effect is particularly valuable when C–H bonds are being formed or broken. In Chapter 22 we told you that the rate-determining step in the nitration of benzene was the attack of the electrophile on the benzene ring. This is easily verified by replacing the hydrogen atoms round the benzene ring with deuteriums. The rate of the reaction stays the same.



If the second step, which does involve the breaking of a C–H bond, were the rate-determining step it would go more slowly if the H were replaced by D. In this case the deuterium isotope effect is $k_{\text{H}}/k_{\text{D}} = 1.0$. If the reaction is the iodination of phenol in basic solution, there is a deuterium isotope effect of $k_{\text{H}}/k_{\text{D}} = 4.1$. Clearly, the other step must now be the rate-determining step—the phenolate ion reacts so rapidly that the first step is faster than the second.

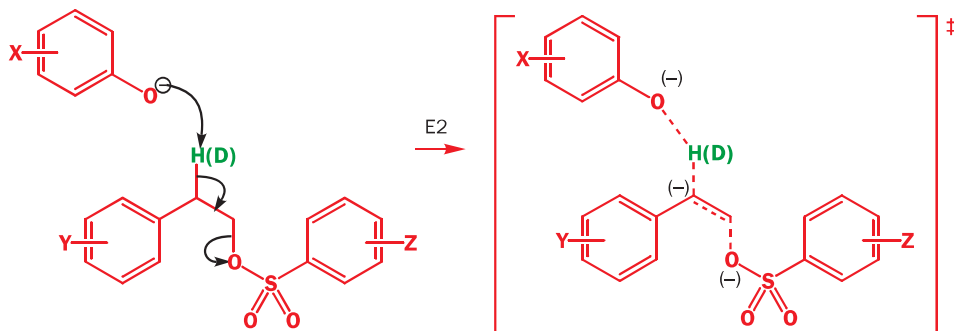


The deuterium isotope effect can add to the information from Hammett plots in building up a picture of a transition state. Three separate Hammett ρ values can be measured for this elimination reaction and this information is very valuable. But it would be sadly incomplete without the information that a large deuterium isotope effect $k_{\text{H}}/k_{\text{D}} = 7.1$ is observed for the hydrogen atom under attack.



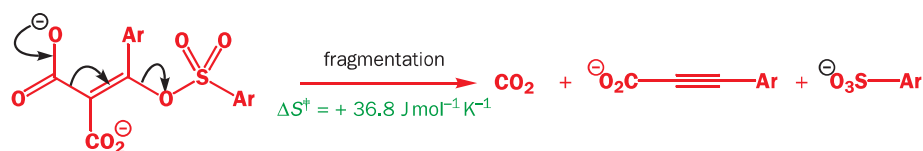
Other kinetic isotope effects are known but they are very small: D is twice as heavy as H but ^{13}C only slightly heavier than ^{12}C .

In this E2 reaction, it is no surprise that the base (ArO^-) donates electrons and the leaving group (ArO_2^-) accepts them. But the large deuterium isotope effect and moderate positive $\rho(\text{Y})$ value for an aromatic ring that might have done nothing suggest some build-up of negative charge in the transition state on that carbon atom as well as on the two oxygen atoms.

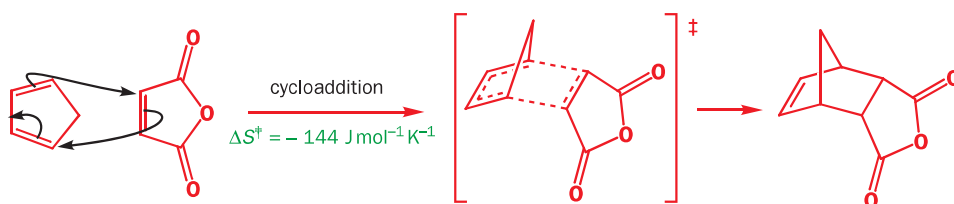


Entropy of activation

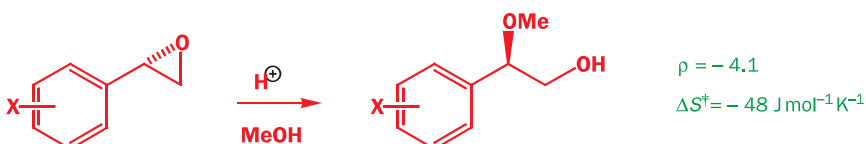
Of all the enthalpies and entropies that we introduced in Chapter 13, the entropy of activation, ΔS^\ddagger , is by far the most useful. It tells us about the increase or decrease in order in a reaction as the starting material goes to the transition state. A positive ΔS^\ddagger means an increase in entropy or a decrease in order and a negative ΔS^\ddagger means an increase in order. Normally, unimolecular reactions in which one molecule gives two products have a positive ΔS^\ddagger and bimolecular reactions have a negative ΔS^\ddagger . Fragmentations (Chapter 38) such as this decarboxylation in which one molecule fragments to three have positive ΔS^\ddagger s. It has $\Delta S^\ddagger = +36.8 \text{ J mol}^{-1} \text{ K}^{-1}$.



At the other extreme are cycloadditions (Chapter 35) such as the Diels–Alder reaction we examined a few pages back. Not only do two reagents become one product but a very precise orientation is required in the transition state usually meaning a large negative ΔS^\ddagger . Diels–Alder reactions usually have ΔS^\ddagger of about -120 to $-160 \text{ J mol}^{-1} \text{ K}^{-1}$. The classic cyclopentadiene addition to maleic anhydride has $\Delta S^\ddagger = -144 \text{ J mol}^{-1} \text{ K}^{-1}$.

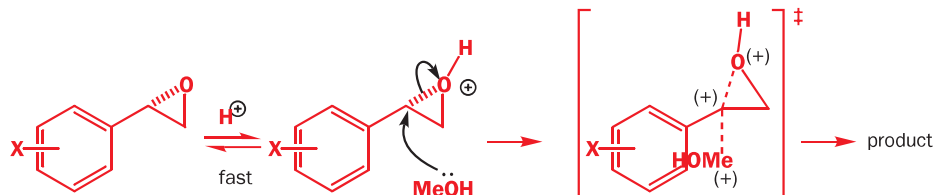


These numbers give you the range of entropies of activation you may expect to find. Large negative numbers are common but only small positive numbers are found. The largest negative numbers apply to bimolecular reactions where neither reagent is in great excess. Smaller negative numbers may mean a bimolecular reaction with solvent or some other reagent in large excess. The acid-catalysed opening of styrene oxides in methanol is a good example.



▶ Entropies of activation are measured in units of $\text{J mol}^{-1} \text{ K}^{-1}$. All the values in this book are in $\text{J mol}^{-1} \text{ K}^{-1}$ but in older books you will see 'entropy units' (e.u.), which are $\text{cal mol}^{-1} \text{ K}^{-1}$. Values in e.u. should be multiplied by about

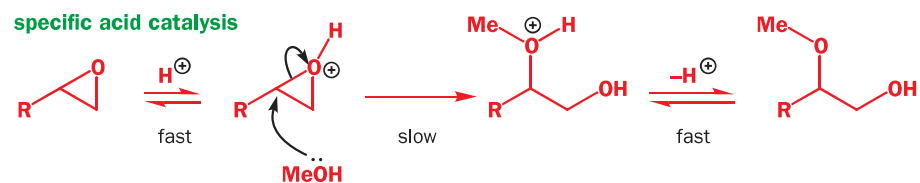
The Hammett ρ value of -4.1 suggests a carbocation intermediate as does the regioselectivity of the reaction (MeOH attacks the benzylic position) but the stereochemistry (the reaction occurs with inversion) and a modest negative entropy of activation ($\Delta S^\ddagger = -48 \text{ J mol}^{-1} \text{ K}^{-1}$) suggest rather an $\text{S}_{\text{N}}2$ reaction with a loose transition state having substantial positive charge at the benzylic carbon. Neither piece of evidence alone would be enough to define the mechanism.



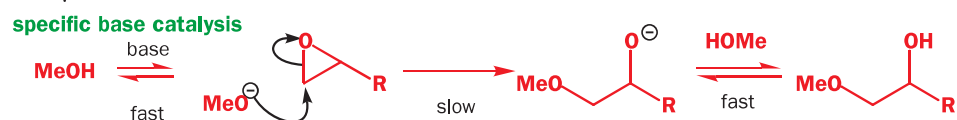
This example with its acid catalyst brings us to the subject of catalysis. We must now analyse the different sorts of acid and base catalysis and see how the mechanisms can be distinguished using the methods we have discussed.

Acid and base catalysis

Acids and bases provide the best known ways of speeding up reactions. If you want to make an ester—add some acid. If you want to hydrolyse an ester—add some base. It may all seem rather simple. However, there are actually two kinds of acid catalysis and two kinds of base catalysis and this section is intended to explain the difference in concept and how to discover which operates. When we talk about acid catalysis we normally mean **specific acid catalysis**. This is the kind we have just seen—epoxides don't react with methanol but, if we protonate the epoxide first, then it reacts. Specific acid catalysis protonates electrophiles and makes them more electrophilic.



We could, on the other hand, have argued that methanol is not a good enough nucleophile but if deprotonated with a base it becomes the much more nucleophilic methoxide. This is **specific base catalysis**.

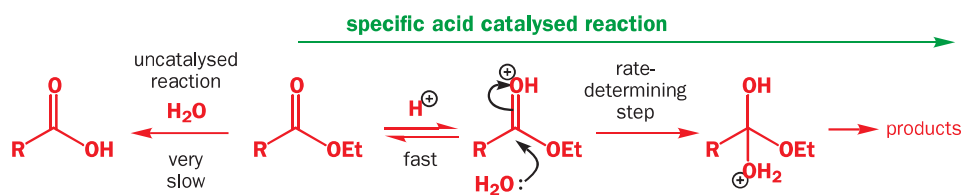


We shall discuss these two types first because they are straightforward. You need to recognize their characteristics, their strengths, and their weaknesses. We hope you will get into the habit of recognizing these types of catalysis so that you hardly have to think about it—it should become second nature.

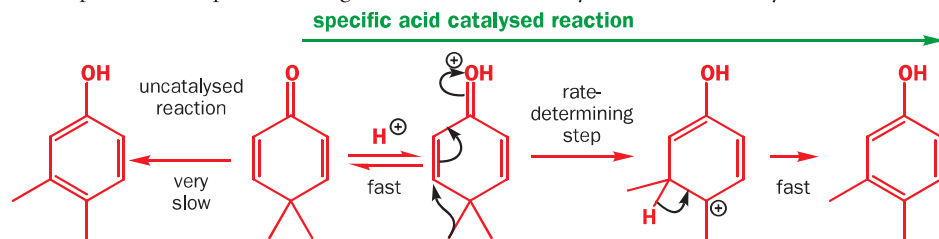
Specific acid catalysis

Specific acid catalysis (SAC) involves a rapid protonation of the compound followed by the slow step, which is accelerated in comparison with the uncatalysed reaction because of the greater reactivity of the protonated compound. You have just seen an example with an epoxide. Ester hydrolysis (or formation) is another. Water attacks esters very slowly: it attacks protonated esters much more quickly. This is just the ordinary mechanism for acid-catalysed ester hydrolysis (or formation) given in Chapter 12.

▶ SAC is the usual method by which acids make reactions go faster and, if you think about the acid-catalysed reactions you already know, you will see that you have been using it all along without realizing it.

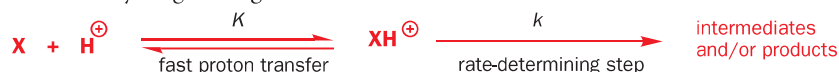


A more interesting reaction is the dienone–phenol rearrangement (Chapter 37). Rearrangement in the absence of acid is very slow but, once the ketone oxygen is protonated, it occurs very rapidly. Again we have fast equilibrium protonation followed by a rate-determining step involving a reaction of the protonated species and again this is the ordinary mechanism that you now know to call SAC.



This catalysis depends only on the protonating power of the solution. The compound must be protonated to react so the catalyst must be a strong enough acid to do the job. It is not necessary that every molecule is protonated, just enough to set the reaction going as the acid is regenerated at the end. So the (log of the) rate of the reaction is inversely proportional to the pH of the solution and significant only in the region of, and of course below, the pK_{aH} of the substrate.

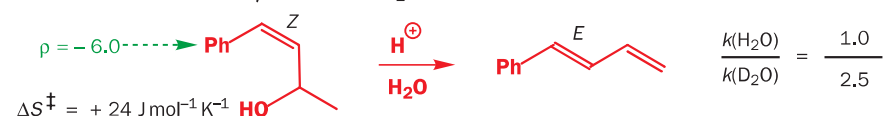
There is one special experimental indication of this mechanism. If the reaction is carried out in a deuterated solvent (D_2O instead of H_2O) the rate of the reaction increases. This is a solvent isotope effect rather than a kinetic isotope effect and needs some explanation. If you examine the three examples of SAC in the previous pages you will see that they share these characteristics: a fast proton exchange is followed by a rate-determining step that does *not* involve the making or breaking of any bonds to hydrogen. In general terms:



The rate of the reaction is the rate of the rate-determining step: $\text{rate} = k[XH^+]$. The concentration of the intermediate $[XH^+]$ is related to the pH and to the concentration of the substrate by the equilibrium constant, K , of the protonation. So we have: $\text{rate} = kK[H^+][X]$. We know that k does not change when hydrogen is replaced by deuterium so K must increase in D_2O .

You will sometimes see in books the statement that D_3O^+ is a stronger acid than H_3O^+ . This is partly true. The full truth is that D_3O^+ in D_2O is a stronger acid than H_3O^+ in H_2O . Water (H_2O) is a better solvating agent for H_3O^+ than D_2O is for D_3O^+ , simply because it forms stronger hydrogen bonds due to the greater O–H vibration frequency. So D_3O^+ in D_2O is less well solvated than H_3O^+ in H_2O and is a stronger acid. You need an example.

The *Z*-allylic alcohol below dehydrates in acid solution to the *E*-diene. We have lots of data on this mechanism, all summarized in the diagrams. You may like to note as well that the product contains no deuterium after dehydration in D_2O .

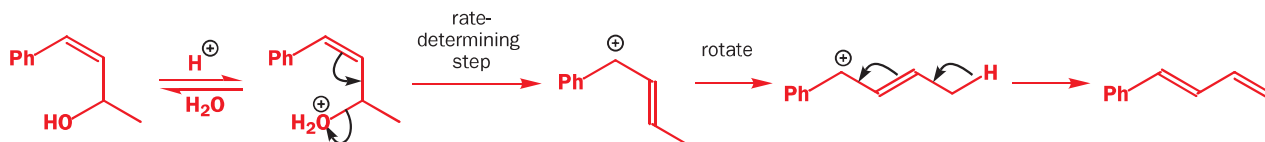


The Hammett ρ value of -6.0 suggests a carbocation intermediate and the positive entropy of activation suggests a rate-determining step in which disorder increases, perhaps one molecule breaking into two. The inverse solvent deuterium isotope effect (faster reaction in D_2O than in H_2O) strongly suggests SAC. Putting all this together we have a mechanism—a simple example of SAC with no protonation at carbon.

▶ A normal kinetic isotope effect has $k_H/k_D > 1$. Deuterium is often put into compounds by exchange with the cheapest source, D_2O , so reactions in D_2O often go slower than reactions in H_2O . Reactions with $k_H/k_D < 1$ have inverse deuterium isotope effects so a reaction that goes faster in D_2O than in H_2O (even when that is the expected pattern) has an *inverse solvent deuterium isotope effect*.

▶ It is not, of course, possible to use D_3O^+ in H_2O as H and D exchange very quickly. The solvent determines which acid is present.

■ You might like to compare this mechanism with the isomerization of the same diene described earlier in this chapter.



One more thing about this example. The rate-determining step is the second step so the other data, the Hammett ρ value and the entropy of activation, also refer to the combination of K and k . The equilibrium ρ value for the protonation will be fairly small and negative as a positive charge is being created some way from the benzene ring. The kinetic ρ value for the loss of water will be large and negative because a positive charge is being created that is delocalized into the ring. A combined value of -6 looks fine. The equilibrium entropy ΔS° for the protonation will probably be small and negative as $\text{ROH} + \text{H}_3\text{O}^+ \rightleftharpoons \text{ROH}_2^+ + \text{H}_2\text{O}$ represents little change in order (two molecules going to two) and the ΔS^\ddagger for the loss of water will be large and positive (one molecule going to two) so a small positive value is about right. It doesn't do to interpret these numbers too closely.

● Summary of features of specific acid catalysis

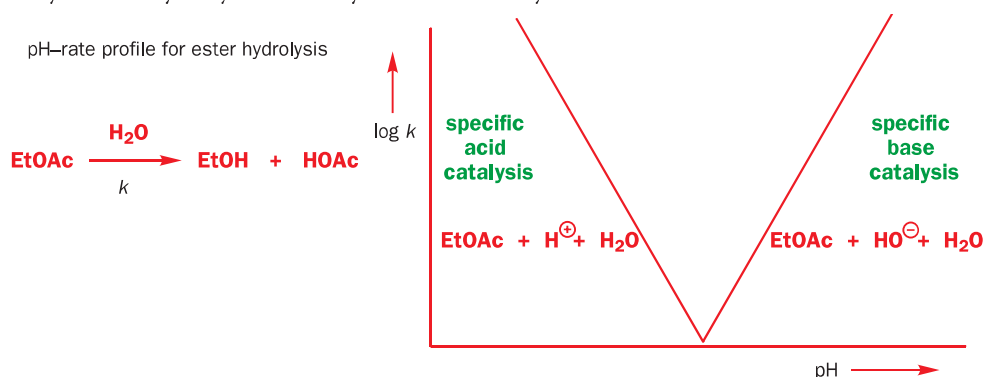
1. Only H_3O^+ is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of protonated species
3. Effective only at pHs near or below the $\text{p}K_{\text{aH}}$ of the substrate
4. Proton transfer is not involved in the rate-determining step
5. Only simple unimolecular and bimolecular steps—moderate $+$ or $-\Delta S^\ddagger$
6. Inverse solvent isotope effect $k(\text{H}_2\text{O}) < k(\text{D}_2\text{O})$

Specific base catalysis

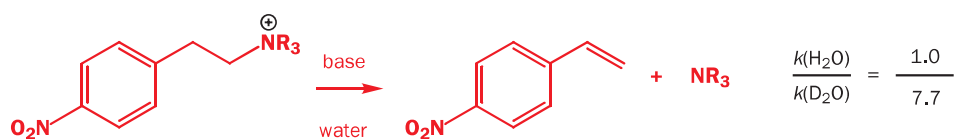
The other side of the coin is specific base catalysis (SBC) which usually involves the removal of a proton from the substrate in a fast pre-equilibrium step followed by a rate-determining reaction of the anion. Most of the base-catalysed reactions you are familiar with work by SBC. Examples include opening of epoxides with thiols.



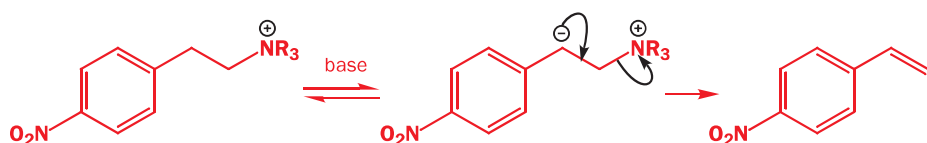
The rate of the reaction depends on the pH of the solution. If it is around or higher than the $\text{p}K_{\text{a}}$ of the thiol, thiolate anion will be formed and this opens the epoxide much faster than does the unionized thiol. The nucleophile is regenerated by the oxyanion produced in the rate-determining step. A more familiar example is the base-catalysed hydrolysis of esters we have mentioned several times in this chapter. The full pH–rate profile (Chapter 13) for the hydrolysis of a simple ester such as ethyl acetate shows just two straight lines meeting each other (and zero rate) at about neutrality. Ethyl acetate hydrolysis occurs by SAC or SBC only.



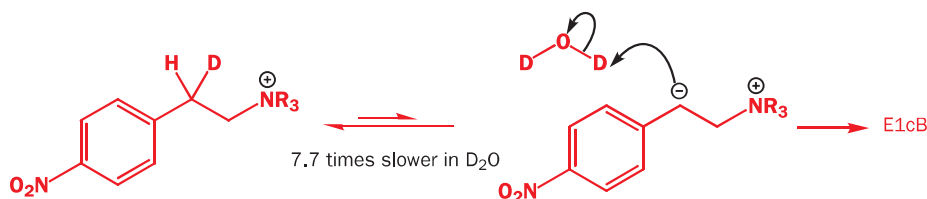
Removal of a proton from heteroatoms by heteroatom bases is always a fast step but removal of a proton from carbon can be the rate-determining step. A remarkably large inverse solvent deuterium isotope effect was found with this elimination of a tertiary amine in basic solution.



The detailed mechanism cannot, of course, be E2 or the isotope effect, if any, would be the other way round. If it is SBC, the mechanism then becomes the well-known E1cB (Chapter 19) having a carbanion as intermediate.



But 1/7.7 is too large to be a solvent isotope effect and looks much more like a normal kinetic isotope effect. And so it is. The tertiary amine is not a very good leaving group in spite of its positive charge ($\text{p}K_{\text{aH}}$ about 10) so the carbanion mostly reverts to starting materials. The isotope effect is a kinetic isotope effect on this reverse step—the protonation of the carbanion. This reaction involves a proton transfer from H_2O or D_2O and will be much faster (could be 7.7 times) in H_2O by the ordinary kinetic isotope effect. The *elimination* reaction goes faster in D_2O because the back reaction goes more slowly and more of the carbanion goes on to product.



► Microscopic reversibility

There is only one least-energy pathway between two interconverting compounds such as the starting material and the intermediate here. Every microscopic detail of the back reaction is exactly the same as that for the forward reaction. This is the principle of microscopic reversibility. Here we use evidence from the back reaction (slow proton transfer from water to the carbanion) to tell us about the forward reaction. This principle will be useful in Chapter 42.

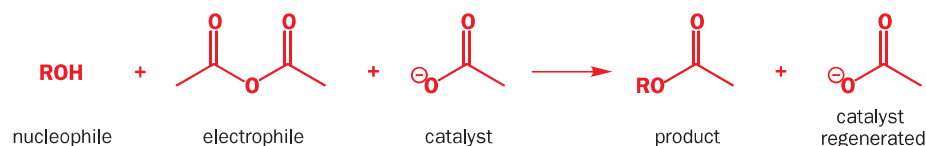
● Summary of features of specific base catalysis

1. Only HO^- is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of deprotonated species
3. Effective only at pHs near or above the $\text{p}K_{\text{a}}$ of the substrate
4. Proton transfer is not involved in the rate-determining step, unless C–H bonds are involved
5. Only simple unimolecular and bimolecular steps—moderate + or $-\Delta S^\ddagger$
6. Inverse solvent isotope effect $k(\text{H}_2\text{O}) < k(\text{D}_2\text{O})$

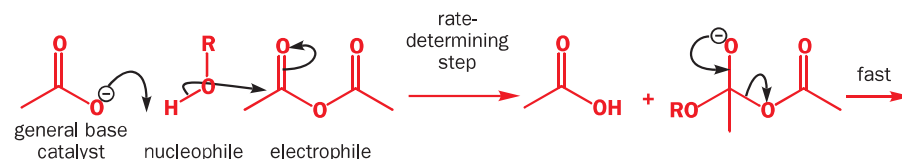
General acid/base catalysis

The other kind of acid/base catalysis is called ‘general’ rather than ‘specific’ and abbreviated GAC or GBC. As the name implies this kind of catalysis depends not only on pH but also on the concentration of undissociated acids and bases other than hydroxide ion. It is a milder kind of catalysis and is used in living things. The proton transfer is not complete before the rate-determining step but occurs during it. A simple example is the catalysis by acetate ion of the formation of esters from alcohols and acetic anhydride.

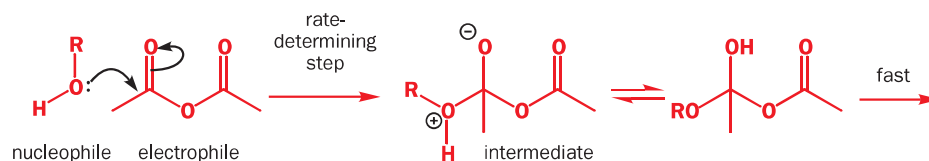
There was some discussion of this reaction in Chapter 13. Chapter 12 refers to the difficulty of pinpointing proton transfers in mechanisms involving the carbonyl group.



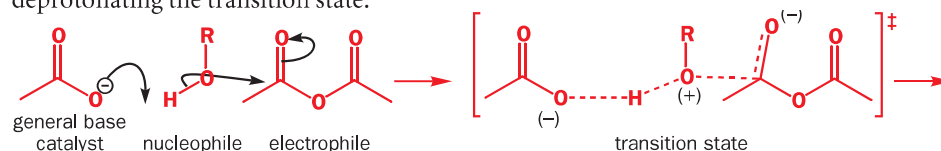
How can this catalysis work? At first sight there seems to be no mechanism available. Acetate cannot act as a specific base—it is far too weak ($\text{p}K_{\text{aH}} 4.7$) to remove a proton from an alcohol ($\text{p}K_{\text{a}}$ about 15). If it acted as a nucleophile (Chapters 12 and 13) there would be no catalysis as nucleophilic attack on acetic anhydride would be a nonreaction simply regenerating starting materials. The only thing it can do is to remove the proton from the alcohol *as the reaction occurs*.



You will see at once that there is a great disadvantage in this mechanism: the rate-determining step is termolecular and this is really termolecular—three molecules colliding—and not just some mathematical kinetic trick. This comes out most clearly in the entropy of activation which is an enormous negative value, around $\Delta S^\ddagger = -168 \text{ J mol}^{-1} \text{ K}^{-1}$ for this reaction. There will also be a normal kinetic isotope effect for ROD against ROH as a bond to hydrogen is being formed and broken in the rate-determining step: it is $k_{\text{H}}/k_{\text{D}} = 2.4$ here. These GBC or GAC reactions are normally effective only if one of the three molecules is present in large excess—this reaction might be done in ROH as a solvent, for example, so that ROH is always present. In understanding how this GBC works it is helpful to look at the mechanism without catalysis.



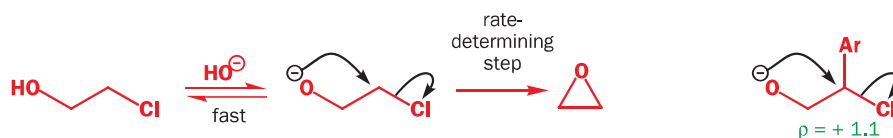
The acetate catalyst cannot remove a proton from the starting material but it can easily remove a proton from the intermediate, which has a complete positive charge on the alcohol oxygen atom. The starting material has a $\text{p}K_{\text{a}}$ above the $\text{p}K_{\text{aH}}$ of acetate but the product has a $\text{p}K_{\text{a}}$ well below it. Somewhere in the middle of the rate-determining step, the $\text{p}K_{\text{a}}$ of the ROH proton passes through the $\text{p}K_{\text{aH}}$ of acetate and then acetate is a strong enough base to remove it. The GBC is effectively deprotonating the transition state.



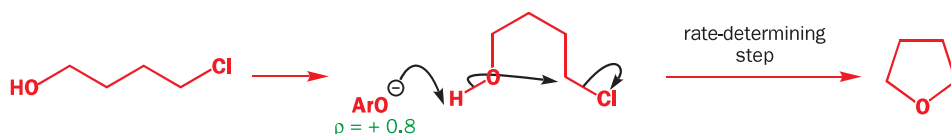
So how do we find GAC or GBC? Normally, general species catalysis is a weak addition to specific catalysis. We must remove that more powerful style of catalysis by working at a specific pH because SAC or SBC depends on pH alone. If we find that the rate of the reaction changes with the concentration of a weak base at constant pH, we have GBC. Note that, if the proton transfer is between heteroatoms, as in this example, some other bond-making or bond-breaking steps must be happening too as proton transfer between heteroatoms is always a fast process. Proton transfer to or from carbon can be slow.

The formation of three- and five-membered cyclic ethers shows the contrast between GBC and SBC. The formation of epoxides is straightforward SBC with a simple linear dependence on pH between pH 8 and 12 and no acceleration at constant pH by carbonate (CO_3^{2-}) ions. There is an

inverse solvent isotope effect and an aryl substituent at the electrophilic carbon atom gives the small positive ρ value expected for S_N2 with an anion.



Formation of tetrahydrofuran (THF) is also faster at higher pH but, by contrast, is also accelerated by various bases at constant pH. If anions of phenols (ArO^-) are used as catalysts, a Hammett ρ value of +0.8 shows that electrons are flowing away from the aromatic ring. There is a small normal kinetic isotope effect $k_{\text{H}}/k_{\text{D}} = 1.4$. There is SBC and GBC in this reaction. Here is the mechanism with ArO^- as GBC.



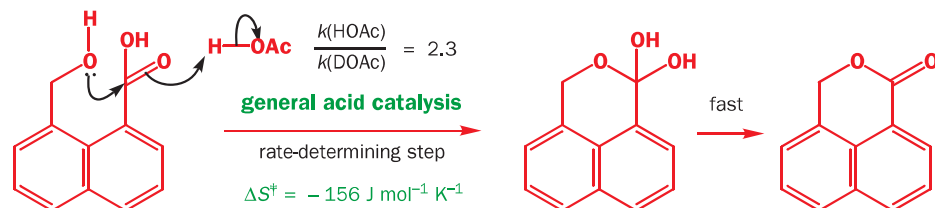
Why are the two different? The THF is easy to form, the transition state is unstrained, and only a little help is needed to make the reaction go. The epoxide is very strained indeed and the starting material needs to be raised in energy before cyclization will occur. Only the most powerful catalysis is good enough.

● Summary of features of general base catalysis

1. Any base is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if below the pK_a of the substrate
4. Catalyst often much too weak a base to deprotonate reagent
5. Catalyst removes proton, which is becoming more acidic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^\ddagger$
8. Normal kinetic isotope effect $k(\text{H}) > k(\text{D})$

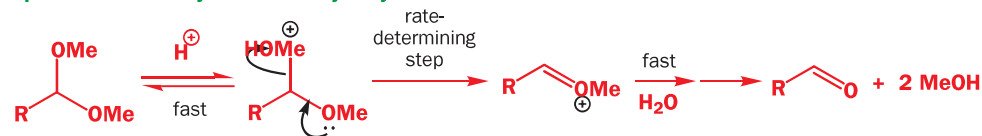
General acid catalysis

We have already discussed this in general terms so a couple of examples will be enough. First, the termolecular problem can be avoided if the reaction is intramolecular. The catalysis is then bimolecular as in the cyclization of this hydroxy-acid. Normally, ester formation and hydrolysis are specific-acid-catalysed only but here there is catalysis by acetic acid; $k(\text{HOAc})/k(\text{DOAc})$ is 2.3 showing that proton transfer occurs in the rate-determining step and there is a large negative $\Delta S^\ddagger = -156 \text{ J mol}^{-1} \text{ K}^{-1}$. This is general acid catalysis of nucleophilic attack on a carbonyl group, admittedly in a special molecule.



Earlier in the book (Chapter 14) we emphasized the importance of the mechanism for the formation and hydrolysis of acetals. These are SAC reactions: alcohols are bad leaving groups and usually need to be fully protonated by strong acids before they will go, even with the help of a lone pair on another oxygen atom.

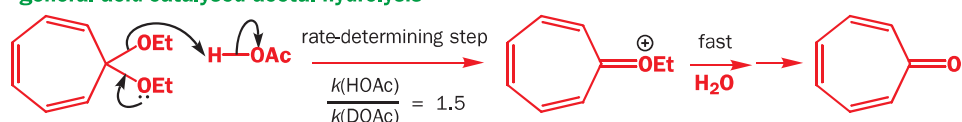
specific acid-catalysed acetal hydrolysis



■ In both these examples the steps after the rate-determining step are omitted and you should look at Chapter 14 for the full details.

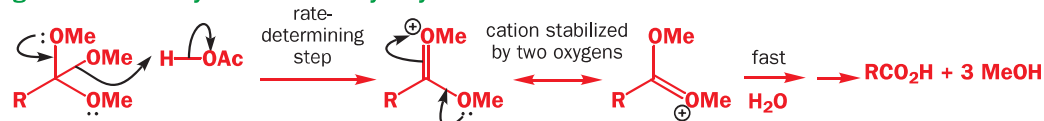
If we speed up the slow step by adding to the molecule some feature that stabilizes the cation intermediate, general acid catalysis may be found. One example is the aromatic cation formed in the hydrolysis of cycloheptatrienone acetals. The normal kinetic isotope effect proclaims GAC.

general acid-catalysed acetal hydrolysis



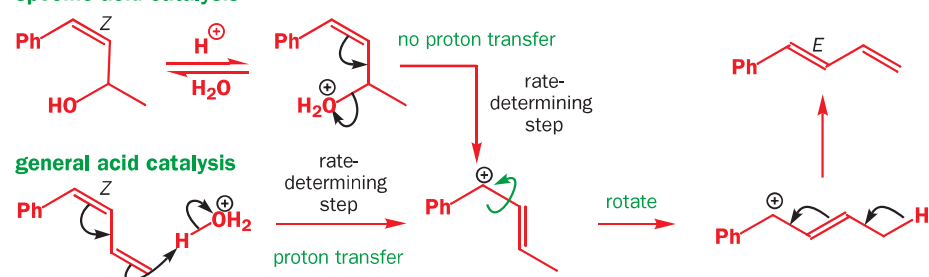
Even adding one extra alkoxy group so that we have an orthoester instead of an acetal is enough. These compounds show catalysis with a variety of weak acids at not very acidic pHs (5–6). As one OMe group is protonated, two others are pushing it out and they both help to stabilize the intermediate cation. Nature prefers these milder methods of catalysis as we will see in Chapter 50.

general acid-catalysed orthoester hydrolysis



For another contrast between SAC and GAC we need only refer you back to the two *Z/E* isomerizations earlier in the chapter. Isomerization of the diene is GAC—protonation at carbon is the slow step—and isomerization of the allylic alcohol is SAC. What we didn't tell you earlier was that the GAC reaction has a normal kinetic isotope effect of $k(\text{H})/k(\text{D}) = 2.5$ and a negative entropy of activation $\Delta S^\ddagger = -36 \text{ J mol}^{-1} \text{ K}^{-1}$ —just what we should expect for a bimolecular reaction involving rate-determining proton transfer from oxygen to carbon. Notice that the intermediate cation is the same whichever the route; only the ways of getting there, including the rate-determining steps, are different.

specific acid catalysis



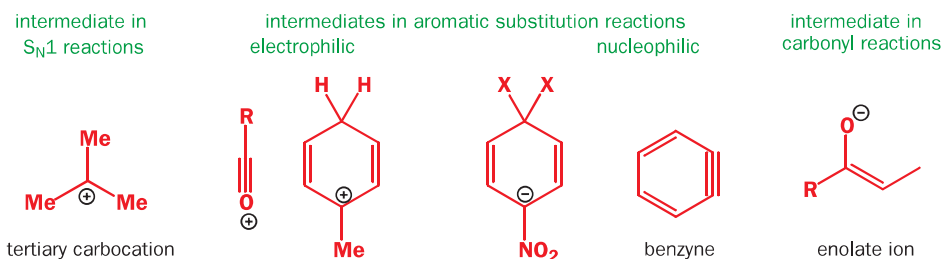
These examples show you that general acid catalysis is possible with strong acids, especially when protonation is at carbon and that, when protonation is at carbon, no other bond-making or -breaking steps need be involved.

● Summary of features of general acid catalysis

1. Any acid is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if above the pK_{aH} of the substrate
4. Catalyst often much too weak an acid to protonate reagent
5. Catalyst adds proton to a site that is becoming more basic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^\ddagger$
8. Normal kinetic isotope effect $k(H) > k(D)$

The detection of intermediates

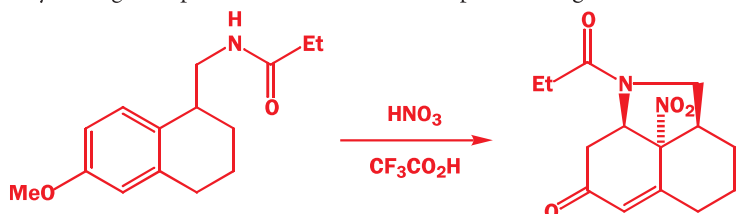
In earlier chapters we revealed how some reactive intermediates can be prepared, usually under special conditions rather different from those of the reaction under study, as a reassurance that some of these unlikely looking species can have real existence. Intermediates of this kind include the carbocation in the S_N1 reaction (Chapter 17), the cations and anions in electrophilic (Chapter 22) and nucleophilic (Chapter 23) aromatic substitutions, and the enols and enolates in various reactions of carbonyl compounds (Chapters 21 and 26–29). We have also used labelling in this chapter to show that symmetrical intermediates are probably involved in, for example, nucleophilic aromatic substitution with a benzyne intermediate (Chapter 23).



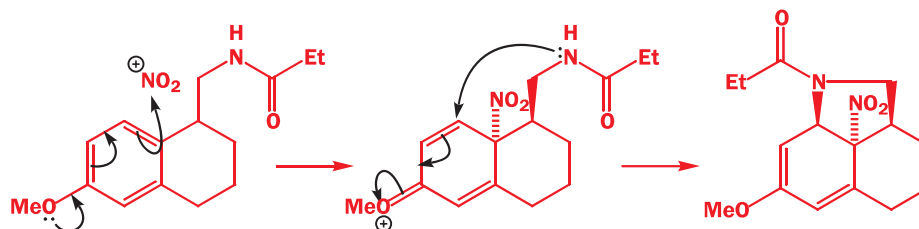
We have hedged this evidence around with caution since the fact that an intermediate can be prepared does not by any means prove that it is involved in a reaction mechanism. In this section we are going to consider other and better evidence for intermediates and at the same time revise some of the earlier material.

Trapping reactions

A more impressive piece of evidence is the design of a molecule that has built into it a functional group that could react with the intermediate in a predictable way but could not reasonably react with other species that might be present. For example, aromatic ethers react with nitrating agents in the *ortho* or *para* positions (Chapter 22). The intermediate has a positive charge delocalized over three of the carbon atoms in the benzene ring. If a nucleophilic group is built into the structure in the right way, it might trap this intermediate and stop it reacting further.



The trapping group is the amide and it has trapped a cation formed by addition of NO_2^+ to the aromatic ring. We are faced with the problem of drawing a mechanism for the formation of this remarkable compound and, when we discover that a necessary intermediate is also an intermediate in our preferred mechanism for aromatic nitration, we feel more confident about that mechanism.

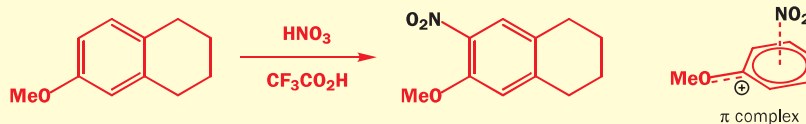


This mechanism explains everything including the stereochemistry. The NO_2^+ attacks the aromatic ring *para* to the OMe group and on the opposite side to the amide. The amide is now in the perfect position to capture the cation at the *meta* position and, because the tether is short, it must form a *cis* bridge.

π complexes in electrophilic aromatic substitution

The weakness in the experiment is that nitration does not occur in that position without the trap but occurs in the *ortho* position. Nevertheless, many chemists believe that aromatic electrophilic substitution actually starts with a loose association of the electrophile with all of the p

orbitals of the benzene ring so that here the NO_2^+ group would initially sit at right angles to the plane of the ring in a ' π complex' and would move afterwards to form a σ bond with one particular carbon atom.



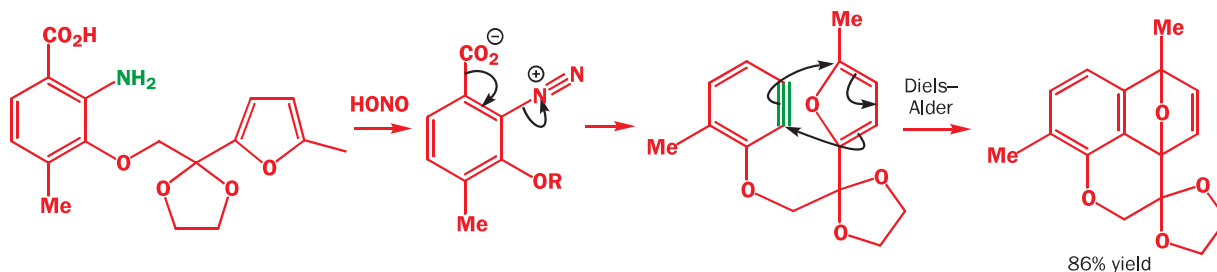
You will meet the related π complexes of metals in Chapter 48.

To be convincing, evidence for an intermediate should include:

- detection of the intermediate in the reaction mixture, perhaps by a trapping reaction
- a demonstration that the intermediate gives the product when added to the reaction mixture (this also means that it must be prepared as an at least reasonably stable compound)
- kinetic evidence that the rate of formation and rate of disappearance are adequate
- other suitable evidence of the kind that we have been discussing in this chapter

What is the cyclic acetal for? It is there to make the cyclization more efficient by the Thorpe-Ingold effect; see Chapter 42.

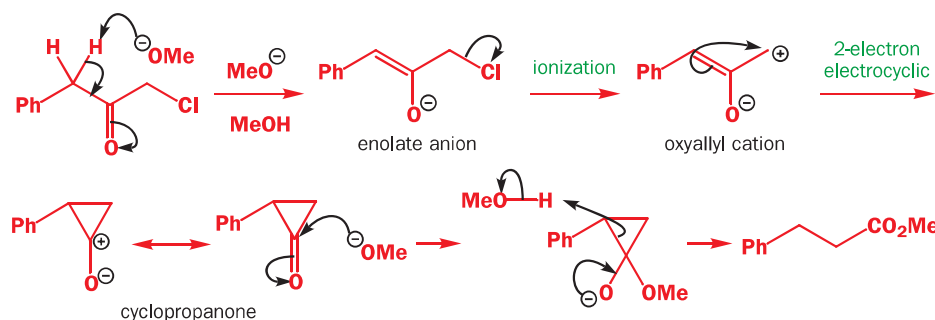
A neat intramolecular trap for benzyne works in this way. A standard benzyne-generating reaction—the diazotization of an *ortho*-amino benzoic acid (Chapter 23) gives a zwitterion that loses nitrogen and CO_2 to release the benzyne. A furan tethered to the next *ortho* position traps the benzyne in an intramolecular Diels-Alder reaction. The yield is impressive and the trap is very efficient.



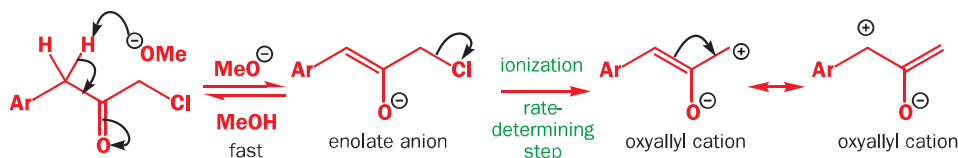
The argument is that this reaction cannot really be explained without a benzyne intermediate. This same method of making benzyne is used on other *o*-amino benzoic acids and so they presumably create benzyne too.

A collection of reactions linked by a common intermediate

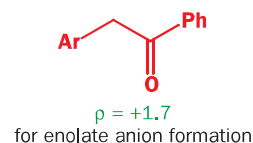
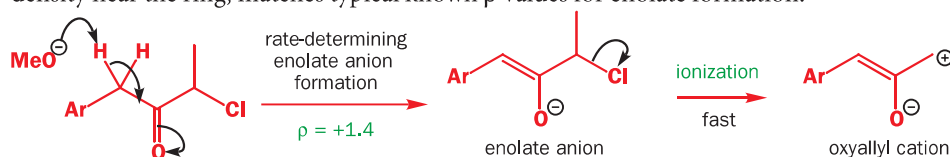
Particularly convincing evidence can develop when a number of chemists suggest the same intermediate for a number of different reactions and show that it is possible to trap the intermediate from one reaction, put it into the others, and get the normal products. We are going to describe one set of such related reactions. In Chapter 37 we suggested a mechanism for the Favorskii rearrangement involving a series of remarkable intermediates. Here is an example.



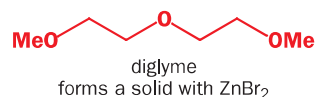
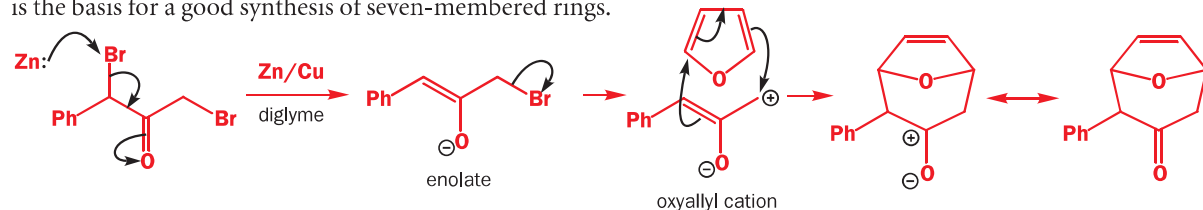
A quick summary of the evidence on this particular example. If the reaction is run in MeOD instead of MeOH, the starting material becomes deuterated at the site of enolate formation suggesting that this is a fast and reversible step. The entropy of activation for the reaction is $\Delta S^\ddagger = +64 \text{ J mol}^{-1} \text{ K}^{-1}$, suggesting that the slow step is one molecule breaking into two. There is only one such step—the second, ionization step. If various substituted phenyl groups are used, the Hammett ρ value is -5 . This large negative value also suggests that the ionization is the slow step as the cation is delocalized into the benzene ring.



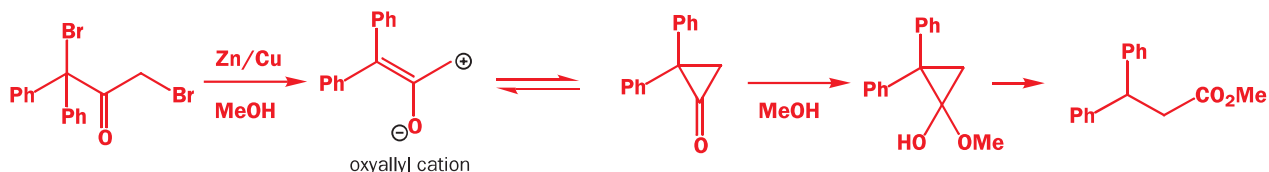
So there is some evidence for the first intermediate—the exchange of deuterium from the solvent. The formation of the enolate can even become the rate-determining step! If we merely add an extra methyl group to the chloro-ketone the reaction becomes 220 times faster and the rate-determining step changes. There is no longer any exchange of deuterium from the solvent and the Hammett ρ value changes from -5 to $+1.4$. This small positive value, showing some modest increase in electron density near the ring, matches typical known ρ values for enolate formation.



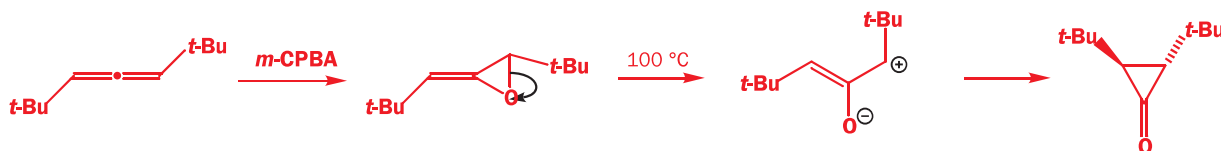
However, we are not surprised that an enolate ion is formed from a ketone in basic solution. The oxyallyl cation is much more surprising. How can we be convinced that it really is an intermediate? There are several alternative ways to make the same intermediate. If basic nucleophiles such as the methoxide ion are avoided and reaction of zinc with an α,α' -dibromoketone in a nonnucleophilic solvent like diglyme is used instead, the oxyallyl cation can be trapped in a Diels–Alder reaction. This is the basis for a good synthesis of seven-membered rings.



But does the oxyallyl cation go on to give cyclopropanones? In fact, there is good evidence that the two are in equilibrium. If the same method is used to create the diphenyl oxyallyl cation in methanol instead of in diglyme, the normal Favorskii product is produced. Evidently, methoxide is needed only to produce the enolate—methanol is enough to decompose the cyclopropanone.

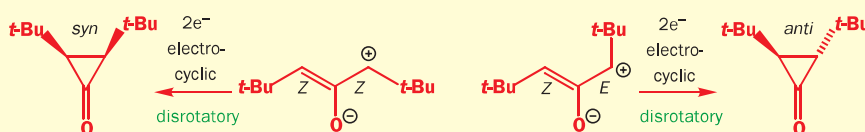


If a suitable (1,3-di-*t*-butyl) allene is epoxidized with *m*-CPBA the unstable allene oxide can actually be isolated. On heating, this epoxide gives a stable *trans*-di-*t*-butylcyclopropanone. It is very difficult to see how this reaction could happen except via the oxyallyl cation intermediate.

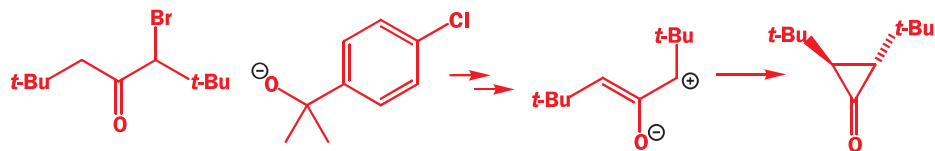


Why draw the oxyallyl cation with this stereochemistry?

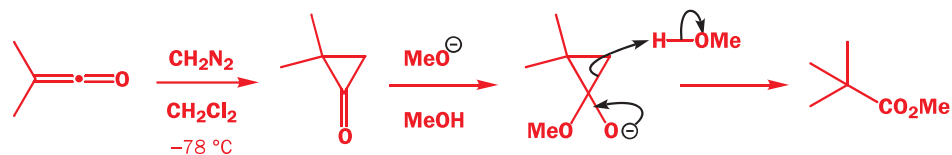
If the closure to the cyclopropanone is electrocyclic then it will be disrotatory (Chapter 36). The *E,Z*-isomer we have drawn gives the *anti* cyclopropanone while either the *E,E* or the *Z,Z*-oxyallyl cation gives the *syn*-di-*t*-butylcyclopropanone.



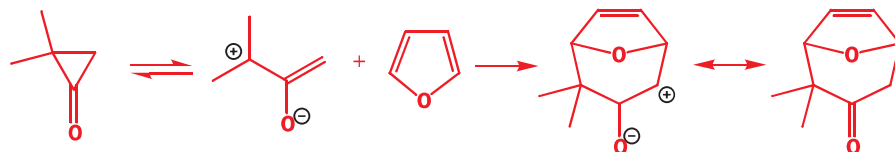
But is the same cyclopropanone an intermediate in the Favorskii reaction? If the bromoketone is treated with methoxide in methanol, it gives the Favorskii product but, if it is treated with a much more hindered base, such as the potassium phenoxide shown, it gives the same cyclopropanone with the same stereochemistry.



Other, less stable cyclopropanones, such as the 2,2-dimethyl compound, can be made by carbene addition (Chapter 40) to ketenes. This compound did the Favorskii reaction with methoxide in methanol: the only product came from the expected loss of the less unstable carbanion. This will, of course, be general-acid-catalysed by methanol as no free carbanion can be released into an alcoholic solvent.



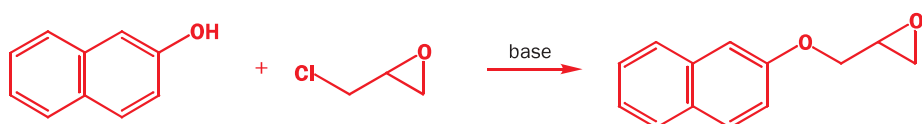
The same cyclopropanone gives a cycloadduct with furans—this must surely be a reaction of the oxyallyl cation and we can conclude that the three isomeric reactive intermediates (allene oxide, cyclopropanone, and oxyallyl cation) are all in equilibrium and give whichever product is appropriate for the conditions.



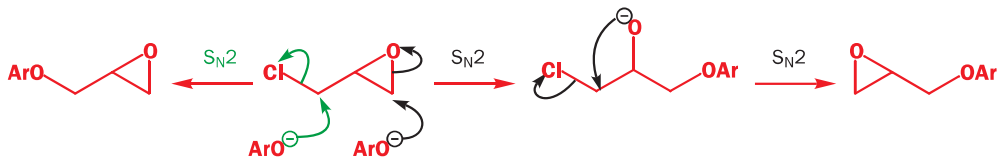
Though it is never possible to prove a mechanism, this interlocking network of intermediates, all known to be formed under the reaction conditions, all being trapped in various ways, and all known to give the products, is very convincing. If any part of the mechanism were not correct, that would throw doubt on all the other reactions as well. Nevertheless, this mechanism is not accepted by all chemists.

Stereochemistry and mechanism

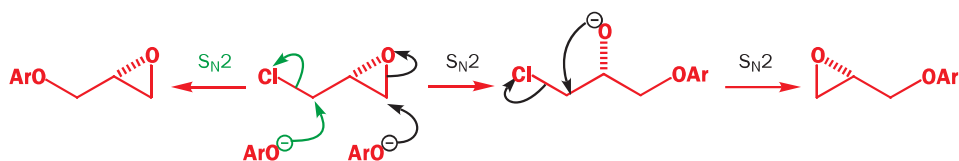
This chapter ends with a survey of the role of stereochemistry in the determination of mechanism. Though we have left stereochemistry to the last, it is one of the most important tools in unravelling complex mechanisms. You have already seen how inversion of configuration is a vital piece of evidence for an S_N2 mechanism (Chapter 17) while retention of configuration is the best evidence for participation (Chapter 37). You have seen the array of stereochemical evidence for pericyclic mechanisms (Chapters 35 and 36). The chapters devoted to diastereoselectivity (33 and 34) give many examples where the mechanism follows from the stereochemistry. We shall not go over that material again, but summarize the types of evidence with new examples. The first example looks too trivial to mention.



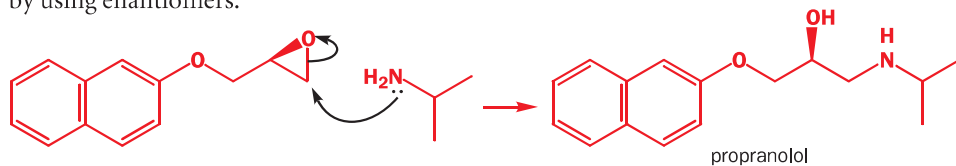
Though this reaction looks like a simple S_N2 displacement by the naphthoxide anion on the primary alkyl chloride, there is, in fact, a reasonable alternative—the opening of the epoxide at the less hindered primary centre followed by closure of the epoxide the other way round. The electrophile is called ‘epichlorohydrin’ and has two reasonable sites for nucleophilic attack.



It looks difficult to tell these mechanisms apart since both involve the same kind of reaction. Stereochemistry is the answer. If enantiomerically pure epichlorohydrin is used, the two mechanisms give different enantiomers of the product. Though each S_N2 reaction takes place at a primary centre and the stereogenic centre remains the same, from the diagrams the two products are obviously enantiomers.

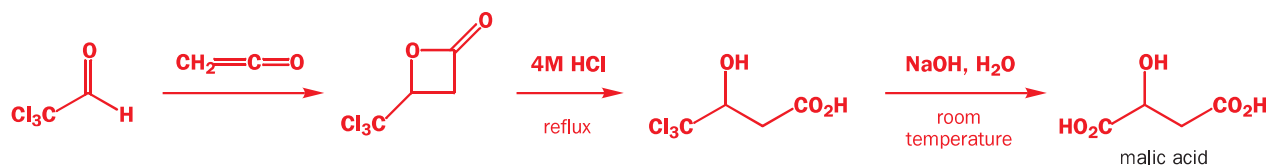


Finding out the mechanism of this process is not idle curiosity as a group of drugs used to combat high blood pressure and heart disease, such as propranolol, are made from epichlorohydrin and it is essential to know which enantiomer to use to get the right enantiomer of the drug. In fact, the more extended mechanism shown in black is correct. This is an example of determination of mechanism by using enantiomers.

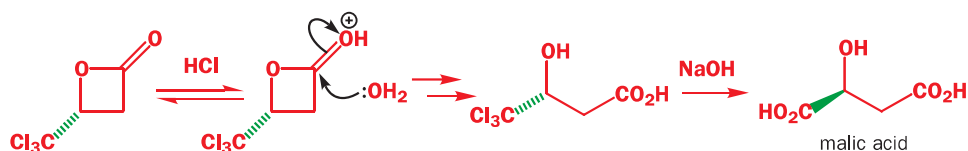


A more complicated example arises from the strange reactions used to make malic acid from chloral and ketene. An initial [2 + 2] cycloaddition (Chapter 35) is followed by acid treatment and then treatment with an excess of aqueous NaOH. Neutralization gives malic acid, an acid found naturally in apples (*Malus* spp.).

■ The full synthesis of propranolol is given in Chapter 30.

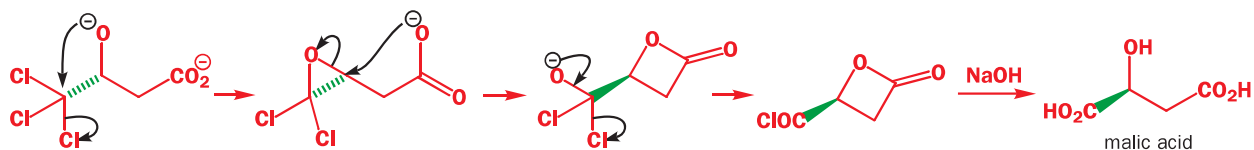


The mechanism of this reaction also looks straightforward: normal ester hydrolysis followed by hydrolysis of the CCl_3 group to CO_2H . Caution suggests investigation, particularly as four-membered lactones sometimes hydrolyse by $\text{S}_{\text{N}}2$ displacement at the saturated ester carbon rather than by attack on the carbonyl group, like the three-membered lactones discussed in Chapter 37 (p. 000). The solution was urgently needed when it was found that enantiomerically pure lactone could be prepared by asymmetric synthesis (Chapter 45). The sequence was repeated with enantiomerically pure lactone: lactone hydrolysis occurred with retention of configuration and must be normal ester hydrolysis by attack of water at the carbonyl group. But the hydrolysis of the CCl_3 group occurred with inversion of configuration.



■ You will see in Chapter 42 that this reaction is governed by 'Baldwin's rules' and why attack on even a CCl_2 group is unfavourable.

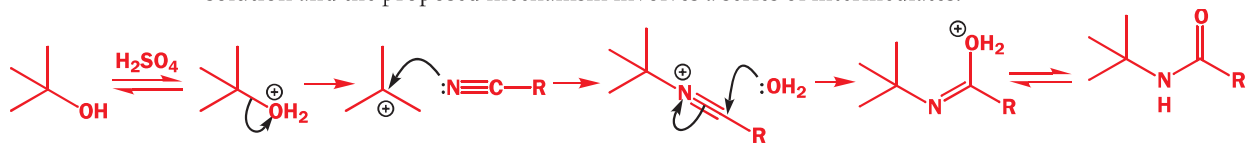
The answer must be a mechanism related to the one we have just seen for epichlorohydrin. Attack by hydroxide on CCl_3 is almost unknown and it is much more likely that intramolecular attack by alkoxide to give an epoxide should occur. The carboxylate anion can then invert the stereogenic centre by intramolecular $\text{S}_{\text{N}}2$ displacement at the central carbon atom. Notice that the tether ensures attack at the central atom. The second four-membered lactone also hydrolyses by attack at the carbonyl group.



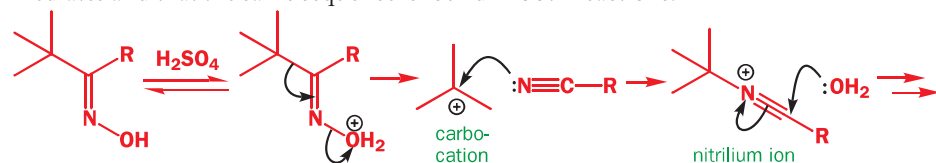
■ The Ritter reaction was introduced in Chapter 17 and the Beckmann fragmentation in Chapter 38.

The Ritter reaction and the Beckmann fragmentation

Another collection of related intermediates occurs in the Ritter reaction and the Beckmann fragmentation. The **Ritter reaction** involves the combination of a tertiary alcohol and a nitrile in acid solution and the proposed mechanism involves a series of intermediates.

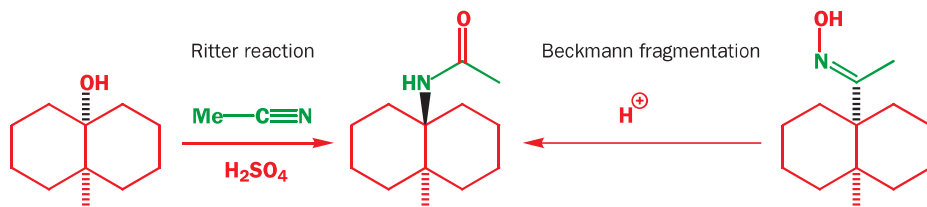


The Beckmann fragmentation also occurs in acid solution upon the fragmentation of an oxime with a *tertiary* alkyl group *anti* to the OH of the oxime. The fragmentation step gives the same cation and the same nitrile together with a molecule of water and these three combine in the same way to give the same amide. We need evidence that the carbocation and the nitrilium ion are genuine intermediates and that the same sequence is found in both reactions.



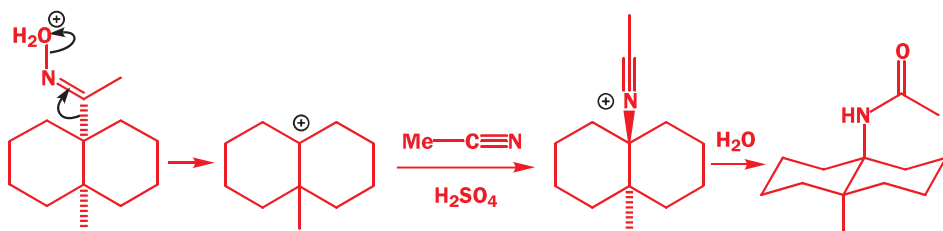
Evidence that the two reactions are intimately related comes from the formation of the same amide from two different starting materials: a tertiary alcohol and an oxime, both based on the

decalin skeleton. The oxime has its OH group *anti* to the ring junction to minimize steric hindrance as oxime formation is under thermodynamic control (Chapter 14).



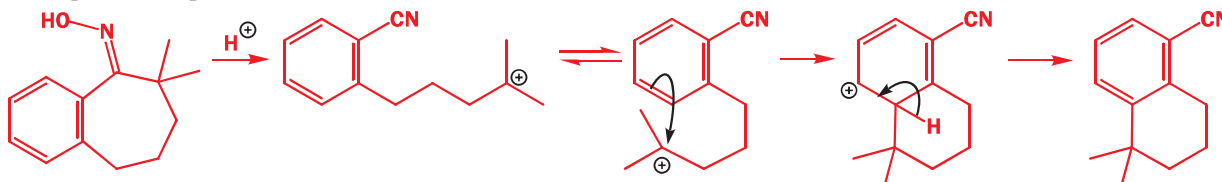
Decalins are widely used in conformational experiments; see Chapter 18.

The experiments also provide stereochemical evidence that a carbocation is an intermediate in both reactions. Both starting materials are *cis*-decalins but the product is a *trans*-decalin. The carbocation intermediate has no stereochemistry and can react with the nitrile from either face. Axial attack is preferred and it gives the stable *trans*-decalin. The formation of the carbocation is shown only by the Beckmann fragmentation: formation from the alcohol by the S_N1 mechanism is obvious.



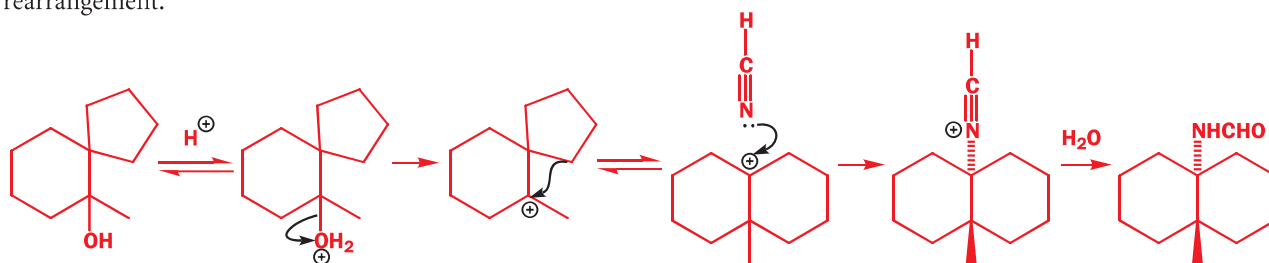
None of these compounds is chiral as there is a plane of symmetry running vertically through each molecule. We are discussing diastereoisomers only.

Trapping the carbocation is also possible. The Beckmann fragmentation on this oxime of an aryl seven-membered ring ketone gives a tertiary carbocation that might be expected to cyclize to give an amide. However, this reaction would give an unfavourable eight-membered ring (see Chapter 42) and does not happen. Instead, the chain twists round the other way and forms a much more stable six-membered ring by intramolecular Friedel–Crafts alkylation. Note that the regioselectivity is *meta* to CN and *ortho* to alkyl. These are both favourable but the main factor is the C_4 tether making any other product impossible.



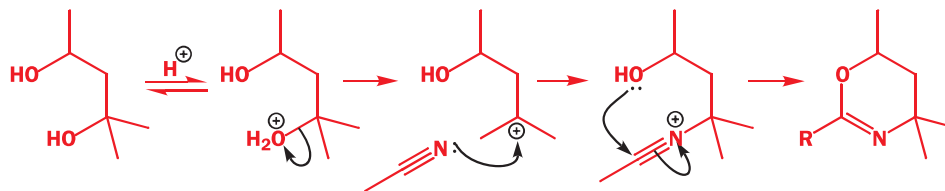
In the Ritter reaction a rather different kind of evidence for the cation is the fact that families of isomeric alcohols all give the same product. In all these cases, rearrangements of the first formed carbocation (Chapter 37) can easily account for the products. Another example in the decalin series is this Ritter reaction with KCN as the nitrile in acidic solution so that HCN is the reagent. The starting material is a spirocyclic tertiary alcohol but the product is a *trans*-decalin formed by rearrangement.

This would be a dangerous experiment to carry out and is not recommended.

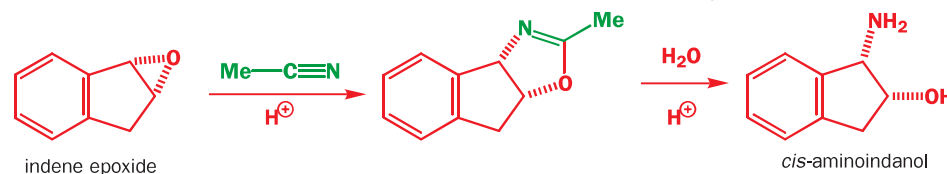


Trapping the nitrilium ion is also possible. The most famous example is probably the heterocycle (an oxazine, Chapter 42) produced by intramolecular capture of the nitrilium ion with a hydrox-

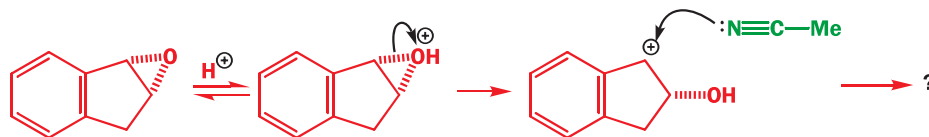
yl group. Note that the tertiary alcohol reacts to give the cation while the secondary alcohol acts as the nucleophilic trap.



An important example in which the diastereoisomer produced was critical in determining the mechanism is the synthesis of *cis*-aminoindanol, a part of Merck's anti-HIV drug Crixivan (indinavir). The reaction involves treatment of indene epoxide with acetonitrile (MeCN) in acidic solution. The product is a *cis* fused heterocycle. It is easy to see which atoms have come from the nitrile (green) but the substitution of nitrogen for oxygen at one end of the epoxide has occurred with retention of configuration as the *cis*-epoxide has given the *cis* product. Clearly, we have some sort of Ritter reaction and the nitrilium ion has been trapped with an OH group.

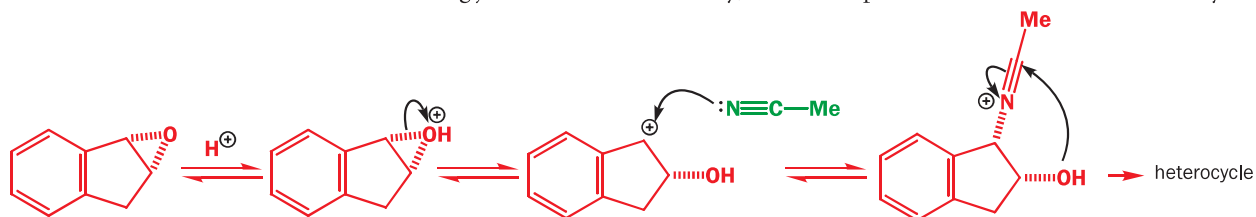


What about the regioselectivity? The obvious explanation is that a cation is formed from the epoxide in a specific acid-catalysed ring opening. But why should the nitrile attack the bottom face of the cation? We should expect it to attack the top face preferentially as the hydroxyl group partly blocks the bottom face.

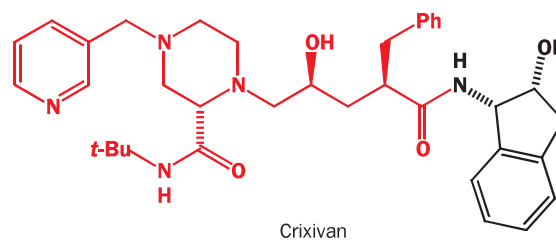


■ This step will be described in Chapter 42 as a favourable '5-*endo-dig*' process (p. 000).

A reasonable mechanism is that in which the nitrile adds reversibly to the cation. Every time it adds to the top face, it drops off again as the OH group cannot reach it to form the heterocycle. Every time it adds to the bottom face, it is quickly captured by the OH group because 5/5 fused rings are favourable when the ring junction is *cis*. Eventually, all the compound is converted to the heterocycle.



Again, the mechanism of this reaction is of great importance because it is the foundation stone of the synthesis of Crixivan—a drug that is saving thousands of lives. These last examples are of reactions that you would find difficult to classify into any of the familiar types we have met so far in the book. Nevertheless, the organic chemist needs to be able to propose mechanisms for new reactions and to have a general idea of the methods available to test these proposals.



Summary of methods for the investigation of mechanism

This brief summary is for guidance only and the figures quoted are approximate ranges only. The full text above should be used for detail. All methods would not be used in one investigation.

1. Make sure of the structure of the product

- Basic structure (Chapters 4 and 11) and stereochemistry (Chapter 32) by spectroscopic methods
- Detail of fate of individual atoms by labelling with D, ^{13}C , and ^{18}O . Double labelling may help
- Stereochemical course of the reaction (enantio- or diastereoselectivity) may be critical

2. Kinetic methods

- Rate equation gives composition of main transition state
- Deuterium isotope effect: $k_{\text{H}} > k_{\text{D}}$ shows bond to H formed and/or broken in transition state. Values $k_{\text{H}}/k_{\text{D}}$ 2–7 typical
- Entropy of activation shows increase (ΔS^{\ddagger} positive) or decrease (ΔS^{\ddagger} negative) in disorder. Typical values and deductions:
 - ΔS^{\ddagger} positive (rarely larger than $+50 \text{ J mol}^{-1} \text{ K}^{-1}$): one molecule breaks into two or three
 - Moderate negative values: no change in number of molecules (one goes to one etc.) or bimolecular reaction with solvent
 - Large negative values: two molecules go to one or unimolecular reaction with ordered TS^{\ddagger} (cycloaddition, etc.)

3. Correlation of structure and reactivity

- Replace one group by another of similar size but different electronic demand (CF_3 for CH_3 or OMe for CH_3)
- Systematic Hammett σ/ρ correlation with *m*- and *p*-substituted benzenes:
 - Sign of ρ : $+\rho$ indicates electrons flowing into and $-\rho$ electrons flowing out of ring in transition state
 - Magnitude of ρ shows effect on the benzene ring:
 - large (around 5), charge on ring ($+\rho$, anion; $-\rho$, cation)
 - moderate (around 2–4), charge on atom next to ring—may be gain or loss of conjugation
 - small (<1), ring may be distant from scene of action or ρ may be balance of two ρ s of opposite sign

4. Catalysis

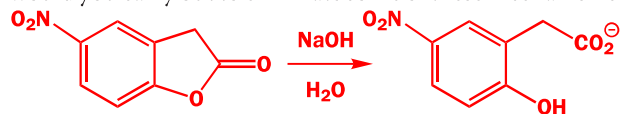
- pH–rate profile reveals specific acid or base catalysis
- Rate variation with $[\text{HA}]$ or $[\text{B}]$ at constant pH reveals GAC or GBC
- Deuterium isotope effect: normal ($k_{\text{H}} > k_{\text{D}}$) shows GA/BC, inverse solvent $k(\text{D}_2\text{O}) > k(\text{H}_2\text{O})$ shows SA/BC
- GA/BC is termolecular and has large negative entropy of activation

5. Intermediates

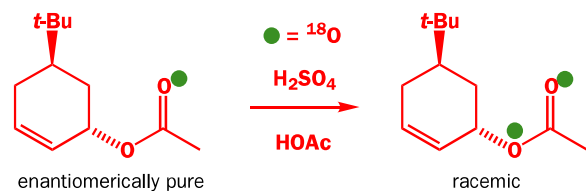
- Independent preparation or, better, isolation from or detection in reaction mixture helps
- Must show that intermediate gives product under reaction conditions
- Designed trapping experiments often most convincing

Problems

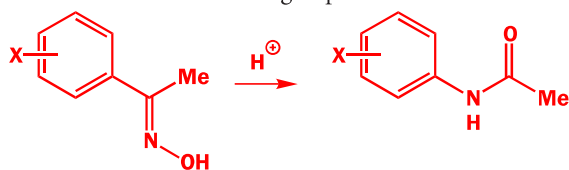
1. Propose three fundamentally different mechanisms (other than variations of the same mechanism with different kinds of catalysis) for this reaction. How would (a) D labelling and (b) ^{18}O labelling help to distinguish the mechanisms? What other experiments would you carry out to eliminate some of these mechanisms?



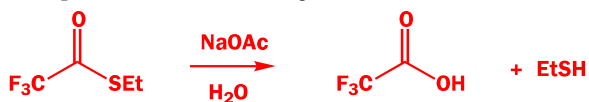
2. Explain the stereochemistry and labelling pattern in this reaction.



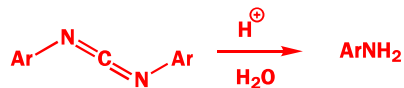
3. The Hammett ρ value for migrating aryl groups in the acid-catalysed Beckmann rearrangement is -2.0 . What does this tell us about the rate-determining step?



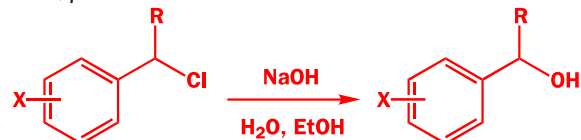
4. Between pH 2 and 7, the rate of hydrolysis of this thiol ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion $[\text{AcO}^-]$ in the solution and the reaction goes twice as fast in D_2O as in H_2O . Suggest a mechanism for the pH-independent hydrolysis. Above pH 7, the rate increases with pH. What kind of change is this?



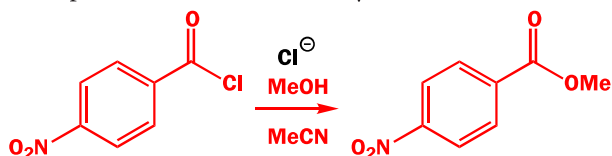
5. In acid solution, the hydrolysis of this carbodiimide has a Hammett ρ value of -0.8 . What mechanism might account for this?



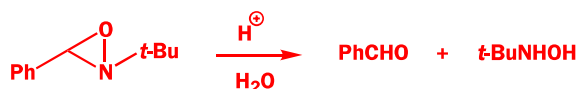
6. Explain the difference between these Hammett ρ values by mechanisms for the two reactions. In both cases the ring marked with the substituent X is varied. When $\text{R} = \text{H}$, $\rho = -0.3$ but, when $\text{R} = \text{Ph}$, $\rho = -5.1$.



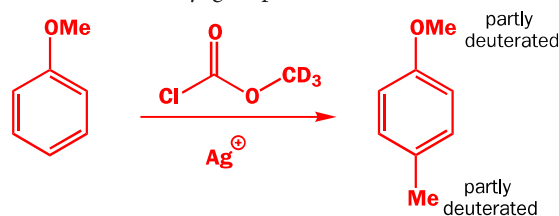
7. Explain how chloride ion catalyses this reaction.



8. The hydrolysis of this oxaziridine in 0.1 M sulfuric acid has $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) = 0.7$ and an entropy of activation of $\Delta S^\ddagger = -76 \text{ J mol}^{-1} \text{ K}^{-1}$. Suggest a mechanism for the reaction.

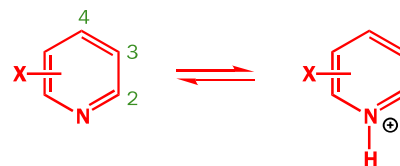


9. Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is re-isolated at 50% reaction, its methyl group is also labelled.



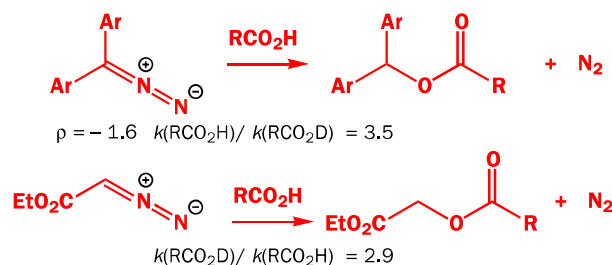
10. The $\text{p}K_{\text{aH}}$ values of some substituted pyridines are as follows.

X	H	3-Cl	3-Me	4-Me	3-MeO	4-MeO	3-NO ₂
$\text{p}K_{\text{aH}}$	5.2	2.84	5.68	6.02	4.88	6.62	0.81

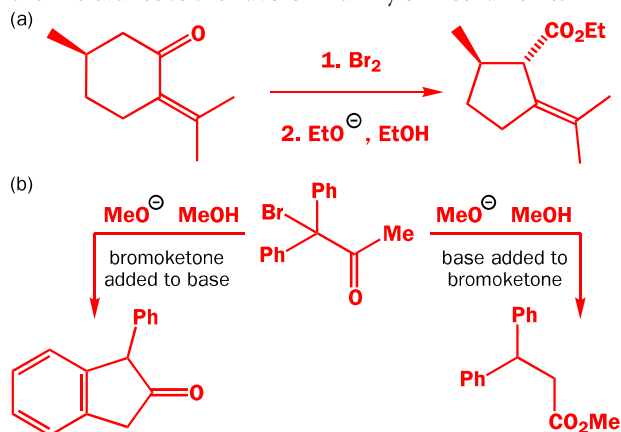


Can the Hammett correlation be applied to pyridines using the σ values for benzenes? What equilibrium ρ value does it give and how do you interpret it? Why are no 2-substituted pyridines included in the list?

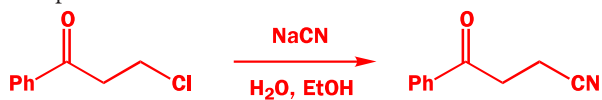
11. These two reactions of diazo compounds with carboxylic acids give gaseous nitrogen and esters as products. In both cases the rate of the reaction is proportional to $[\text{diazo compound}] \cdot [\text{RCO}_2\text{H}]$. Use the data for each reaction to suggest mechanisms and comment on the difference between them.



12. Suggest mechanisms for these reactions and comment on their relevance to the Favorskii family of mechanisms.



13. If you believed that this reaction went by elimination followed by conjugate addition, what experiment would you carry out to try and prove that the enone is an intermediate?

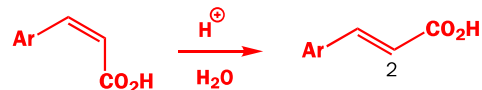


14. This question is about three related acid-catalysed reactions: (a) the isomerization of *Z*-cinnamic acids to *E*-cinnamic acids; (b) the dehydration of the related hydroxy-acids; (c) the racemization of the same hydroxy-acids. You should be able to use the information provided to build up a complete picture of the interaction of the various compounds and the intermediates in the reactions.

(a) Data determined for the acid-catalysed isomerization of *Z*-cinnamic acids in water include the following.

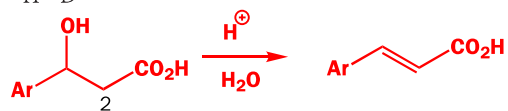
- The rate is faster in H₂O than in D₂O: $k(\text{H}_2\text{O})/k(\text{D}_2\text{O}) = 2.5$.
- The product contains about 80% D at C2.
- The Hammett ρ value is -5 .

Suggest a mechanism for the reaction that explains the data.



(b) The dehydration of the related hydroxy-acids also gives *E*-cinnamic acids at a greater rate under the same conditions but the data for the reaction are rather different.

- Hydroxy-acid deuterated at C2 shows a kinetic isotope effect: $k_{\text{H}}/k_{\text{D}} = 2.5$.



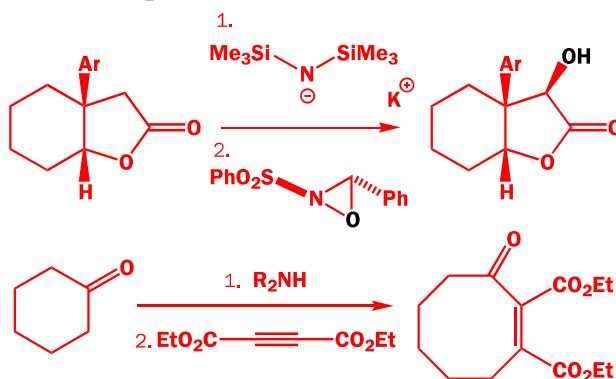
(c) If the dehydration reaction is stopped after about 10% conversion to products, the remaining starting material is completely racemized. Data for the racemization reaction include the following.

- The rate is slower in H₂O than in D₂O.
- Hydroxy-acid deuterated at C2 shows practically no kinetic isotope effect.
- The Hammett ρ value is -4.5 .

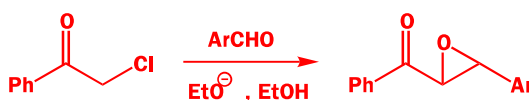
What conclusions can you draw about the dehydration?

Recalling that the dehydration goes faster than the isomerization, what would be present in the reaction mixture if the isomerization were stopped at 50% completion?

15. Propose mechanisms for the two reactions at the start of the chapter. The other product in the first reaction is the imine $\text{PhCH}=\text{NSO}_2\text{Ph}$.



16. A typical Darzens reaction involves the base-catalysed formation of an epoxide from an α -haloketone and an aldehyde. Suggest a mechanism for the Darzens reaction consistent with the results shown below.



- The rate expression is:
 $\text{rate} = k_3[\text{PhCO}\cdot\text{CH}_2\text{Cl}][\text{ArCHO}][\text{EtO}^-]$
- When Ar is varied, the Hammett ρ value is $+2.5$.
- The following attempted Darzens reactions produced unexpected products.

