The base attacks the methyl hydrogens because they are less hindered—they are attached to a primary carbon atom, well away from the other axial hydrogens. E2 eliminations with hindered bases typically give the less substituted double bond, because the fastest E2 reaction involves deprotonation at the least substituted site. The hydrogens attached to a less substituted carbon atom are also more acidic. Think of the conjugate bases: a *t*-butyl anion is more basic (because the anion is destabilized by the three alkyl groups) than a methyl anion, so the corresponding alkane must be less acidic. Steric factors are evident in the following E2 reactions, where changing the base from ethoxide to *t*-butoxide alters the major product from the more to the less substituted alkene.

NaOEt	69%	31%
t-BuOK	28%	73%
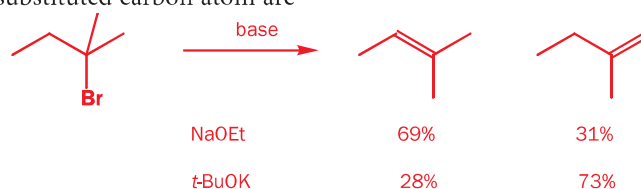
> ● **Elimination regioselectivity**
>
> • E1 reactions give the more substituted alkene
> • E2 reactions may give the more substituted alkene, but become more regioselective for the less substituted alkene with more hindered bases

Hofmann and Saytsev

Traditionally, these two opposite preferences—for the more or the less substituted alkenes—have been called 'Saytsev's rule' and 'Hofmann's rule', respectively. You will see these names used (along with a number of alternative spellings—acceptable for Saytsev, whose name is transliterated from Russian, but not for Hofmann: this Hofmann had one f and two n's), but there is little point remembering which is which (or how to spell them)—it is far more important to understand the reasons that favour formation of each of the two alkenes.

Anion-stabilizing groups allow another mechanism—E1cB

To finish this chapter, we consider a reaction that at first sight seems to go against what we have told you so far. It's an elimination catalysed by a strong base (KOH), so it looks like E2. But the leaving group is hydroxide, which we categorically stated cannot be a leaving group in E2 eliminations.

The key to what is going on is the carbonyl group. In Chapter 8 you met the idea that negative charges are stabilized by conjugation with carbonyl groups, and the table on p. 000 demonstrated how acidic a proton adjacent to a carbonyl group is. The proton that is removed in this elimination reaction is adjacent to the carbonyl group, and is therefore also rather acidic (pK_a about 20). This means that the base can remove it without the leaving group departing at the same time—the anion that results is stable enough to exist because it can be delocalized on to the carbonyl group.

best representation of anion adjacent to C=O delocalized on to oxygen
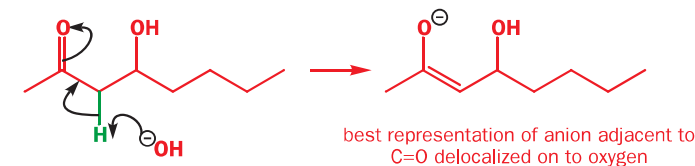
green proton acidified (pK_a ca. 20) by adjacent carbonyl group

> ▶ This delocalized anion is called an **enolate**, and we will discuss enolates in more detail in Chapter 21 and beyond.

Although the anion is stabilized by the carbonyl group, it still prefers to lose a leaving group and become an alkene. This is the next step.

This step is also the rate-determining step of the elimination—the elimination is unimolecular, and so is some kind of E1 reaction. But the leaving group is not lost from the starting molecule, but from the *conjugate base* of the starting molecule, so this sort of elimination, which starts with a deprotonation, is called **E1cB** (cB for conjugate Base). Here is the full mechanism, generalized for other carbonyl compounds.

the E1cB mechanism
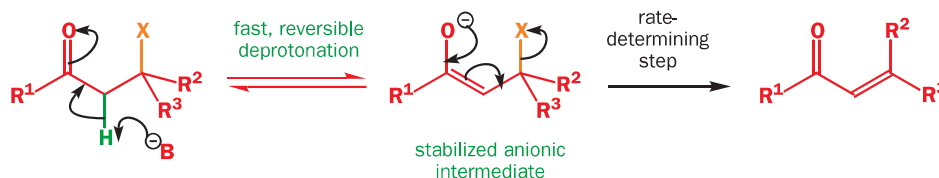
It's important to note that, while HO⁻ is never a leaving group in E2 reactions, it can be a leaving group in E1cB reactions. The anion it is lost from is already an alkoxide—the oxyanion does not need to be created. The establishment of conjugation also assists loss of HO⁻. As the scheme above implies, other leaving groups are possible too. Here are two examples with methanesulfonate leaving groups.
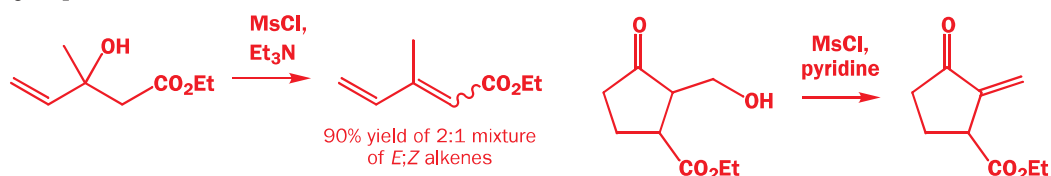
The first looks E1 (stabilized cation); the second E2—but in fact both are E1cB reactions. The most reliable way to spot a likely E1cB elimination is to see whether the product is a conjugated carbonyl group. If it is, the mechanism is probably E1cB.
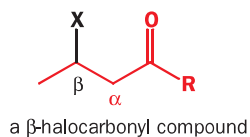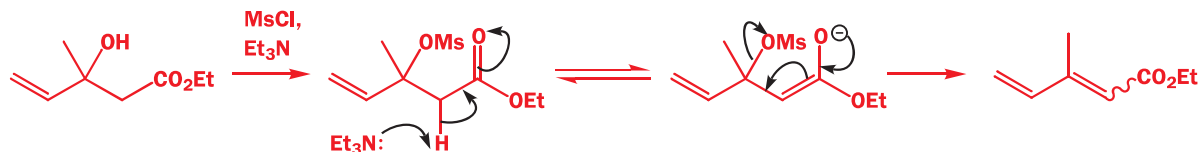

β-Halocarbonyl compounds can be rather unstable: the combination of a good leaving group and an acidic proton means that E1cB elimination is extremely easy. This mixture of diastereoisomers is first of all lactonized in acid (Chapter 12), and then undergoes E1cB elimination with triethylamine to give a product known as **butenolide**. Butenolides are widespead structures in naturally occurring compounds.



a β-halocarbonyl compound
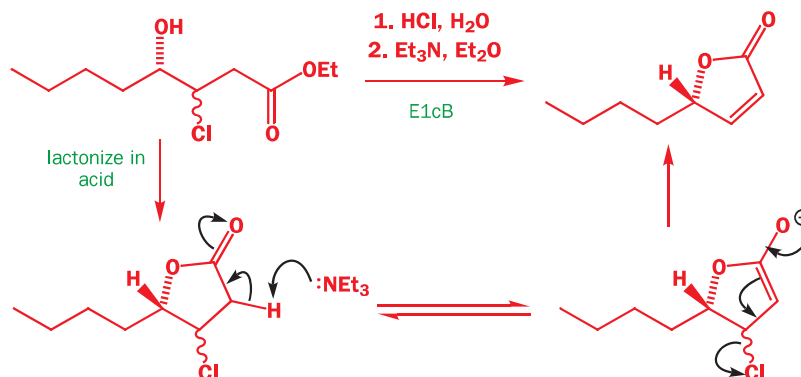
You will have noticed that we have shown the deprotonation step in the last few mechanisms as an equilibrium. Both equilibria lie rather over to the left-hand side, because neither triethylamine (pK_{aH} about 10) nor hydroxide (pK_{aH} = 15.7) is basic enough to remove completely a proton next

to a carbonyl group ($pK_a \geq 20$). But, because the loss of the leaving group is essentially irreversible, only a small amount of deprotonated carbonyl compound is necessary to keep the reaction going. The important point about substrates that undergo E1cB is that there is some form of anion-stabilizing group next to the proton to be removed—it doesn't have to stabilize the anion very well but, as long as it makes the proton more acidic, an E1cB mechanism has a chance. Here is an important example with two phenyl rings helping to stabilize the anion, and a carbamate anion ($R_2N-CO_2^-$) as the leaving group.
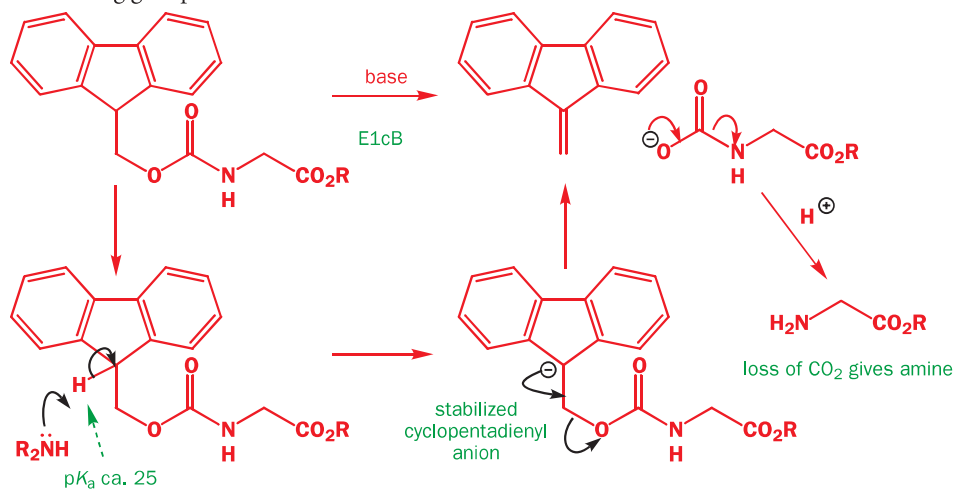

The proton to be removed has a pK_a of about 25 because its conjugate base is an aromatic cyclopentadienyl anion (we discussed this in Chapter 8). The E1cB elimination takes place with a secondary or tertiary amine as the base. Spontaneous loss of CO_2 from the eliminated product gives an amine, and you will meet this class of compounds again shortly in Chapter 25 where we discuss the Fmoc protecting group.

6 π electrons
aromatic
cyclopentadienyl
anion
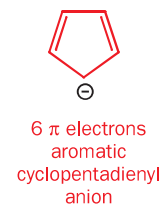
The E1cB rate equation

The rate-determining elimination step in an E1cB reaction is unimolecular, so you might imagine it would have a first-order rate equation. But, in fact, the rate is also dependent on the concentration of base. This is because the unimolecular elimination involves a species—the anion—whose concentration is itself determined by the concentration of base by the equilibrium we have just been discussing. Using the following general E1cB reaction, the concentration of the anion can be expressed as shown.
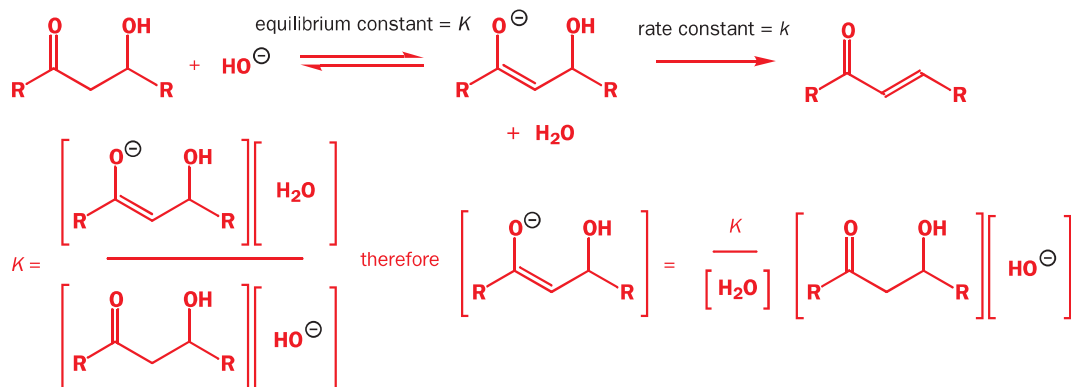
The rate is proportional to the concentration of the anion, and we now have an expression for that concentration. We can simplify it further because the concentration of water is constant.

Just because the base (hydroxide) appears in this rate equation doesn't mean to say it is involved in the rate-determining step. Increasing the concentration of base makes the reaction go faster by increasing the amount of anion available to eliminate.

> ● For reactions with several steps in which the rate-determining step is not the first, the concentrations of species involved in those earlier steps will appear in the rate equation, even though they take no part in the rate-determining step itself.

E1cB eliminations in context

It is worthwhile comparing the E1cB reaction with some others with which you are familiar: for a start, you may have noticed that it is the reverse of the conjugate addition reactions we introduced in Chapter 10. In Chapter 10, conjugated carbonyl compounds were the starting materials; now they are the products—but both reactions go through a stabilized anion intermediate. E1cB reactions are so general that they are by far the most common way of making the enone starting materials for conjugate additions.
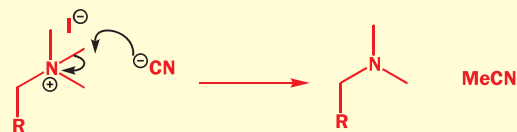
E1cB elimination

conjugate addition
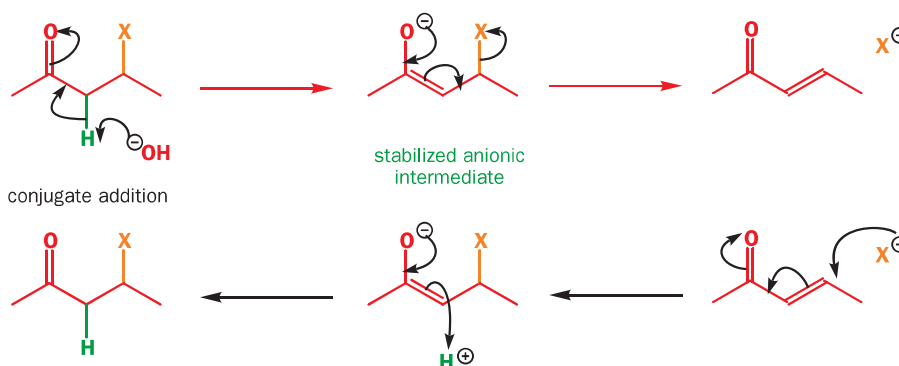
**A deceptive S$_N$2 substitution**

In some rare cases, you may see E1cB elimination and conjugate addition taking place in a single reaction. Look at this 'substitution' reaction, for example. Apparently, the ammonium salt has been substituted by the cyanide in what looks to be an S$_N$2 reaction.
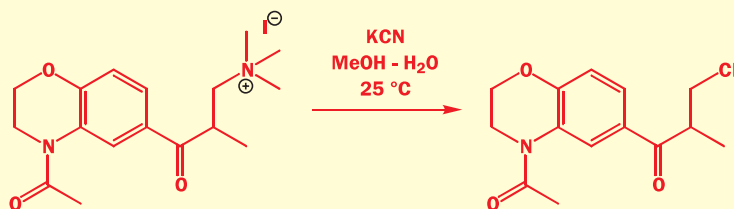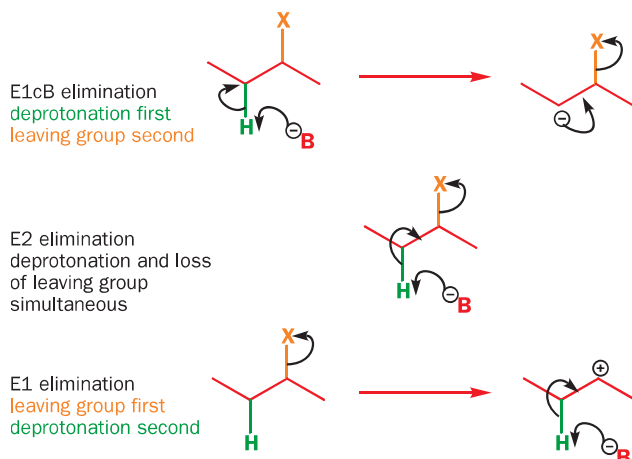

A little consideration will tell you that it can't be S$_N$2 though, because, if it were, it would go like this.


Instead, the mechanism is first an E1cB elimination, followed by conjugate addition.
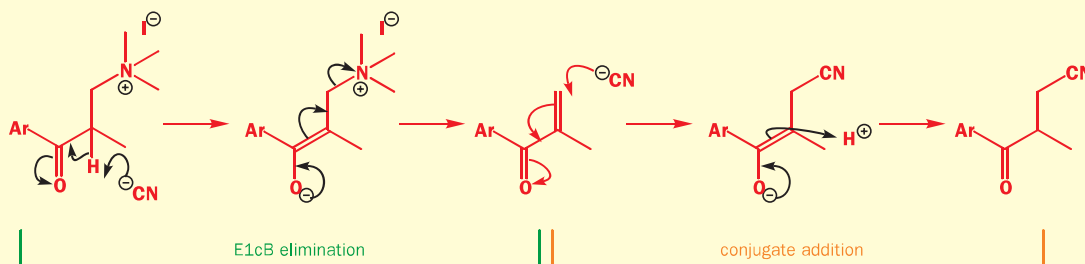
We can also compare it with the other elimination reactions you have met by thinking of the relative timing of proton removal and leaving group departure. E1 is at one end of the scale: the leaving group goes first, and proton removal follows in a second step. In E2 reactions, the two events happen at the same time: the proton is removed as the leaving group leaves. In E1cB the proton removal moves in front of leaving group departure.

E1cB elimination
deprotonation first
leaving group second

E2 elimination
deprotonation and loss
of leaving group
simultaneous

E1 elimination
leaving group first
deprotonation second

We talked about regio- and stereoselectivity in connection with E1 and E2 reactions. With E1cB, the regioselectivity is straightforward: the location of the double bond is defined by the position of: (a) the acidic proton and (b) the leaving group.

leaving group

double bond has no   acidic proton
choice: must go here

2 : 1 ratio
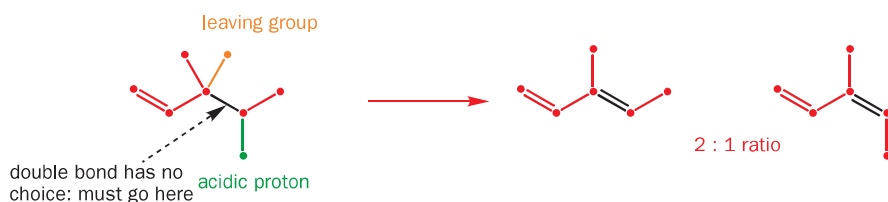
E1cB reactions may be stereoselective—this one, for example, gives mainly the *E*-alkene product (2:1 with *Z*). The intermediate anion is planar, so the sterochemistry of the starting materials is irrelevant, the less sterically hindered (usually *E*) product is preferred. This double E1cB elimination, for example, gives only the *E,E*-product.

To finish this chapter we need to tell you about two E1cB eliminations that you may meet in unexpected places. We have saved them till now because they are unusual in that the leaving group is actually part of the anion-stabilizing group itself. First of all, try spotting the E1cB elimination in this step from the first total synthesis of penicillin V in 1957.

penicillin V
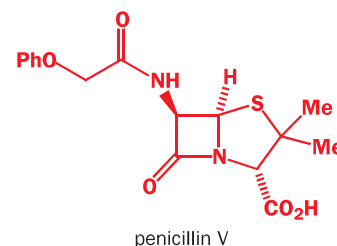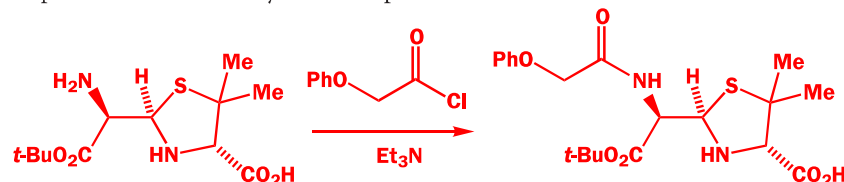
The reaction is deceptively simple—formation of an amide in the presence of base—and you would expect the mechanism to follow what we told you in Chapter 12. But the acyl chloride is, in fact, set up for an E1cB elimination—and you should expect this whenever you see an acyl chloride *with acidic protons next to the carbonyl group* used in the presence of triethylamine.
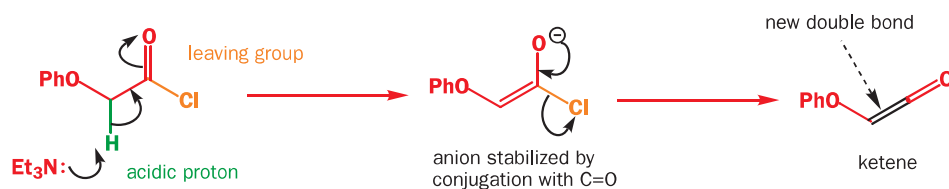
The product of the elimination is a substituted ketene—a highly reactive species whose parent ($CH_2=C=O$) we talked about in Chapter 15. It is the ketene that reacts with the amine to form the amide.
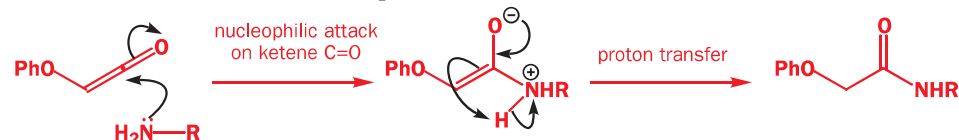
The second 'concealed' E1cB elimination is in the elimination of HCl from MsCl, which we showed you on p. 000 of this chapter. You can now see the similarity with the acyl chloride mechanism above.
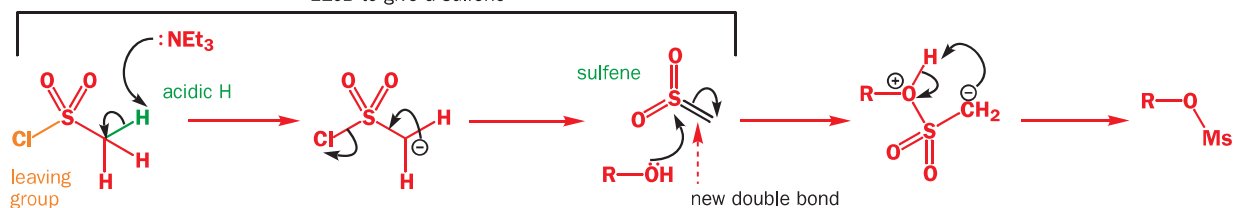
To conclude...

The table summarizes the general pattern of reactivity expected from various structural classes of alkyl halides (or tosylates, mesylates) in reactions with a representative range of nucleophiles (which may behave as bases).

	Poor nucleophile (e.g. H_2O, ROH)[a]	Weakly basic nucleophile (e.g. I⁻, RS⁻)	Strongly basic, unhindered nucleophile (e.g. RO⁻)	Strongly basic, hindered nucleophile (e.g. DBU, DBN, t-BuO⁻)
methyl H_3C—X	no reaction	S_N2	S_N2	S_N2
primary (unhindered)	no reaction	S_N2	S_N2	E2
primary (hindered)	no reaction	S_N2	E2	E2
secondary	S_N1, E1 (slow)	S_N2	E2	E2
tertiary	E1 or S_N1	S_N1, E1	E2	E2
β to anion-stabilizing group	E1cB	E1cB	E1cB	E1cB

[a] Acid conditions.

Some points about the table:

- Methyl halides cannot eliminate as there are no appropriately placed protons

- Increasing branching favours elimination over substitution and strongly basic hindered nucleophiles always eliminate unless there is no option

- Good nucleophiles undergo substitution by S_N2 unless the substrate is tertiary and then the intermediate cation can eliminate by E1 as well as substitute by S_N1

- High temperatures favour elimination by gearing up the importance of entropy in the free energy of reaction ($\Delta G = \Delta H - T\Delta S$). This is a good way of ensuring E1 in ambiguous cases