But what are the 'special chemical features' of saturated heterocycles? Putting a heteroatom into a ring does two important things, and these lead to the most important new topics in this chapter. Firstly, the heteroatom makes the ring easy to make by a ring-closing reaction, or (in some cases) easy to break by a ring-opening reaction. Closing and opening reactions of rings are subject to constraints that you will need to know about, and the principles that govern these reactions are discussed in the second half of the chapter.

Secondly, the ring fixes the orientation of the heteroatom—and, in particular, the orientation of its lone pairs—relative to the atoms around it. This has consequences for the reactivity and conformation of the heterocycle which can be explained using the concept of stereoelectronics.

Although this is the only chapter in which stereoelectronics appears in the title, you will soon recognize the similarity between the ideas we cover here and concepts like the stereospecificity of E2 elimination reactions (Chapter 19), the Karplus relationship (Chapter 32), the Felkin–Anh transition state (Chapter 33), and the conformational requirements for rearrangement (Chapter 37) and fragmentation (Chapter 38) reactions.

Reactions of heterocycles

Nitrogen heterocycles: amines, but more nucleophilic

In many reactions the simple saturated nitrogen heterocycles—piperidine, pyrrolidine, piperazine, and morpholine—behave simply as secondary amines that happen to be cyclic. They do the sorts of things that other amines do, acting as nucleophiles in addition and substitution reactions. Morpholine, for example, is acylated by 3,4,5-trimethoxybenzoyl chloride to form the tranquillizer and muscle relaxant trimetozine, and N-methylpiperazine can be alkylated in an $S_{N}1$ reaction with diphenylmethyl chloride to give the travel-sickness drug cyclizine.
The addition of pyrrolidine to aldehydes and ketones is a particularly important reaction because it leads to enamines, the valuable enol equivalents discussed in Chapter 26.

Enamines formed from pyrrolidine and piperidine are particularly stable, because pyrrolidine and piperidine are rather more nucleophilic than comparable acyclic amines such as diethylamine. This is a general feature of cyclic amines (and cyclic ethers, too, as you will see shortly), and is a steric effect. The alkyl substituents, being tied back into a ring, are held clear of the nucleophilic lone pair, allowing it to approach an electrophile without hindrance. This effect is well illustrated by comparing the rates of reaction of methyl iodide with three amines—tertiary this time. The two cyclic compounds are bridged—quinuclidine is a bridged piperidine while the diamine known as ‘DABCO’ (1,4-DiAzaBiCyclo[2.2.2]Octane) is a bridged piperazine. Table 42.1 shows the relative rates, along with $pK_{a\text{H}}$ values, for triethylamine, quinuclidine, and DABCO.

Quinuclidine and DABCO are 40–60 times more reactive than triethylamine. This is again due to the way the ring structures keep the nitrogen’s substituents away from interfering with the lone pair as it attacks the electrophile. You should contrast the effect that the cyclic structure has on the $pK_{a\text{H}}$ of the amines: none! Triethylamine and quinuclidine are equally basic and, as you can see in the margin, so (more or less) are diethylamine, dibutylamine, and piperidine. A proton is so small that it cares very little whether the alkyl groups are tied back or not.

Much more important in determining $pK_{a\text{H}}$ is how electron-rich the nitrogen is, and this is the cause of the glaring discrepancy between the basicity of quinuclidine and that of DABCO, or between the basicities of piperidine ($pK_{a\text{H}} 11.2$) and morpholine ($pK_{a\text{H}} 9.8$) or piperazine ($pK_{a\text{H}} 8.4$). The extra heteroatom, through an inductive effect, withdraws electron density from the nitrogen atom, making it less nucleophilic and less basic. In this

![Table 42.1 Rates of reaction of amines with methyl iodide](image-url)

<table>
<thead>
<tr>
<th>Relative Rate of Reaction</th>
<th>Triethylamine</th>
<th>Quinuclidine</th>
<th>DABCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>$pK_{a\text{H}}$</td>
<td>10.7</td>
<td>11.0</td>
<td>8.8</td>
</tr>
</tbody>
</table>

$^a$ Relative rate of reaction with MeI in MeCN at 20 °C.
sense, morpholine can be a very useful base, less basic than triethylamine but somewhat more so than pyridine ($pK_a$ 5.2). Notice how much lower is the second $pK_a$ (that is, the $pK_a$ for protonation of the second nitrogen) of the diamines DABCO and piperazine: the protonated nitrogen of the monoprotonated amine withdraws electrons very effectively from the unprotonated one.

The Baylis–Hillman reaction

One of the most important uses of DABCO is in the Baylis–Hillman reaction, discovered in 1972 by two chemists at the Celanese Corporation in New York. Their reaction is a modification of the aldol reaction (Chapter 27), except that, instead of the enolate being formed by deprotonation, it is formed by conjugate addition. You have seen the enolate products of conjugate addition being trapped by alkylating agents in Chapter 26, but in the Baylis–Hillman reaction, the electrophile is an aldehyde and is present right from the start of the reaction, which is done just by stirring the components at room temperature. Here is a typical example.

The reaction starts with the (relatively nucleophilic) DABCO undergoing conjugate addition to ethyl acrylate. This will form an enolate that can then attack the acetaldehyde in an aldol reaction.

$\text{OEt}$ $\text{O}$ $\text{DABCO}$ $\text{OH}$ $\text{OEt}$ $\text{O}$ $\text{OH}$

E1cB eliminations often follow aldol reactions and lead to $\alpha,\beta$-unsaturated products. In this case, though, DABCO is a much better leaving group than the hydroxyl group, so enolization leads to loss of DABCO in an E1cB elimination, giving the product of the reaction. DABCO is recovered unchanged, and is a catalyst.

A disadvantage of the Baylis–Hillman reaction is its rate: typically, several days’ reaction time are required. Pressure helps speed the reaction up, but as a catalyst DABCO is about the best. It is nucleophilic, because of the ‘tied back’ alkyl groups, but importantly it is a good leaving group because it has a relatively low $pK_a$, meaning that it leaves easily in the last step. As you have seen before, good nucleophiles are usually bad leaving groups, though there are many exceptions. DABCO’s combination of nucleophilicity and leaving group ability is perfect here.

The exposed nature of the nitrogen atom in cyclic amines means that nitrogen heterocycles are very frequently encountered in drug molecules, particularly those operating on the central nervous system (cocaine, heroin, and morphine all contain nitrogen heterocycles, as do codeine and many tranquillizers such as Valium). But the ring can also be used as a support for adding substituents that hinder the nitrogen’s lone pair. Just as the nitrogen atom of piperidine is permanently exposed, the nitrogen atom of 2,2,6,6-tetramethylpiperidine (TMP) nestles deep in a bed of methyl groups. The lithium salt of TMP (LiTMP) is an analogue of LDA—a base that experiences enormous steric hindrance that can be used in situations where the selectivity even of LDA fails.

Aziridine: ring strain promotes ring opening

Aziridine and azetidine are stable, if volatile, members of the saturated nitrogen heterocycle family, and aziridine has some interesting chemistry of its own. Like pyrrolidine and piperidine, aziridine can be acylated by treatment with an acyl chloride, but the product is not stable. The ring opens with attack of chloride, a relatively poor nucleophile, and an open-chain secondary amide results.
You can view this ring opening as very similar to the ring opening of an epoxide (Chapter 20)—in particular, a protonated epoxide, in which the oxygen bears a positive charge. The positive charge is very important for aziridine opening because, when the reaction is done in the presence of a base, removal of the proton leads immediately to the neutral acyl aziridine, which is stable.

The ring opening of aziridine is a useful way of making larger heterocycles: anything that puts a positive charge on nitrogen encourages the opening by making N a better leaving group, whether it's protonation, as shown below, or alkylation.

Alkylation of aziridine in base gives the N-substituted aziridine as you might expect, but a second alkylation leads to a positively charged aziridinium salt that opens immediately to the useful bromoamine. In this case, the product is an intermediate in the synthesis of two natural products, sandaverine and corgoine.

We have just mentioned the protonation of aziridine, and you might imagine from what we said earlier about the comparative nucleophilicity and basicity of nitrogen heterocycles and their acyclic counterparts that aziridine will be even more nucleophilic than pyrrolidine, and about as basic. Well,
It isn’t. The idea that ‘tying back’ the alkyl groups increases nucleophilicity is only valid for ‘normalized’ (five- or six-membered) rings: with small rings another effect takes over.

Aziridine is, in fact, much less basic than pyrrolidine and piperidine: its $pK_{a\text{H}}$ is only 8.0. This is much closer to the $pK_{a\text{H}}$ of a compound containing an $sp^2$ hybridized nitrogen atom—the imine in the margin, for example. This is because the nitrogen’s lone pair is in an orbital with much more $s$ character than is typical for an amine, due to the three-membered ring. This is an effect we have discussed before, in Chapter 15, and you should re-read pp. 000–000 if you need to refresh your memory. There we compared three-membered rings with alkynes, explaining that both could be deprotonated relatively easily. The anion carries a negative charge in a low-energy orbital with much $s$ character: the same type of orbital carries aziridine’s lone pair.

The $s$ character of the aziridine nitrogen’s lone pair has other effects too. The lone pair interacts very poorly with an adjacent carbonyl group, so $N$-acyl aziridines such as the one you saw on p. 000 behave not at all like amides. The nitrogen atom is pyramidal and not planar, and the stretching frequency of the $C=O$ bond (1706 cm$^{-1}$) is much closer to that of a ketone (1710 cm$^{-1}$) than that of an amide (1650 cm$^{-1}$).

Lack of conjugation leads to increased reactivity, and $N$-acyl aziridines are useful in synthesis because they react with organolithium reagents only once to give ketones. No further reactions of the product ketone occur because the $N$-acyl aziridine is reactive enough to compete with it for the organolithium reagent.

The $s$ character of the lone pair means that the nitrogen atom inverts very slowly, rather like a phosphine (which also carries its lone pair in an $s$ orbital: see Chapter 4, p. 000). Usually it is not possible for nitrogen to be a stereogenic centre because inversion is too rapid—the transition state for nitrogen inversions (in which the lone pair is in a $p$ orbital) is low in energy. But with an aziridine, getting the lone pair into a $p$ orbital would require an awful lot of energy, so nitrogen can be stereogenic and, for example, these two stereoisomers of an $N$-substituted aziridine can be separated and isolated.

**Oxygen heterocycles**

Ring-opening chemistry is characteristic of oxygen heterocycles too, and there is no need for us to revisit epoxide opening here. Epoxides are particularly reactive because ring opening releases ring strain, driving the reaction forward. However, we can tell you about some chemistry of the most important simple oxygen heterocycle, THF. You may be surprised that THF does any real chemistry: after all, the very reason it is used as a solvent is precisely because it is so unreactive. Oxygen heterocycles are cyclic ethers, and ethers are the least reactive of all the common functional groups.

To make ethers more reactive, they must be complexed with strong Lewis acids. BF$_3$ is commonly used with cyclic ethers, and even with epoxides it increases the rate and yield of the reaction when organometallic reagents are used as nucleophiles. BF$_3$ is most easily handled as its complex with diethyl ether, written BF$_3$:OEt. BuLi does not react with oxetane, for example, unless a Lewis acid, such as BF$_3$, is added, when it opens the four-membered ring to give a quantitative yield of $n$-heptanol.