Here are the two conformations drawn out for ethyl acetate. When the ethyl group (= R) and O are cis, not only can one oxygen lone pair interact with the C=O π*, but the other lone pair can also donate into the σ* of the C=O bond. This is not possible when Et and O are trans: they are no longer anti-periplanar. The cis conformation of esters is generally the preferred one, even in formate esters, where the alkyl group ends up in what is clearly a more sterically hindered orientation.

Making heterocycles: ring-closing reactions

We have talked about the structure of saturated heterocycles, particularly with regard to stereoelectronic control over conformation, and before that we looked at some of their reactions. In this last section of the chapter we will look at how to make saturated heterocycles. By far the most important way of making them is by ring-closing reactions, because we can usually use the heteroatom as the nucleophile in an intramolecular substitution or addition reaction. Ring-closing reactions are, of course, just the opposite of the ring-opening reactions we talked about earlier in the chapter, and we can start with a reaction that works well in both directions: ring closure to form an epoxide. You know well that epoxides can be formed using m-CPBA and an alkene, but you have already seen examples (including one earlier in the chapter) where they form by an intramolecular substitution reaction such as this.

The same method can also be used to generate larger cyclic ethers. Oxetane, for example, is conveniently made by adding 3-chloropropyl acetate to hot potassium hydroxide.

The first step in this reaction is the hydrolysis of the ester. The alkoxide produced then undergoes an intramolecular substitution reaction to yield oxetane.

Tetrahydropyran was prepared as early as 1890 by a ring closure that occurs when a mixture of 1,5-pentanediol with sulfuric acid is heated.

These are all S_N2 reactions, so you will not be surprised that nitrogen heterocycles can be prepared in the same way. Aziridine itself, for example, was first prepared in 1888 from 2-chloroethylamine.

This method works well to form three-, five-, and six-membered nitrogen heterocycles, but does not work well to form four-membered rings. In fact, four-membered rings are generally among the
hardest of all to form. To illustrate this, the first two columns of Table 42.2 show the rates (relative to six-membered ring formation = 1) at which bromoamines of various chain lengths cyclize to saturated nitrogen heterocycles of three to seven members.

Table 42.2 Rates of ring-closing reactions

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Product</th>
<th>Relative rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Product&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Relative rate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Assessment of rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>NH</td>
<td>0.07</td>
<td></td>
<td></td>
<td>moderate</td>
</tr>
<tr>
<td>4</td>
<td>NH</td>
<td>0.001</td>
<td>E</td>
<td>0.58</td>
<td>slow</td>
</tr>
<tr>
<td>5</td>
<td>NH</td>
<td>100</td>
<td>E</td>
<td>833</td>
<td>very fast</td>
</tr>
<tr>
<td>6</td>
<td>NH</td>
<td>1</td>
<td>E</td>
<td>1</td>
<td>fast</td>
</tr>
<tr>
<td>7</td>
<td>NH</td>
<td>0.002</td>
<td>E</td>
<td>0.0087</td>
<td>slow</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>E</td>
<td>0.00015</td>
<td>very slow</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative to the six-membered ring formation (= 1).

<sup>b</sup> E = CO<sub>2</sub>Et.

The first thing that strikes you perhaps is that the figures in the third column have been produced by a random number generator! There seems to be no rhyme or reason to them, and no consistent trend. To convince you that these numbers mean something, Table 42.2 also shows, in its next two columns, the relative rates for a quite different ring-closing reaction, this time forming four- to seven-membered rings that are not even heterocycles by intramolecular alkylation of a substituted malonate. Though the numbers are quite different in the two cases, the ups and downs are the same, and the final column summarizes the relative rates. Put another way, a rough guide (only rough!—it doesn’t work in all cases) to the rate of ring formation is this.

**Rough guide to the rate of formation of saturated rings**

5 > 6 > 3 > 7 > 4 > 8–10
We show the numbers in colour to highlight the fact that this seemingly illogical ordering of numbers actually conceals two superimposed trends. Once you get to five-membered rings, the rate of formation drops consistently as the ring size moves from ‘normal’ to ‘medium’. ‘Small’ (three- and four-membered) rings insert into the sequence below six.

The reason for the two superimposed trends is two opposing factors. Firstly, small rings form slowly because forming them introduces ring strain. This ring strain is there even at the transition state, raising its energy and slowing down the reaction. \( \Delta G^\ddagger \) is very large for a three-membered ring (due to strain) but decreases as the ring gets larger. This explains why three- and four-membered rings don’t fit straightforwardly into the sequence.

But, if the reaction rate simply depended on the strain of the product, the slowest reaction would be the formation of the three-membered ring, and six-membered rings (which are essentially strain-free) would form fastest. But as it is, four-membered rings form more slowly than three-membered ones, and five-membered ones faster than six-membered ones. To explain this, we need to remind you of an equation we presented in Chapter 13.

\[
\Delta G^\ddagger = \Delta H^\ddagger - T \Delta S^\ddagger
\]

The activation energy barriers \( \Delta G^\ddagger \) of our reactions are made up of two parts: an enthalpy of activation \( \Delta H^\ddagger \), which tells us about the energy required to bring atoms together against the strain and repulsive forces they usually have, and an entropy of activation \( \Delta S^\ddagger \), which tells us about how easy it is to form an ordered transition state from a wriggling and randomly rotating molecule.

\( \Delta G^\ddagger \) for three- and four-membered ring formation is large because \( \Delta H^\ddagger \) is large: energy is needed to bend the molecule into the strained small-ring conformation. \( \Delta H^\ddagger \) for five-, six-, and seven-membered rings is smaller: this is the quantifiable representation of the ‘ring strain’ factor we have just introduced. The second factor is one that depends on \( \Delta S^\ddagger \): how much order must be imposed on the molecule to get it to react. Think of it this way: a long chain has a lot of disorder, and to get its ends to meet up and react means it has to give up a lot of freedom. So, for the formation of medium and large rings, \( \Delta S^\ddagger \) is large and negative, contributing to a large \( \Delta G^\ddagger \) and slow reactions. For three-membered rings, on the other hand, the reacting atoms are already very close together and almost no order needs to be imposed on the molecule to get it to cyclize; rotation about just one bond is all that is needed to ensure that the amine group is in the perfect position to attack the \( \sigma^* \) of the C–Br bond in our example above. \( \Delta S^\ddagger \) is very small for three-membered rings so, while \( \Delta H^\ddagger \) is large, there is little additional contribution from the \( T \Delta S^\ddagger \) term and cyclization is relatively fast. Four-membered rings suffer the worst of both worlds: forming a four-membered ring introduces ring strain (\( \Delta H^\ddagger \)) and requires order (\( \Delta S^\ddagger \)) to be imposed on the molecule. They form very slowly as a result.
Thermodynamic control

In this section we have discussed the rate at which rings form: in other words the kinetics of ring formation. However, there are many ring-forming reactions that are under thermodynamic and not kinetic control. For example, you have already seen that glucose exists predominantly as a six-membered ring in solution. It could also exist as a five-membered ring: it doesn’t because, although five-membered rings form faster than six-membered ones, they are usually less stable (remember, a six-membered ring is essentially strain-free). For similar thermodynamic reasons, it doesn’t exist as a seven-membered ring, even though you can draw a reasonable structure for it.

Thermodynamic control is important in other ways in carbohydrate chemistry, because control over ring size allows selective protection of the hydroxyl groups of sugars. Compare these two reactions. Both of them give acetals from the same starting material, mannitol.