NASÝTENÉ
KYSLÍKATÉ A SÍRNE
HETEROCYKLICKÉ
ZLÚČENINY
Saturated $O,S$-heterocycles – Nomenclature

oxirane  oxetane  tetrahydrofuran (THF)  dioxolane  tetrahydropyran (THP)  1,4-dioxane

thiirane  thietane  thiolane  tetrahydrothiophene (THT)  sulfolane  tetrahydrothiophene-1,1-dioxide  thiapyran  tetrahydro-2H-thiapyrane
Saturated $O,S$-heterocycles – Natural & Bioactive compounds

- Taxol® (Paclitaxel, Bristol-Myers-Squibb)
  - Isolated from the bark of *Taxus brevifolia*
  - Used in anticancer chemotherapy

- EDO® (Insecticide)
  - 25x more potent than DDT
  - Biodegradable

- epoxide or oxirane ring
- sex pheromone of the Grey Duiker antelope
- dioxane: a common solvent
- musty taste of "corked" wine
Saturated $O$-heterocycles – Oxirane
Structure & Properties

• The oxirane with its 3-membered $O$-ring features an inherent strain with calculated energy $112 \text{ kJ/mol}$.

• This is $6 \text{ kJ/mol}$ more than in oxetane and $87 \text{ kJ/mol}$ more than in tetrahydrofuran. Geometrically, the oxirane ring forms an almost equilaterial triangle, with a slightly relaxed bond angle at the oxygen.

OXIRANE (*ethylene oxide*)

Colourless gas (at $25^\circ\text{C}$) with *sweet odour* of ether

Mutagen & carcinogen!
Saturated $O$-heterocycles – Oxetane – Structure & Properties

- The oxetane with its 4-membered $O$-ring features an inherent strain with calculated energy 106 kJ/mol.
- This is only 6 kJ/mol less than in oxirane and 81 kJ/mol more than in tetrahydrofuran. In contrast to cyclobutane, the oxetane ring is only weakly puckered, or essentially planar, as determined by MW.

![Diagram showing oxetane structure with bond angles and distances]

- The isosteric relationship of oxetane with gem-dimethyl groups makes it attractive for drug discovery.
- Moreover, oxetane’s high polarity and outstanding hydrogen acceptor ability are extremely attractive.
- This property is due to the more effective exposure of the lone pairs of $O$-atom to the H-bond donors.
- In addition, similarity of oxygen lone pairs in oxetane and C=O compounds makes them analogous.

Oxetane as a carbonyl surrogate

Spirocyclic oxetane may serve as a viable substitute for morpholine
Reactivity of $O$-heterocycles – Oxirane opening

- The inherent strain of 3-membered ring and the leaving-ability of $O$-atom leads to opening reactions.
- Most epoxide ring-openings occur by $S_N2$ displacements at carbon with ROH, RSH, RNH$_2$, LAH, etc.

![Diagram of epoxide opening](image)

- Epoxides react with amines to give 1,2-aminoalcohols via initial $S_N2$ with subsequent H$^+$-transfer.

![Diagram of epoxide opening with amines](image)

- The epoxide-opening via $S_N2$ displacement proceeds with the clean inversion of configuration.
Reactivity of $O$-heterocycles – Oxirane opening – Regioselectivity

• Assistance by protic solvents ($ROH$) or Lewis acids ($BF_3$) dramatically increases the reaction rate.
• However, in such a case, the reaction outcome can be totally different in terms of regioselectivity.

![Diagram showing the reaction of epoxide with basic methoxide and acidic methanol]

• Protonation by acid produces a cationic intermediate. The two alkyl groups ($2 \times l^*$) stabilise a charge on the tertiary carbon of the protonated epoxide, and MeOH attacks here. Thus, electronic effects dominate.

![Diagram showing charge stabilised by alkyl groups]

• Without protonation in base, the epoxide oxygen is a poor leaving group, and leaves only if pushed by a strong nucleophile: the reaction becomes pure $S_N2$. Steric hindrance becomes the controlling factor.
Reactivity of $O$-heterocycles – Oxirane opening

Complex problem

- However, the regioselectivity of oxirane ring opening is a complex issue. Even with acid catalysts, $S_N2$ substitution at a primary centre is very fast. For example, $Br^-$ in acid attacks this epoxide mainly at the less substituted end, and only 24% of the product is produced by the ‘cation-stabilised’ pathway. It is very difficult to override the preference of epoxides unsubstituted at one end to react at that end.

![Oxirane opening reaction](image)

- The regiochemistry of ring-opening is determined mainly by steric, and, to a lesser extent, by inductive and electronic effects. Where strong Lewis acids are used or where a highly stabilised (incipient) carbonium ion can be formed, reaction occurs mainly at the most substituted position.
Reactivity of S-heterocycles – Thiirane opening

• Thiiranes similarly undergo ring-opening reactions with nucleophiles, such as amines. In this case, the regioselectivity of attack is primarily governed by steric hindrance at electrophilic carbon atoms.

• However, with lithium reagents the nucleophilic attack takes place at sulfur, thus leading to alkenes.
Reactivity of $O$-heterocycles – Oxetane opening

- The inherent strain of 4-membered ring and the leaving-ability of $O$-atom leads to opening reactions.
- Oxetane undergoes a very fast hydrolysis with mineral acids (e.g. $H_2SO_4$) similarly to the oxirane.
- Synthetically useful is the selective opening of the spiro-oxetane with HBr to the 1,3-bromoalcohol.

As strong base as $n$-butyllithium does not react with oxetane, unless a strong Lewis acid, such as $BF_3\cdot Et_2O$, is added, when it opens the four-membered ring to give a quantitative yield of $n$-heptanol.
Reactivity of $O$-heterocycles – Oxetane opening

• On the other hand, in the presence of a base, however, ring opening of oxetane is extremely slow.

• Oxetane undergoes hydrolysis 3-orders of magnitude slower than oxirane under alkaline conditions. The plausible explanation could be the following: in the case of 3-membered oxirane more strain is released in the transition state, which leads to a lower activation energy than in 4-membered rings.

• This reactivity difference towards nucleophiles means that ring-opening reactions of oxetanes often require the use of strong Brønsted or Lewis acids and/or higher reaction temperatures.
Reactivity of O-heterocycles – THF opening

- Unlike acyclic ethers, saturated 5- (THF) and 6-membered (THP) cyclic ethers are rather inert to the C–O bond cleavage, and thus requiring strong conditions for a successful ring-opening.
- As an example: the same reaction as with oxetane, happens with THF, but only in much lower yield.

Such a relative unreactivity of tetrahydrofuran against BuLi has found its practical application.
- THF is actually a good solvent for organolithiums and/or organomagnesium (Grignard) reagents - the nucleophilic lone pair of the oxygen atom stabilises the electron-deficient Li or Mg atom of the organometallics via strong complexation.
Reactivity of $O$-heterocycles – THF opening with BuLi

- A more important reaction between $n$-BuLi and THF is not nucleophilic attack, but deprotonation.
- The reactions involving $n$-BuLi in THF are invariably carried out at low temperatures (0 to -78°C). This is because, at temperatures above 0°C, deprotonation of tetrahydrofuran begins to take place.
- The trouble is that deprotonated THF is unstable, and it undergoes a reverse [2+3] cycloaddition, producing the (much less basic) enolate of acetaldehyde and (volatile) ethylene. The first tends to polymerize, and the second usually evaporates from the reaction mixture - and THF is all gone...

<table>
<thead>
<tr>
<th>RLi</th>
<th>Solvent</th>
<th>Half life ($t_{1/2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>-20°C</td>
</tr>
<tr>
<td>$n$-BuLi#</td>
<td>THF</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>Et₂O</td>
<td>-</td>
</tr>
<tr>
<td>$t$-BuLi</td>
<td>THF</td>
<td>45 min</td>
</tr>
<tr>
<td></td>
<td>Et₂O</td>
<td>7.5 hrs</td>
</tr>
</tbody>
</table>

#Stabilised with TMEDA ($N,N,N',N'$-tetramethyl-ethane-1,2-diamine)
Reactivity of $O$-heterocycles – THF opening with BuLi

Experimental evidence

• Chemists were studying the reactions of the organolithium shown below to find out whether the anionic centre would attack the double bond to form a five-membered ring (like a radical would).

• The reaction was slow, and they stirred the organolithium in THF for 6 hours at 0°C. When they worked the reaction up they found no five-membered ring products: instead they got a compound with an extra ethyl group attached! They showed that this ethyl group, in fact, comes from THF...

• The organolithium did not add to the double bond in the same molecule, but it did add slowly and in low yield to the double bond of the ethylene that is formed by decomposition of THF with RLi.
Reactivity of $O$-heterocycles – Baldwin’s rules & ring opening

Principle of microscopic reversibility

**Principle of microscopic reversibility:** „There is only one least-energy pathway between two interconverting compounds such as the substrate and the intermediate. Every microscopic detail of the back reaction is exactly the same as that for the forward reaction.“

- In other words, if a reaction goes via a certain mechanism, the reverse reaction must follow exactly the same path in the opposite direction. So, if Baldwin’s rules work for the prediction of cyclisation, they will also work for ring-opening reactions.
- This is where the unfavourability of 5-endo-trig really is important: the tetrahydrofuranyl ester below looks set up to do an $E_1cB$ elimination in base. Indeed, when it is treated with methoxide in $CD_3OD$, it exchanges the proton $\alpha$ to the ester for deuterium, proving that the enolate forms. But it does not eliminate: elimination would be a reverse 5-endo-trig process and is disfavoured.
Reactivity of S-heterocycles – 1,3-Dithiane deprotonation

- The ability of sulfur to stabilise an anion means that S-heterocycles are easier to deprotonate than THF.
- Treatment of 1,3-dithiane with strong base produces an anion (or a lithium derivative if BuLi is used).
- It was long thought that delocalisation into sulfur’s empty 3d orbitals provided the anion stabilisation required, but this is not case, as the C–S bond in -CH₂SH anion is longer than in CH₃SH itself.
- More likely as an additional factor is delocalisation into the σ* orbital of the C–S bond on the other side of the sulfur atom - the equatorial proton of dithiane is more acidic than the axial one, and the equatorial anion is more stable because it is delocalised into the C–S bond’s σ* orbital.

Dithiolane, the five-membered version of dithiane, cannot be used in this reaction because, although it is easy to deprotonate, once deprotonated it quickly decomposes by the same mechanism as lithiated THF.
Reactivity of S-heterocycles – 1,3-Dithiane utilisation

- The substituted dithiane is deprotonated by BuLi to give a nucleophilic organolithium that will attack electrophiles - even oxygen heterocycles - provided BF₃ is present. The products are formed in excellent yield, even when the electrophile is protonated THP, with no ring strain to drive the reaction.

- After the Adₙ reaction the dithiane can be hydrolysed with Hg(II) to give a ketone having useful groups.
Synthesis of oxiranes – Epoxidation with \textit{m}CPBA

- The most common method for the preparation of \textit{oxiranes} is the (ep)\textit{oxidation} of \textit{alkenes}.
- The \textit{alkene} attacks the \textit{peroxy-acid} (usually \textit{m-CPBA}) with the centre of its \textit{\pi}-orbital (HOMO).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) [align=center] {\textbf{bonding interaction}};
\node (b) at (-2,-1.5) [align=center] {HOMO = filled \textit{\pi} orbital};
\node (c) at (2,-1.5) [align=center] {LUMO = empty \textit{\sigma^*} orbital};
\node (d) at (4,0) [align=center] {transition state for epoxidation};
\node (e) at (0,0) [align=center] {electrophilic attack by a peroxo-acid on an alkene};
\end{tikzpicture}
\end{center}

- The reaction is strictly \textit{stereospecific}, thus (\textit{E})-\textit{alkene} yields only trans-\textit{epoxide} and \textit{vice versa}.
- In addition, the more substituted \textit{alkenes} epoxidise \textit{faster}, thus the \textit{chemoselectivity} is attained.
Dimethyldioxirane (DMDO) is made by oxidising acetone with potassium peroxymonosulfate (Oxone®). DMDO is not commercially available because of its instability (but can be stored in freezer for 2 weeks).

The advantage of DMDO use is that after it has transferred an oxygen atom in the epoxidation step, only innocuous (and volatile) acetone (b.p. 56°C) is left, thus simple evaporation leaves a product.

Application:

$$\text{MeCH=CHMe} \xrightarrow{\text{OXONE®, NaHCO}_3, \text{aq. Me}_2\text{CO}} [\text{MeCH=CHMe}] \xrightarrow{\text{MeCN, Me}_2\text{CO, rt}} \text{85%} \xrightarrow{\text{phenanthrene}}$$
The photochemical [2+2]-cycloaddition of an activated carbonyl with an alkene yields an oxetane.

The mechanism starts with the C=O photoexcitation (n,π* and π,π* transition) to the singlet/triplet state. Next, an alkene in the ground state is attacked and inherently reactive diradical intermediates are formed. Breaking of the new σ-bonds requires more energy, and the reverse reaction is impossible with same hν.

The reaction of benzaldehyde and enol ethers can lead to the diastereoselective ring formation.
Synthesis of O-heterocycles – $S_N^2$ cyclisations

- Important way of making O-heterocycles is by ring-closing reactions, because we can usually use the heteroatom as the nucleophile in an intramolecular substitution ($S_N$) or addition (Ad$_N$) reaction.

**OXIRANES:**
(via $S_N^2$)

**OXETANES:**
(via Ad$_N$ - $S_N^2$)

**THP:**
(via $S_N^2$)
Synthesis of $O$-heterocycles – Thorpe-Ingold effect

Kinetic phenomenon

- The Thorpe-Ingold effect is the way in which substituents on the ring increase the rate, or equilibrium constant, for ring-forming reactions. Thus, it is both a kinetic and a thermodynamic phenomenon.

**OXIRANES:**
(via $S_N^2$)

**OXETANES:**
(via $A_d - S_N^2$)
Synthesis of \textit{O}-heterocycles – Thorpe-Ingold effect

Thermodynamic phenomenon

- The \textit{Thorpe-Ingold} effect is the way in which \textit{substituents} on the ring \textit{increase} the \textit{rate}, or \textit{equilibrium constant}, for \textit{ring-forming} reactions. Thus, it is both a \textit{kinetic} and a \textit{thermodynamic} phenomenon.
Conformations of saturated \(N-, O-, S\)-heterocycles

• The conformation of 5- and 6-membered saturated heterocycles follows the same principles as the conformation of carbocyclic compounds, *i.e.* chairs and boats, or axial and equatorial substituents.
• Since the \(N-, O-, S\)-heteroatoms possess lone pairs, they occupy *axial* and *equatorial* positions.

![Dithiane, Dioxane, Piperidine](image)

- Equatorial lone pairs in black
- Axial lone pairs in green

• As indicated here, black lone pairs are *parallel* with C–C or C–heteroatom bonds in the ring; green lone pairs are *parallel* with axial C–H bonds outside the ring, or, if the ring has substituents, with the bonds to those substituents. This substituted tetrahydropyran illustrates all this. Notice that the equatorial substituents next to the heteroatom are *parallel* with neither the green nor the black lone pair.
Conformations of saturated heterocycles – Reactivity issues

• The overlap of parallel orbitals is very important in fragmentation reactions. Consider the fragmentation that can take place only if the nitrogen’s lone pair is equatorial, because only that one can overlap with the antibonding $\sigma^*$-orbital of the breaking C–C bond. The chloride leaving group must be equatorial too.

\[
\begin{align*}
\text{Cl} & \quad \text{equiv.} \quad \text{base} \quad -\text{H}^+ \\
\text{equiv} & \quad \text{H}_2\text{O} \\
\text{equiv} & \quad \text{equiv}
\end{align*}
\]

• Compare this bicyclic acetal whose ‘fragmentation’ (actually just an acetal hydrolysis) looks possible by this mechanism. However, in this case, neither oxygen lone pair overlaps with the C–O bond that is breaking and so neither can donate its electron density into the C–O antibonding $\sigma^*$-orbital.

\[
\begin{align*}
\text{OAr} & \quad \text{equiv.} \\
\text{equiv} & \quad \text{OH}_2 \\
\text{equiv} & \quad \text{equiv}
\end{align*}
\]

Not surprisingly, the rate of hydrolysis of this acetal is extremely slow compared with similar ones in which overlap between the oxygen lone pair and the C–O $\sigma^*$ is possible. The acetal with leaving group in axial position hydrolyses about $10^{10}$ times faster.
Conformations of 6-membered saturated heterocycles

**Anomeric effect**

- **Tetrahydropyran**, like piperidine, usually adopts an energetically favourable chair conformation.
- Bearing a methoxyl group at C-2, and unlike cyclohexane, THP prefers to reside in a chair, in which the substituent having the heteroatom (N, O, S, halogen, etc.) occupies an axial position.

![Chemical structures showing conformations](image)

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**The anomeric effect**

In general, any tetrahydropyran bearing an electronegative substituent in the 2-position will prefer that substituent to be axial. This is known as the **anomeric effect**.

![Chemical structures illustrating anomeric effect](image)
Conformations of 6-membered saturated heterocycles

Anomeric effect – Background

• Low-lying antibonding ($\sigma^*$) orbitals of C–X bonds are stabilised by an adjacent heteroatom lone pairs.
• However, only the axial conformation may benefit from it, hence the origin of the anomeric effect.
• The C–X bond is thus longer and weaker, as some of the O-electron density is delocalised on to X.

• In the equatorial orientation, there are unfavourable dipole-dipole interactions between lone pairs on the two heteroatoms, and the energy gain when these are relieved in a conformation with the C-2 substituent axial, more than offsets the unfavourable 1,3-diaxial interactions that are introduced.
Conformations of 6-membered saturated heterocycles

Anomeric effect – Monosaccharides
Conformations of 6-membered saturated heterocycles

Anomeric effect – Thioglycosides

β-anomer

Major product

α-anomer

Stable conformers of 1-thio-D-altrose

/PCMMP2/6-31+G(d,p)/

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