Organic Chemistry-2
Semester-2, CBCS
Course: CEMA CC-2-3-TH

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Recommended texts:
Tautomerism in Organic Chemistry

Ring-chain tautomerism:

In organic chemistry there are molecules capable of existing in two different isomeric forms, one of which is cyclic, the other being open-chain. When these isomers rapidly interconvert into one another, they are considered to be tautomers.

Valence tautomers represent one such class where a ring and a chain form exist with each other in dynamic equilibrium. This interconversion of a linear system into the ring system (or vice versa) involves reorganization of the bonding network and electron arrangement without the migration of any atoms or groups. We have already seen examples of this. Here is one more for recapitulation purpose:

\[
\begin{align*}
\text{HO} & \quad \text{H} \\
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{H}
\end{align*}
\]

In a second group of ring-chain isomeric interconversions, a linear system transforms into a cyclic one by intramolecular addition of a functional group (such as -OH) to a polar multiple bond (such as C=O).

As in the case of the valence tautomers shown above, a \(\alpha\)-bond is transformed into a \(\gamma\)-bond with reorganization of the electron distribution. However, in this case, simultaneously with the ring closure (or opening), the migration of atom or group occurs. Most commonly a proton is the migrating species.

This is the ring-chain tautomerism and they encompass both the characters of classic tautomerism (such as prototropy) and valence tautomerism. The following are two examples:

\[
\begin{align*}
\text{(R)-lactol} & \quad \text{4-hydroxybutanal} \\
\text{(S)-lactol} & \quad \text{4-hydroxybutanal - achiral}
\end{align*}
\]

In the first example the hydroxyl group attacks the C=O of the aldehyde and closes the ring, while the second example demonstrates ring-closure via a reaction between C=O of the ketone and OH of the COOH group.

Since the carbonyl group is planar, ring closure is possible in two ways and may therefore give rise to two different products. When the open-chain form is achiral, the two products will be related as enantiomers in a 1:1 ratio. This the case with both the examples outlined above.
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Ring-chain tautomerism:

Otherwise, when the open-chain form is itself chiral, the products will be diastereomers and their ratio other than 1:1. Consider the ring-chain tautomerism observed for D-glucose:

In an aqueous solution of D-glucose, there is present 36% of the \( \alpha \)-form, almost 64% is the \( \beta \)-form and a very small amount of the open-chain form. Because the cyclic products can interconvert via the open-chain form, they also form a tautomeric equilibrium.

A special feature of such cyclic tautomers is that they are stereoisomers to each other.

This is completely unlike any other tautomerisms we have seen, including the ring-chain tautomeric relation between the open-chain form and any one of the cyclic form where the two tautomers are constitutional isomers to each other.

The 4-hydroxybutanal and the each of the lactols are tautomeric to each other and they are constitutional isomers.

But the tautomeric \( S \)-lactol and the \( R \)-lactol are enantiomers.

Similarly, the open-chain form of D-glucose is tautomeric to both the \( \alpha \) - and \( \beta \)-D-glucopyranose structures, but the \( \alpha \)- and \( \beta \)-forms are tautomers as well as diastereomers to each other.

The stereoisomeric relationship is, however, completely independent to the tautomeric relation, it's just that for ring-chain tautomerism this special feature appears.

To clarify, S-2-bromobutane and R-2-bromobutane are definitely not tautomers because they do not interconvert to each other under normal conditions. But in aqueous solution, the \( S \)-lactol and the \( R \)-lactol do.
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Ring-chain tautomerism:

Now that we have understood what the ring-chain tautomerism is, there are two issues we need to address:

i) when we can expect to see this type of tautomerism, and

ii) to which direction the equilibrium lies for such tautomeric pairs?

We have dealt with only three examples, but many more can be found. In general, for molecules where a nucleophilic group like hydroxyl, amino or mercapto (SH, thiol) is capable of making an intramolecular attack on a polar multiply bonded group such as C=O and C=N, we can expect to see a ring-chain tautomeric equilibrium.

As this means a ring-closing process from an open-chain compound, the relative stability of the open-chain form and the cyclic form determines which one should be the dominant species in equilibrium.

The $\Delta G^0$ associated with formation of a ring from its open-chain precursor has two terms, an enthalpy factor ($\Delta H^0$) and an entropy factor ($\Delta S^0$).

Enthalpy depends upon the internal strain of the ring that include angle strain (Baeyer strain), eclipsing strain (Pitzer strain), steric strain (van der Waals strain) or transannular strain (Prelong strain), while entropy factor takes into account the loss of conformational freedom upon cyclisation.

Recall from our previous discussions relating to inter- versus intramolecular reactions that the intermolecular reactions are associated with a loss of translational entropy while intramolecular reaction leads to loss of conformational entropy.

This means that as the ring that is formed via an intramolecular reaction increases in size, an increasing number of randomly oriented bonds in the flexible, open-chain form needs to be fixed in place so that the two ends of the molecule can successfully meet.

When the target ring is sufficiently large, the intramolecular reaction results in a severe loss of conformational freedom. The cyclisation process then suffers a substantial loss of conformational entropy ($\Delta S^0 << 0$) and becomes thermodynamically untenable.

Instead, the system promotes intermolecular reaction to form dimers and higher aggregates.

Thus, for seven-membered ring onwards, ring formation becomes increasingly difficult on account of entropy.

There is also the matter of internal strains that are present in those rings and hinder their formation.

On the other hand, the five- and six-membered rings carry a much lower strain. The three- or four-membered rings are, however, highly strained (why?). Therefore, formation of such small rings is unfavourable in terms of enthalpy ($\Delta H^0 > 0$) and these rings are thermodynamically unstable.

This principle can be extrapolated to the ring-chain tautomerism equilibrium.
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Ring-chain tautomerism:

In absence of any additional destabilising factors and if the ring size is correct, it is generally the cyclic tautomer that dominates the equilibrium involving hydroxyaldehydes. You have already seen this in case of D-glucose where the major forms present in the tautomeric equilibrium are the two six-membered glucopyranose rings with only a very small amount of the open-chain form being present.

\[
\begin{align*}
\alpha-D\text{-glucopyranose} \leftrightarrow & \quad \text{CHO} \\
& \quad \text{HO} \\
& \quad \text{HO} \\
& \quad \text{HO} \\
& \quad \text{H} \\
& \quad \text{H} \\
& \quad \text{H} \\
& \quad \text{D-glucose} \leftrightarrow \beta-D\text{-glucopyranose}
\end{align*}
\]

This is also true for the hydroxyaldehydes and lactols:

\[
K_T = \frac{[\text{ring tautomer}]}{[\text{chain tautomer}]}\]

\(K_T\) is the tautomerization constant for chain-ring tautomeric eqm.

The six-membered ring incorporates considerably less strain that the five-membered one. This can be appreciated if we accept that these rings are not planar but puckered, as we have seen for the \(\alpha\)- and \(\beta\)-glucopyranoses.

On the other hand, closing a five-membered ring involves a lower conformational entropy penalty than the six-membered ring because a lesser number of bonds need to lose their conformational freedom for the former to happen. It is evident from the slightly higher tautomerization constant for the six-membered ring that the strain factor is more important.

For seven-membered lactols, \(K_T\) drops to 0.2, implying that the unfavourable entropy associated with the ring-closing process is too much now.
Tautomerism in Organic Chemistry

Ring-chain tautomerism:
Along with the size of the ring being formed, several other factors such as structural rigidity, electronic effects of different substituents, solvent effects also affect this equilibrium strongly. A striking example is the hydroxyacetones where the open-chain forms are preferred:

\[ K_T = \frac{[\text{ring tautomer}]_o}{[\text{chain tautomer}]_o} \]

5-hydroxypentan-2-one

\[ 0.83 \]

5-hydroxyhexan-2-one

\[ 0.85 \]

Considering the fact that the C=O bonds of ketones are - i) more stable, and ii) less reactive towards nucleophilic attack than those of aldehydes, this result is expected.

If we impose conformational restrictions in the open-chain form, the percentage of the ring form is expected to increase, because cyclisation will levy a lower entropy penalty then. Think of it in this way, if the open-chain form were fully flexible with all possible conformers of it being present, it would be rather difficult to set up the correct conformation from which cyclisation could proceed because it would mean sacrificing a large entropy. On the other hand, if you impose certain constraints in the open-chain form so that only a few of all the possible conformers remain available and the rest are not accessible due to some destabilising influence, cyclisation would be easier because you will lose less entropy in this case.

This case will almost certainly have a larger \( K_T \) value in the ring-chain tautomeric equilibrium.

It may so happen that the very factor that is preventing the open-chain molecule to access it's all possible conformations, is also responsible for setting up the molecule to forcibly stay in the conformation from where cyclisation could ensue. In this case the rate of cyclisation would go up as well.

Consider the following example:

These lactols are stable in the solid state.
Tautomerism in Organic Chemistry

Ring-chain tautomerism:

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Consider the following example:

![Diagram of 2-acylphenylcarbinol and lactol tautomers](image)

The cyclisation is favoured because -

i) presence of the aromatic ring ensures that the conformational freedom is reduced in the open-chain form to a significant extent:

![Diagram showing no rotation possible and free rotation possible](image)

and ii) due to the presence of the aromatic ring and also the geminal methyl groups, the two ends of the open-chain form are forced in close proximity, favouring cyclisation. This happens because these methyls sterically interfere with other conformers and force the molecule to stay in the "reactive" rotamer:

![Diagram showing more populated and less populated conformers](image)

Thus the lactols dominate the tautomeric equilibrium in this case. This effect of geminal alkyl groups in enhancing the rate and the equilibrium constant for cyclisation reaction is known as the gem-dialkyl effect or Thorpe-Ingold effect.