Chem Factsheet

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The Stereochemistry of Nucleophilic Substitution Reactions

Nucleophilic substitution reactions are commonplace in synthetic organic chemistry. They are extremely useful for interconverting functional groups. Typically, nucleophilic substitution is described using the reactions of halogenoalkanes with various small nucleophilic species such as hydroxide and cyanide ions (OH^- or CN^- respectively), water, and ammonia among many. The ability to switch functional groups is extremely useful in the design and production of novel compounds, including those manufactured by the pharmaceutical industry.

Nucleophilic substitution

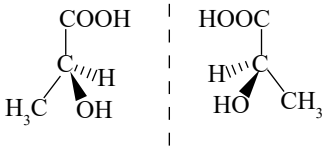
Overall equation: $RX + Nu^- \rightarrow RNu + X^-$

e.g., $CH_3CH_2Br + OH^- \rightarrow CH_3CH_2OH + Br^-$

In the example above, a halogen atom is replaced by a hydroxyl group turning the molecule from a halogenoalkane into an alcohol. Depending on the type of halogenoalkane used, the reaction may proceed via two different mechanisms: S_N1 favoured by tertiary compounds, and S_N2 favoured by primary compounds.

Importance of stereochemistry

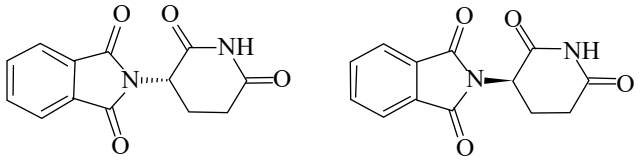
Stereochemistry is a branch of chemistry concerned with the three-dimensional positioning of the atoms within a molecule. Various types of stereoisomerism are possible such as *cis*/*trans*, *E*/*Z* and optical isomerism. These forms of isomerism are distinct from structural isomerism in which the order in which the atoms are bonded is different between molecules of the same molecular formula. In this Factsheet, we are concerned with optical isomerism, that is, the ability of a molecule to exist as a pair of non-superimposable mirror images, or **enantiomers**. This form of stereoisomerism may occur when a carbon atom is attached to four different groups; such carbons are called **chiral centres**.



The figure above shows the enantiomers of 2-hydroxypropanoic acid (lactic acid). The two molecules are related by a mirror plane (dashed line). The fact that some compounds exist as enantiomers is crucial to understanding how they might interact with biological molecules inside the body. The enzymes that perform vital catalytic functions within our cells are chiral; they exist as a specific stereoisomer and have a unique three-dimensional shape. This three-dimensional shape dictates which molecules the enzymes can and cannot interact with. Current understanding demonstrates that some enzymes will only recognise a specific enantiomer of a compound. The other enantiomers may not interact at all or may interact with a second, different enzyme.

The impact of specific enzyme-enantiomer interactions is that enantiomers of a compound may elicit very different effects inside an organism. In some cases, one enantiomer may be a highly effective medication whilst its mirror image is highly toxic.

The molecules on the top right of this page are the two enantiomers of the drug thalidomide.



This history of this molecule provides an important lesson in the understanding of stereoisomerism in biological context. The enantiomers interact with different enzymes within the body due to their different three-dimensional shapes. One of the enantiomers exhibits beneficial activity. The other is teratogenic, causing birth defects in a developing foetus.

This knowledge is essential when synthesising compounds that exist as enantiomers. Nucleophilic substitution reactions are able to alter the stereochemistry of a compound and this may have an important impact further down the line. Organic chemists need to use their understanding of organic mechanisms to control the stereochemistry of the molecules they produce.

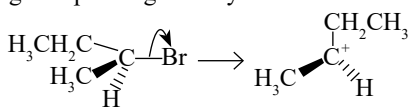
Nucleophilic reactions may proceed via one of two routes, S_N1 or S_N2. Each mechanism has a different effect on the stereochemistry of the compounds involved. The reaction of 2-bromobutane (which exists as enantiomers) with hydroxide ions will be used to illustrate the effects of both routes.

(NOTE: the stereochemical effects of nucleophilic substitution are only observed if the starting material is optically active, i.e., a pure enantiomer).

> In the following sections, do not worry about the use of the prefixes *(S)* and *(R)*, they are simply used to denote the different enantiomers of a compound. In a pair of enantiomers, one is the *(S)* form and the other the *(R)* form.

S_N1 mechanism

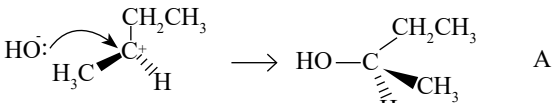
Nucleophilic substitution reactions that proceed via the S_N1 route occur in two steps. In the first step, there is spontaneous heterolytic fission of the C—X bond. This process yields a carbocation intermediate. The key effect here is that the enantiomerically pure starting material, (*S*)-2-bromobutane, which exhibits tetrahedral geometry about its chiral carbon atom, is converted to an intermediate with trigonal planar geometry.



(*S*)-2-bromobutane

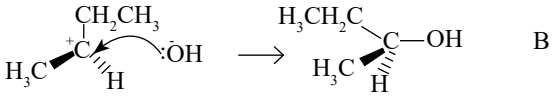
trigonal planar intermediate carbocation

In the second step, the nucleophile undergoes a rapid reaction with the electrophilic carbon (C^+). The attack of the nucleophile occurs from either side of the carbocation with equal probability. Approximately equal numbers of nucleophiles attack from both the left and right resulting in equimolar amounts of two products, A and B (see diagram on page 2).



A

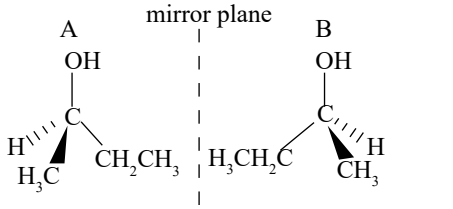
nucleophile attacks from the left



B

nucleophile attacks from the right

The formation of a co-ordinate (dative) bond between the nucleophile and the electrophilic carbon atom re-establishes the tetrahedral geometry around the chiral carbon. When the structures of the two products are compared, it is clear to see that they are related by a mirror plane. Molecules A and B are enantiomers of the product, butan-2-ol.



(*S*)-butan-2-ol (*S*)-butan-2-ol

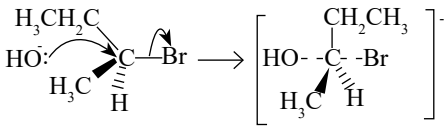
Although each molecule is optically active in isolation, the equimolar mixture of the pair of enantiomers is **optically inactive**. Mixtures of this type are termed **racemic mixtures**.

The overall effect of reaction via the S_N1 mechanism is to destroy the optical activity that was present in the starting material. In this example, a pure enantiomer, *(S)*-2-bromobutane was used but the product of the reaction was an optically inactive mixture of two enantiomers. The S_N1 mechanism is described as being **non-stereospecific**, that is it does not permit the production of a single stereoisomer.

S_N2 mechanism

The S_N2 mechanism occurs in a single step and differs from the S_N1 mechanism in that it does not proceed via a carbocation intermediate but rather through a trigonal-bipyramidal transition state.

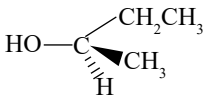
Again, the starting material is the pure enantiomer, *(S)*-2-bromobutane. In S_N2 reactions, the nucleophile approaches the electrophilic carbon atom at 180° to the C—X bond. As the nucleophile donates an electron pair to the electrophilic (and chiral) carbon atom, the tetrahedral geometry moves through a transitional trigonal-bipyramidal geometry before the tetrahedral geometry of the product is re-established.



(*S*)-2-bromobutane tetrahedral geometry

transition state trigonal-bipyramidal geometry

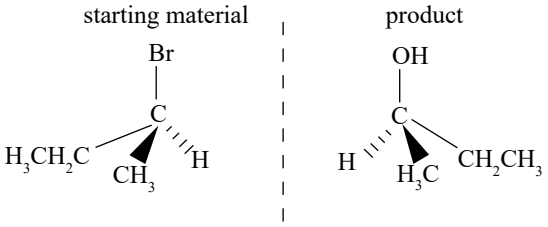
In the diagram of the mechanism shown here, the nucleophile is attacking from the left-hand side of the molecule and the halide ion leaves from the right-hand side. In the product, the hydroxyl group remains on the left-hand side of the electrophilic carbon atom.



final organic product tetrahedral geometry

In contrast to the S_N1 mechanism, the S_N2 mechanism leads to the production of a single enantiomer; optical activity is retained. The S_N2 mechanism is, therefore, described as being **stereospecific.**

A side-by-side comparison of the starting material and the final product show that the stereochemistry has been affected. Although the product is a pure enantiomer, the chiral carbon atom has undergone **chiral inversion**; the original *(S)*-form starting material has been converted to *(R)*-form product.



During the synthesis of a molecule, there may be several steps that involve stereospecific or non-stereospecific reactions. Careful control of each step is required in order to produce the desired product which exhibits the correct stereochemistry.

Questions

1. State the full name(s) of the organic product(s) of the following reactions; include the *(R)* or *(S)* prefix.
   (a) *(R)*-2-chloro-3-methylbutane and water via the S_N1 route.
   (b) *(R)*-1-iodoethanol with cyanide ions, CN^- via the S_N2 route.

2. Outline why controlling the stereochemistry of an organic synthesis is important.

3. Explain why the S_N1 mechanism is described as non-stereospecific.

Answers

1. (a) *(R)*-3-methylbutan-2-ol and *(S)*-3-methylbutan-2-ol
   (b) *(S)*-2-hydroxypropanenitrile, $CH_3CH(OH)CN$.

2. Enzymes and many other biological molecules are chiral and demonstrate stereospecific interactions. The various stereoisomers of a compound may exhibit different biological effects in an organism due to different interactions with enzymes, etc. Some stereoisomers may be toxic or ineffective whereas others may show excellent medicinal activity.

3. The S_N1 mechanism leads to the production of (equimolar quantities of) two enantiomers from a single, pure enantiomer.

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