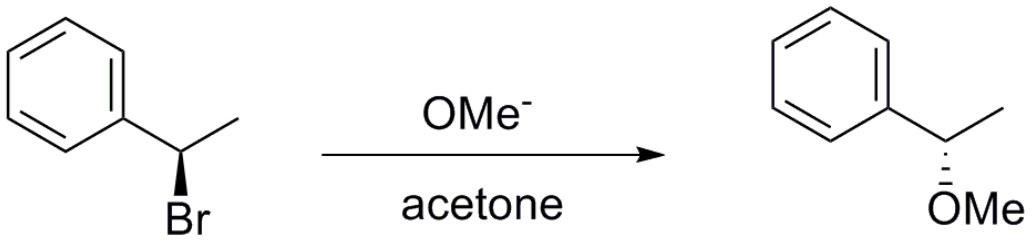
S_N2 Reactions: Stereochemistry of Consecutive Displacement Reactions

The S_N2 reaction is a very useful tool in synthetic organic chemistry because:

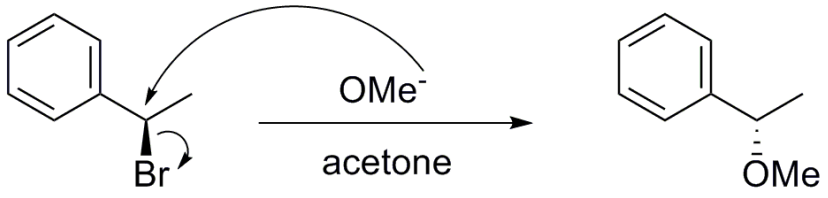
- **It allows for the displacement of good leaving groups (halides, tosylates, mesylates, diazo groups) by a wide variety of nucleophiles (Lewis bases) leading to a large number of functional group transformations**
- **The stereochemistry of the transformation is predictable: inversion of stereochemistry occurs at the carbon undergoing displacement**
- **The reaction occurs without rearrangement of the carbon skeleton**

An example:

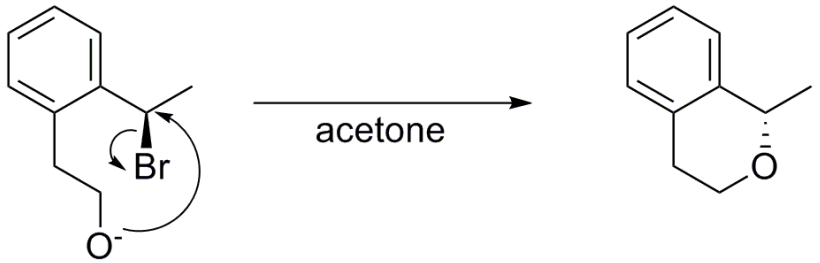


In CHM 241 lecture you have concentrated on the standard intermolecular S_N2 displacement reaction, but there is another version of the reaction in which the nucleophile is already attached to the substrate by a carbon chain so that it is part of the same molecule. This is an intramolecular nucleophilic displacement.

There are similarities and differences between these reactions. Both involve inversion of stereochemistry, and are typically run in the same type of solvent, but the kinetics are different. For the intermolecular reaction the rate depends on the concentration of the substrate and the nucleophile. For the intramolecular reaction the rate depends only on the concentration of the substrate since the nucleophile is part of the substrate.

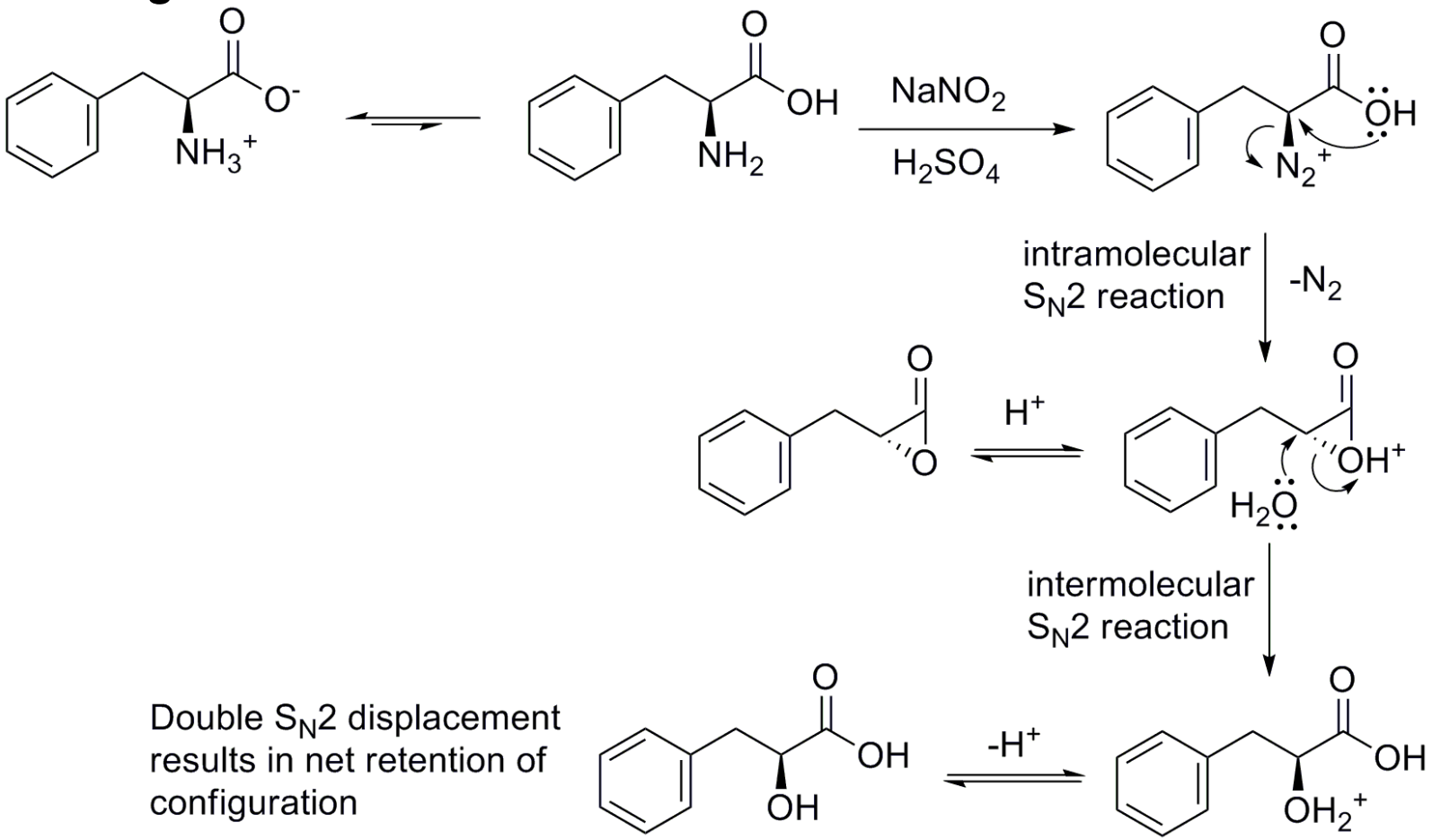


Inversion of stereochemistry
rate = k_2[MeO$^-$][RBr] (2nd order)
bimolecular transition state

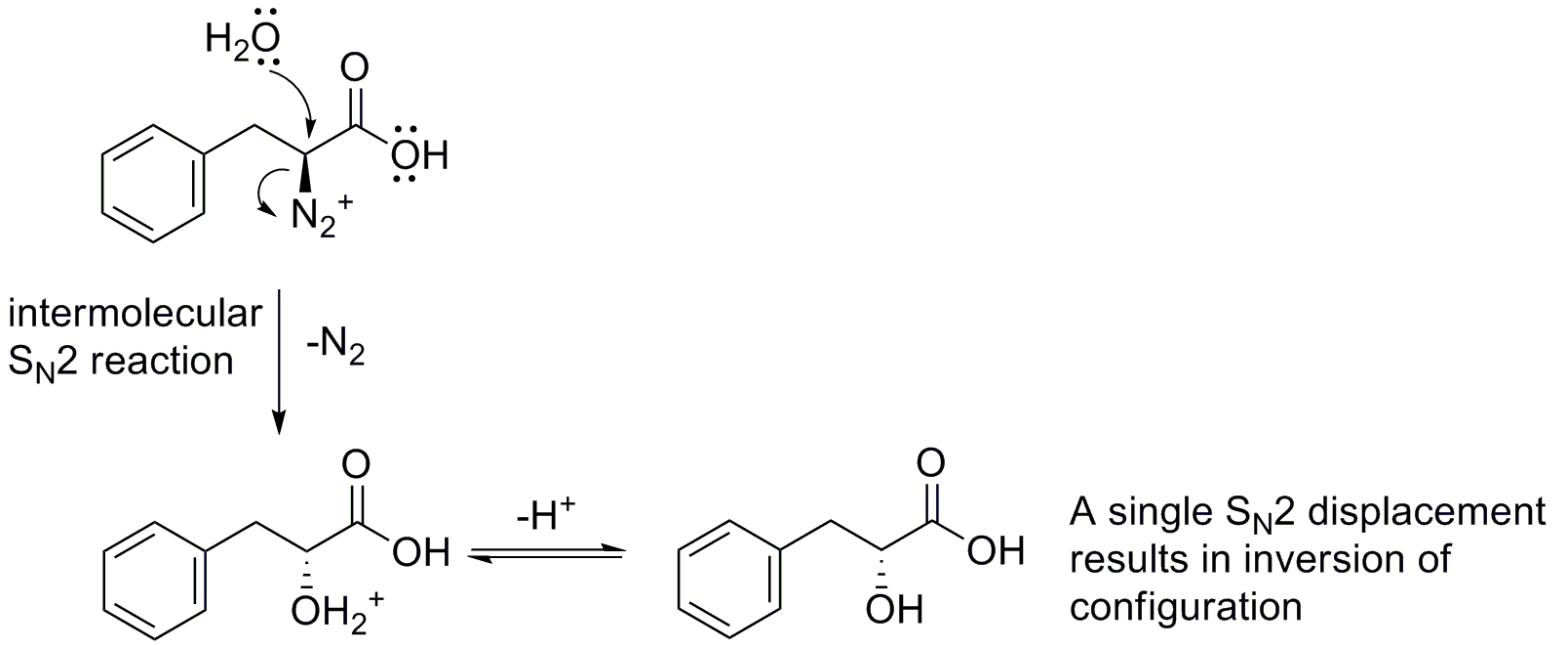


Inversion of stereochemistry
rate = k_1[RBr] (first order)
unimolecular transition state

In the S_N2 experiment that you are running, there is the possibility that the reaction occurs by two consecutive S_N2 reactions, the first is an intramolecular displacement, and the second is an intermolecular displacement. The double displacement should result in net retention of configuration.



There is another possibility. If the reaction occurs in one step then the product should exhibit inversion of stereochemistry.



The Experiment

Each student pair will be assigned to start with either L- or D-phenylalanine, and will convert their particular enantiomer into phenyllactic acid.

Each pair will then perform a stereochemical analysis to determine which enantiomer of phenyllactic acid they have made, or whether they have a racemic mixture.

This information will be used to deduce the mechanism of the substitution reaction, double displacement or single displacement, or a combination of both.

- **L-phenylalanine is inexpensive because it is the naturally occurring amino acid**
- **D-phenylalanine is also inexpensive because it is used to make aspartame, an artificial sweetener**

Stereochemical Analysis

You will use the techniques of mixed melting points and polarimetry to determine the stereochemistry of the product.

Mixed melting points:

For most enantiomeric pairs, the racemic mixture of the two enantiomers is a eutectic mixture with a significantly lower melting point than the two pure enantiomers that would have the same melting point. This is true for phenyllactic acid:

L- or D-phenyllactic acid: mp 124-125 °C

Racemic phenyllactic acid: mp 94-95 °C

You will determine the stereochemistry of the reaction product by determining the melting point of your product and comparing it with that of a mixture of equal parts of your product and one of the pure enantiomers. The sample for the mixed melting point needs to be well mixed by grinding the two samples together or the results may not be conclusive. If you started with L-phenylalanine, use D-phenyllactic acid, for the mixed melting point. Use L-phenyllactic acid if you started with D-phenylalanine.

Polarimetry

Enantiomers rotate the plane of plane polarized light in equal, but opposite directions. The rotation angle can be measured with a polarimeter.

The specific rotation is $[\alpha] = \alpha/(l \cdot c)$, where α is the observed angle of rotation in degrees (º), *l* is the cell pathlength in units of decimeters (dm), and *c* is the concentration of the sample in g/mL.

The observed specific rotation of your sample will be compared to the known values for the two enantiomers of phenyllactic acid:

L-phenyllactic acid -26.9° (acetone)
D-phenyllactic acid +26.9° (acetone)

Experimental Hints

1. **This experiment requires two lab days. In the first day you generate the diazo compound and let it undergo reaction. Keep the reaction mixture as close as you can to 0 °C and add the $NaNO_2$ slowly so that you do not generate large amounts of yellow-brown nitrogen dioxide.**
2. **On the second day, collect the product by vacuum filtration, and perform the stereochemical analysis.**
3. **Do not waste material, you need at least 1.5 g of product to perform the polarimetry accurately.**
4. **The sample for the mixed melting point should be composed of equal parts your product and equal parts D- or L-phenyllactic acid that are well mixed by grinding before the melting point is obtained.**
5. **The polarimetry measurements require careful preparation of the phenyllactic acid solution since you need to know the concentration of the solution to calculate [α].**