Synthesis and Properties of the Amino Acid: 

*d, l*-Norleucine


Introduction:

Norleucine is better known as 2-aminohexanoic acid, or *α*-aminocaproic acid. Although not a naturally occurring amino acid, it is a structural isomer of leucine and isoleucine, both essential amino acids. Leucine has been isolated from wool, wheat, and hemoglobin. The "nor" prefix is often used by chemists to define a structural isomer of a parent compound. In this case, norleucine has a straight chain 4-carbon side chain while the naturally occurring leucine or isoleucine have branched 4-carbon groups.

![Amino acid structures](image)

**d,l-norleucine**  
**L-leucine**  
**L-isoleucine**

Amino acids, the building blocks of proteins, are difunctional compounds containing a carboxylic acid and an amine. As a result, peptide bonds can form between the amine of one amino acid and the carboxylic acid of another amino acid. Different combinations of amino acids joined by these peptide bonds lead to protein formation.

Norleucine is prepared by a nucleophilic substitution reaction between 2-bromohexanoic acid and ammonia:

![Reaction mechanism](image)

It occurs via an S\(_{N}\)2 displacement reaction of the bromide ion. While amino acids can be drawn in the neutral form, in reality they exist in the zwitterionic form in which a proton has been transferred from the acidic carboxylic acid group onto the basic amino group yielding a molecule containing a positively charged ammonium cation and a negatively charged carboxyl anion. This species, neutral overall, is water soluble.
PreLab Exercise:

Draw 3-dimensional representations for R-2-bromohexanoic acid and the major product with \( \text{NH}_3 \). (Draw these with the lowest priority group pointing away from you, going into the paper.)

Caution:

2-Bromohexanoic acid is corrosive and toxic. Concentrated ammonia is noxious. Work in a hood. If you spill these chemicals on your skin, immediately wash the affected area with water.

Synthesis:

Place 1.0 g (\( \pm \))-2-bromohexanoic acid and 10 mL of concentrated aqueous ammonia in a tared 20-mL vial. Cap and let stand in your locker until the next laboratory period.

Isolation and Purification:

Place the vial in an ice bath for ten minutes. Draw off excess ammonia with a Pasteur pipette to the level of the crystals. Do not penetrate the crystals with the pipet. Add 5 mL of 95% ethanol. Cap and gently shake the mixture. Remove all of the ethanol using the pipet filtration method, this time penetrating the crystals. Now dry the product in the vial using a bell jar apparatus. Use the house vacuum system as your vacuum source. If the crystals are not completely dry, let stand until the next laboratory period. Determine the percent yield. Do not attempt to determine the melting point of d,l-norleucine due to its very high decomposition point of 334°C.

Properties of amino acids versus amines and carboxylic acids:

To see the effect of the zwitterionic nature of amino acids on their water solubility, test the solubility of a small amount of your product in water, 5% HCl and 1N NaOH and compare this with the solubility of an amine and a carboxylic acid in these same solvents. Place a few mg of your product in each of three test tubes and add about 1 mL of water to one, 1 mL of 5% HCl to another, and 1 mL of 1N NaOH to the third. Do the same with hexanoic acid (caproic acid) placing a drop of the hexanoic acid in each of three test tubes and adding 1 mL of water to one, 1 mL of 5% HCl to another, and 1 mL of 1N NaOH to the third. Repeat these solubility tests with n-hexylamine (1-aminohexane). Record your solubility observations in all nine cases.

Cleaning Up:

The liquid filtrate is flushed down the drain with water. The product, d,l-norleucine, can be discarded in the nonhalogenated organics container after spectral analysis.

Analysis

You may be instructed to analyze your final product by IR or NMR (use \( \text{D}_2\text{O} \) as your NMR solvent; available at the stockroom). Analyze your sample according to your assignment sheet and the instructions on Sample Preparation in the Lab Guide (inside back cover).

Postlab Questions:

1. Define zwitterionic. Explain your solubility results based on this concept.
2. Starting with a racemic mixture of 2-bromohexanoic acid, one expects a racemic mixture of norleucine. If one started with (S)-2-bromohexanoic acid, would be the final product be R or S or racemic?

3. Would you expect the reaction to proceed faster or slower if a solvent less polar than water were used? Explain.