Objectives

After completing this section, you should be able to

1. recognize that atoms other than carbon can be chiral centres.
2. explain why enantiomers of compounds such as ethylmethylamine cannot normally be isolated.

Study Notes

The first example of a resolvable compound containing a chiral nitrogen atom was resolved by William Pope and Stanley Peachey in 1899. It had the structure shown below.

![a resolvable compound with a chiral nitrogen centre](image)

Chiral sulfoxides find application in certain drugs such as esomeprazole and armodafinil and are a good example of a stereogenic sulfur center.

Chirality at Nitrogen

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of chiral amines cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp\(^3\) hybridized amine momentarily rehybridizes to a sp\(^2\) hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to tetrahedral sp\(^3\) hybridization causing the lone pair electrons to enter to a hybrid orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer, analogous to the Walden inversion seen in S\(_{N2}\) reactions. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic
mixture of R and S configurations.

Quaternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quaternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.

Example \(\PageIndex{1}\)

The Enantiomers of a chiral quaternary amine.

Chirality at Phosphorus

Trivalent phosphorus compounds called phosphines have a tetrahedral electron-group geometry which makes them structurally analogous to amines. The rate of inversion for phosphines are so much slower than amines that chiral phosphines can be isolated. In this case the set of lone pair electrons are considered a substituent and given the lowest Cahn-Ingold-Prelog priority.
The phosphorus center of phosphate ions and organic phosphate esters is also tetrahedral, and thus potentially a stereocenter. In order to investigate the stereochemistry of reactions at the phosphate center, $^{17}\text{O}$ and $^{18}\text{O}$ isotopes of oxygen (the ‘normal’ isotope is $^{16}\text{O}$) can be incorporated to create chiral phosphate groups. Phosphate triesters are chiral if the all four substituent groups are different (including the carbonyl oxygen).

Chirality at Sulfur

Trivalent sulfur compounds called sulfonium salts ($R_3\text{S}^+$) have a tetrahedral electron-group geometry similar to amines and can be chiral if the $R$ groups are all different. In a similar fashion as phosphorus, the inversion rates are slow enough for chiral sulfonium salts to be isolated. Here again the set of lone pair electrons are considered a substituent and given the lowest CIP priority. Sulfonium salts will be discussed in greater detail in Section 18.8.

An excellent example of a chiral sulfonium salt in biological systems is the coenzyme (S)-adenosylmethionine (SAM). The presence of a sulfonium allows SAM to be a biological methyl group donor in many metabolic pathways. Note that SAM has an (S) configuration at the sulfur atom.
The sulfur in sulfoxides (R'SOR") can be chiral if both R groups are different. Here again the inversion rate is slow enough to allow chiral sulfoxides to be isolated. An excellent example is methyl phenyl sulfoxide. Sulfoxides will also be discussed in greater detail in Section 18.8.

enantiomers of methyl phenyl sulfoxide