STRUCTURE-REACTIVITY RELATIONSHIPS: NUCLEOPHILIC SUBSTITUTION REACTIONS

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Experimental procedure;

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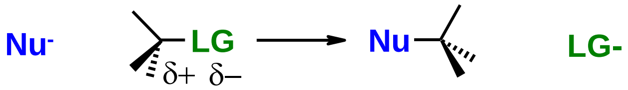
INTRODUCTION

Nucleophilic substitution reactions at sp^3-hydridised carbons are important reactions, *e.g.* for the conversions of alcohols to alkyl halides, and for the reactions of alkyl halides themselves. This experiment will investigate the SN reactivity of alkyl halides probing the correlation of structure and reactivity. But in this experiment, the observed reactivity will be used to deduce the structure.

To provide a little background: alkyl halides (especially R-Cl, -Br or -I) or alkyl sulfonate esters (*e.g.* tosylates) very commonly undergo nucleophilic substitution reactions (this **only** occurs where the C atom is sp^3 hybridised). Since the carbon-halogen or carbon-oxygen bond is very polar with the carbon bearing a partial positive charge, the carbon atom with the electronegative atom attached is the electrophilic center, and, is therefore susceptible to attack by nucleophiles. The halide ion or the sulfonate ion are relatively stable species and are readily displaced, *i.e.* they are "good leaving groups". Overall the reaction is termed a "nucleophilic substitution" (or SN) because a nucleophile (Nu) has substituted (replaced) a leaving group (LG), this is shown in very general terms below:



Nucleophilic Substitution

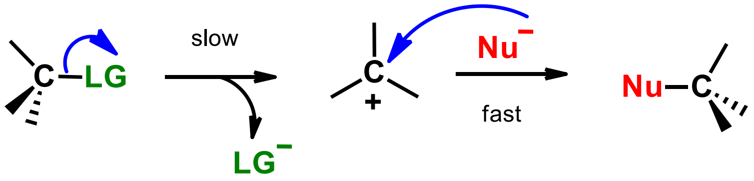
At the molecular level, nucleophilic substitution can occur via different pathways or **mechanisms**. There are two common mechanisms by which alkyl halides are substituted by nucleophiles, *i.e.* substitution, nucleophilic:

1. Unimolecular (rate = k [R-LG]) hence SN1
2. Bimolecular (rate = k [R-LG][Nu] hence SN2

However, these are the extreme (limiting) situations. In many cases the product may be formed, in part, by both mechanisms "operating concurrently" or via a pathway that has a flavour of both. However, by careful choice of reaction conditions, such as the nucleophile and solvent it is possible to ensure that the reaction follows a "single" pathway.

Whether a particular starting material (or substrate) reacts via SN1 or SN2 depends on many experimental features including the structure and nature of the starting material (the nature of the alkyl group and the leaving group), the nature of the nucleophile and the even the reaction solvent.

SN1



SN1 reactions are stepwise reactions with breaking to the C-LG bond to form an intermediate, followed by the formation of the new C-Nu bond. The rate determining step of the reaction is the loss of the leaving group from the substrate to form an intermediate carbocation. The stability of the intermediate carbocation formed dictates the rate of reaction. The stability of carbocations follows a similar trend to the stability of alkyl radicals, so in terms of stability tertiary > secondary > primary > methyl. Other additional factors such as resonance can also affect the stability of the intermediate carbocations. In terms of SN1 reactivity, for the same leaving group and nucleophile, the relative reactivity sequence is tertiary > secondary > primary > methyl (*i.e.* the more stable the carbocation, the easier it is to form and hence the faster the reaction proceeds).

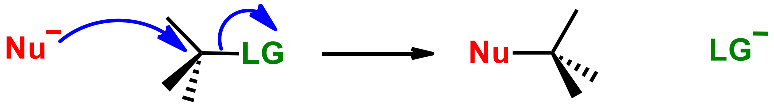
Since the C-LG bond is broken in the rate determining step (the first step), the better the leaving, the faster the SN1 reaction.

In this experiment, the $AgNO_3$ / aq EtOH combination promotes SN1 reactivity because:

a. Silver forms insoluble precipitates with halides (AgCl = white, AgBr = pale yellow) which promotes the loss of the leaving group

b. The polar solvent mixture stabilizes the polar intermediate

SN2



SN2 reactions are concerted with simultaneous formation of the new C-Nu bond and breaking of the C-LG bond. This means that the transition state for the SN2 has a crowded central C atom. The more alkyl groups there are around this central C, the higher the energy and the less stable the transition state. This means a reaction with a more crowded transition state is slower. So, in terms of crowding in the transition state, tertiary > secondary > primary > methyl which means that tertiary is the slowest to react (least reactive) and methyl fastest (most reactive). In terms of SN2 reactivity, for the same leaving group and nucleophile, the relative reactivity sequence is (least hindered) methyl > primary > secondary > tertiary (most hindered).

Since the C-LG bond is broken at the same time the new C-Nu bonds forms, the better the leaving, the faster the SN2 reaction.

In this experiment, the NaI / acetone combination promotes SN2 reactivity because:

a. Iodide is a very good nucleophile
b. Acetone is a polar aprotic solvent that enhances nucleophilicity

In this experiment you will be investigating the nucleophilic substitution reactions of a series of "unknown" organic halides with NaI / acetone and with $AgNO_3$ / aqueous ethanol. The principle aim is use the relative reactivity to identify the organic halides.

Each pair of students is required to investigate the reactivity of the eight unknown, different alkyl halides. Based on the observed relative reactivity from the SN1 and SN2 reactivity experiments, you should then be able to match each unknown to one of the structures in the list below.

ALKYL HALIDES

n-butyl chloride (1-chlorobutane)
n-butyl bromide (1-bromobutane)
sec-butyl chloride (2-chlorobutane)
sec-butyl bromide (2-bromobutane)
tert-butyl chloride (2-chloro-2-methylpropane)
tert-butyl bromide (2-bromo-2-methylpropane)
benzyl chloride (chlorophenylmethane)
chlorobenzene

As background preparation, draw out the structures of each of the alkyl halides listed above.

You may find it useful to familiarize yourself with the sections in your text book or the course website OLC (https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch08/ch8-0.html) on nucleophilic substitutions of alkyl halides.

REFERENCES

Organic Chemistry etext Ch8, https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch08/ch8-0.html