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Phase Transfer Catalysts : A Method for Synthesis of Nucleophilic Substitution Products

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ABSTRACT: In chemistry, a phase-transfer catalyst or PTC is a catalyst that facilitates the transition of a reactant from one phase into another phase where reaction occurs. Phase-transfer catalysis is a special form of catalysis and can act through homogeneous catalysis or heterogeneous catalysis methods depending on the catalyst used. Ionic reactants are often soluble in an aqueous phase but insoluble in an organic phase in the absence of the phase-transfer catalyst. The catalyst functions like a detergent for solubilizing the salts into the organic phase. Phase-transfer catalysis refers to the acceleration of the reaction upon the addition of the phase-transfer catalyst. By using a PTC process, one can achieve faster reactions, obtain higher conversions or yields, make fewer byproducts, eliminate the need for expensive or dangerous solvents that will dissolve all the reactants in one phase, eliminate the need for expensive raw materials and/or minimize waste problems.^[1] Phase-transfer catalysts are especially useful in green chemistry—by allowing the use of water, the need for organic solvents is reduced.^{[2][3]} Contrary to common perception, PTC is not limited to systems with hydrophilic and hydrophobic reactants. PTC is sometimes employed in liquid/solid and liquid/gas reactions. As the name implies, one or more of the reactants are transported into a second phase which contains both reactants.

KEYWORDS: Phase transfer catalyst, nucleophilic substitution, products, homogeneous, heterogeneous, green chemistry

I. INTRODUCTION

Phase-transfer catalysts for anionic reactants are often quaternary ammonium salts. Commercially important catalysts include benzyltriethylammonium chloride, methyltricaprylammonium chloride and methyltributylammonium chloride. Organic phosphonium salts are also used¹, e.g., hexadecyltributylphosphonium bromide. The phosphonium salts tolerate higher temperatures, but are unstable toward base, degrading to phosphine oxide.^[4]

For example, the nucleophilic substitution reaction of an aqueous sodium cyanide solution with an ethereal solution of 1-bromooctane does not readily occur. The 1-bromooctane is poorly soluble in the aqueous cyanide solution, and the sodium cyanide does not dissolve well in the ether.² Upon the addition of small amounts of

hexadecyltributylphosphonium bromide, a rapid reaction ensues to give nonyl nitrile:

By the quaternary phosphonium cation,³ cyanide ions are "ferried" from the aqueous phase into the organic phase.^[5]

Subsequent work demonstrated that many such reactions can be performed rapidly at around room temperature using catalysts such as tetra-n-butylammonium⁴ bromide and methyltrioctylammonium chloride in benzene/water systems.^[6]

An alternative to the use of "quat salts" is to convert alkali metal cations into hydrophobic cations. In the research lab, crown ethers are used for this purpose. Polyethylene glycols are more commonly used in practical applications. These ligands encapsulate alkali metal cations (typically Na⁺ and K⁺), affording large lipophilic cations. These polyethers have a hydrophilic "interiors" containing the ion and a hydrophobic exterior.⁵

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Chiral phase-transfer catalysts have also been demonstrated.^[7]

PTC is widely exploited industrially.^[4] Polyesters for example are prepared from acyl chlorides and bisphenol-A. Phosphothioate-based pesticides are generated by PTC-catalyzed alkylation of phosphothioates. One of the more complex applications of PTC involves asymmetric alkylations, which are catalyzed by chiral quaternary ammonium salts derived from cinchona alkaloids.^[8] In chemistry, a nucleophilic substitution is a class of chemical reactions in which an electron-rich chemical species (known as a nucleophile)⁶ replaces a functional group within another electron-deficient molecule (known as the electrophile). The molecule that contains the electrophile and the leaving functional group is called the substrate.^{[1][2]}

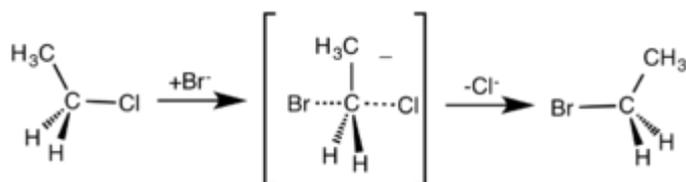
The most general form of the reaction may be given as the following:

The electron pair (:) from the nucleophile (Nuc) attacks the substrate (R-LG) and bonds with it. Simultaneously, the leaving group (LG) departs with an electron pair. The principal product in this case is R-Nuc. The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged.⁷

An example of nucleophilic substitution is the hydrolysis of an alkyl bromide, R-Br under basic conditions, where

the attacking nucleophile is hydroxyl (OH⁻) and the leaving group is bromide (Br⁻).⁸

Nucleophilic substitution reactions are common in organic chemistry. Nucleophiles often attack a saturated aliphatic carbon. Less often, they may attack an aromatic or unsaturated carbon.^[3]



Nucleophilic substitution at carbon

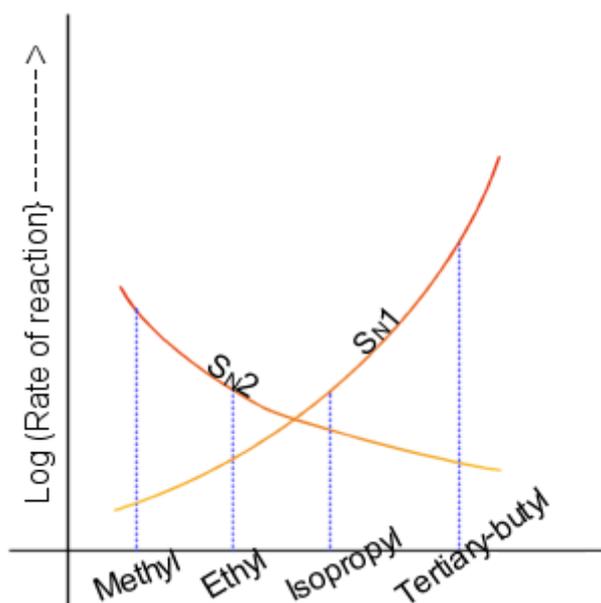
In 1935, Edward D. Hughes and Sir Christopher Ingold studied nucleophilic substitution reactions of alkyl halides and related compounds. They proposed that there were two main mechanisms at work, both of them competing with each other.⁹ The two main mechanisms were the S_N1 reaction and the S_N2 reaction, where S stands for substitution, N stands for nucleophilic, and the number represents the kinetic order of the reaction.^[4]

In the S_N2 reaction, the addition of the nucleophile and the elimination of leaving group take place simultaneously (i.e. a concerted reaction). S_N2 occurs when the central carbon atom is easily accessible to the nucleophile.^[5]

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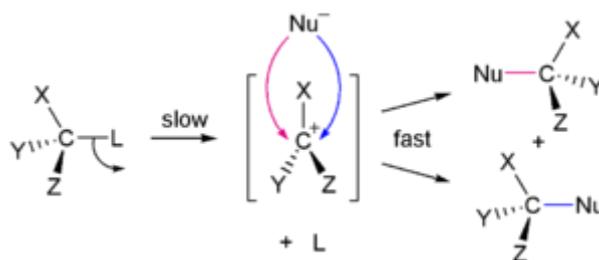


A graph showing the relative reactivities of the different alkyl halides towards SN1 and SN2 reactions¹⁰

II. DISCUSSION

In S_N2 reactions, there are a few conditions that affect the rate of the reaction. First of all, the 2 in S_N2 implies that there are two concentrations of substances that affect the rate of reaction: substrate (Sub) and nucleophile. The rate equation for this reaction would be $\text{Rate} = k[\text{Sub}][\text{Nuc}]$. For a S_N2 reaction, an aprotic solvent is best, such as acetone, DMF, or DMSO. Aprotic solvents do not add protons (H^+ ions) into solution; if protons were present in S_N2 reactions, they would react with the nucleophile and severely limit the reaction rate. Since this reaction occurs in one step, steric effects drive the reaction speed. In the intermediate step, the nucleophile is 180 degrees from the leaving group and the stereochemistry is inverted as the nucleophile bonds to make the product. Also, because the intermediate is partially bonded to the nucleophile and leaving group, there is no time for the substrate to rearrange itself: the nucleophile will bond to the same carbon that the leaving group was attached to. A final factor that affects reaction rate is nucleophilicity; the nucleophile must attack an atom other than a hydrogen.¹¹

By contrast the S_N1 reaction involves two steps. S_N1 reactions tend to be important when the central carbon atom of the substrate is surrounded by bulky groups, both because such groups interfere sterically with the S_N2 reaction (discussed above) and because a highly substituted carbon forms a stable carbocation.¹²



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Nucleophilic substitution at carbon, SN1 mechanism

Like S_N2 reactions, there are quite a few factors that affect the reaction rate of S_N1 reactions. Instead of having two concentrations that affect the reaction rate, there is only one, substrate. The rate equation for this would be Rate=k[Sub]. Since the rate of a reaction is only determined by its slowest step, the rate at which the leaving group "leaves" determines the speed of the reaction. This means that the better the leaving group, the faster the reaction rate. A general rule for what makes a good leaving group is the weaker the conjugate base, the better the leaving group. In this case, halogens are going to be the best leaving groups, while compounds such as amines, hydrogen, and alkanes are going to be quite poor leaving groups. As S_N2 reactions were affected by sterics, S_N1 reactions are determined by bulky groups attached to the carbocation. Since there is an intermediate that actually contains a positive charge, bulky groups attached are going to help stabilize the charge on the carbocation through resonance and distribution of charge. In this case, tertiary carbocation will react faster than a secondary which will react much faster than a primary. It is also due to this carbocation intermediate that the product does not have to have inversion. The nucleophile can attack from the top or the bottom and therefore create a racemic product. It is important to use a protic solvent, water and alcohols, since an aprotic solvent could attack the intermediate and cause unwanted product. It does not matter if the hydrogens from the protic solvent react with the nucleophile since the nucleophile is not involved in the rate determining step.¹³

Table 1. Nucleophilic substitutions on RX (an alkyl halide or equivalent)

| Factor | S _N 1 | S _N 2 | Comments |
|-----------------|--|--|---|
| Kinetics | Rate = k[RX] | Rate = k[RX][Nuc] | |
| Primary alkyl | Never unless additional stabilising groups present | Good unless a hindered nucleophile is used | |
| Secondary alkyl | Moderate | Moderate | |
| Tertiary alkyl | Excellent | Never | Elimination likely if heated or if strong base used |
| Leaving group | Important | Important | For halogens, I > Br > Cl >> F |
| Nucleophilicity | Unimportant | Important | |

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| | | | |
|-------------------|---|-------------------------------------|------------------------------|
| Preferred solvent | Polar protic | Polar aprotic | |
| Stereochemistry | Racemisation (+ partial inversion possible) | Inversion | |
| Rearrangements | Common | Rare | Side reaction |
| Eliminations | Common, especially with basic nucleophiles | Only with heat & basic nucleophiles | Side reaction esp. if heated |

Reactions

There are many reactions in organic chemistry involving this type of mechanism. Common examples include:¹⁴

- Organic reductions with hydrides, for example
 $R-X \rightarrow R-H$ using $LiAlH_4$ (S_N2)
- Hydrolysis reactions such as
 $R-Br + OH^- \rightarrow R-OH + Br^-$ (S_N2) or
 $R-Br + H_2O \rightarrow R-OH + HBr$ (S_N1)
 - Williamson ether synthesis
 $R-Br + OR' \rightarrow R-OR' + Br^-$ (S_N2)
 - The Wenker synthesis, a ring-closing reaction of aminoalcohols.
 - The Finkelstein reaction, a halide exchange reaction. Phosphorus nucleophiles appear in the Perkow reaction and the Michaelis–Arbuzov reaction.
 - The Kolbe nitrile synthesis, the reaction of alkyl halides with cyanides.¹⁵

III.RESULTS

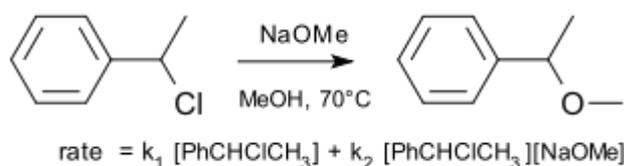
Borderline mechanism

An example of a substitution reaction taking place by a so-called borderline mechanism as originally studied by Hughes and Ingold^[6] is the reaction of 1-phenylethyl chloride with sodium methoxide in methanol.

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The reaction rate is found to be the sum of S_N1 and S_N2 components with 61% (3.5 M , 70°C) taking place by the latter.

Other mechanisms

Besides S_N1 and S_N2 , other mechanisms are known, although they are less common. The S_Ni mechanism is observed in reactions of thionyl chloride with alcohols, and it is similar to S_N1 except that the nucleophile is delivered from the same side as the leaving group.¹⁴

Nucleophilic substitutions can be accompanied by an allylic rearrangement as seen in reactions such as the Ferrier rearrangement. This type of mechanism is called an S_N1' or S_N2' reaction (depending on the kinetics). With allylic halides or sulphonates, for example, the nucleophile may attack at the γ unsaturated carbon in place of the carbon bearing the leaving group. This may be seen in the reaction of 1-chloro-2-butene with sodium

hydroxide to give a mixture of 2-buten-1-ol and 1-buten-3-ol:

The S_N1CB mechanism appears in inorganic chemistry. Competing mechanisms exist.^{[7][8]}

In organometallic chemistry the nucleophilic abstraction reaction occurs with a nucleophilic substitution mechanism.¹⁵

IV. CONCLUSIONS

Unsaturated carbon centres

Nucleophilic substitution via the S_N1 or S_N2 mechanism does not generally occur with vinyl or aryl halides or related compounds. Under certain conditions nucleophilic substitutions may occur, via other mechanisms such as those described in the nucleophilic aromatic substitution article.¹⁶

When the substitution occurs at the carbonyl group, the acyl group may undergo nucleophilic acyl substitution. This is the normal mode of substitution with carboxylic acid derivatives such as acyl chlorides, esters and amides.¹⁶

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