# **Organic Chemistry I**

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## **Solvation impedes nucleophilicity**

Nucleophilicity *increases* in the progression down the periodic table, a trend *directly opposing* that expected from the basicity of the nucleophiles tested. For example, in the series of halides, iodide is the fastest, although it is the weakest base.



Sulfide nucleophiles are more reactive than the analogous oxide systems, and their selenium counterparts are even more reactive.

**Experiment 6** 

$$CH_{3}CH_{2}CH_{2}\dot{B}\dot{R}: + CH_{3}\ddot{O}: \xrightarrow{CH_{3}OH} CH_{3}CH_{2}CH_{2}\ddot{O}CH_{3} + \dot{B}\dot{R}: \xrightarrow{-} Not very fast$$

$$CH_{3}CH_{2}CH_{2}\dot{B}\dot{R}: + CH_{3}\ddot{S}: \xrightarrow{-} \xrightarrow{CH_{3}OH} CH_{3}CH_{2}CH_{2}\dot{S}CH_{3} + \dot{B}\dot{R}: \xrightarrow{-} Very fast$$

Interaction of the solvent (methanol) with the anionic nucleophile:

Nucleophilic substitution features polar starting materials and a polar mechanism, and the nature of the solvent becomes more important.

When a solid dissolves, the intermolecular forces that held it together are replaced by intermolecular forces between molecules and solvent.

Such molecules, especially the ions derived from the starting salts of many  $S_N 2$  reactions, are said to be **solvated**.

Salts dissolve well in alcohols and water, because these solvents contain highly polarized  $^{\delta^+}H-O^{\delta^-}$  bonds that act by ion-dipole interactions. Thus, cations are solvated by the negatively polarized oxygens, anions by the positively polarized hydrogens.

This solvation of anions is particularly strong, because the small size of the hydrogen nucleus makes the  $\delta^+$  charge relatively dense.

Solvents capable of hydrogen bonding are also called **protic**, in contrast to **aprotic** solvents, such as acetone.

The *solvation weakens the nucleophile* by forming a shell of solvent molecules around the nucleophile and thus impeding its ability to attack an electrophile.

As we move down the periodic table, such as from  $F^-$  to  $I^-$ , the solvated ion becomes larger and its charge more diffuse. As a result, solvation is diminished along the series and nucleophilicity increases.

The smaller fluoride ion is much more heavily solvated than the larger iodide.



# Aprotic solvents: the effect of solvation is diminished

Other solvents that are useful in  $S_N 2$  reactions are highly polar but aprotic. All lack protons capable of hydrogen bonding but do exhibit polarized bonds. Nitromethane even exists as a charge-separated species.

Polar, aprotic solvents also dissolve salts by ion-dipole interactions, albeit not as well as protic solvents. Since they cannot form hydrogen bonds, they solvate anionic nucleophiles relatively weakly.

The consequences are twofold.

First, compared to protic solvents, the *reactivity of the nucleophile is raised,* sometimes dramatically. For example, bromomethane reacts with potassium iodide 500 times faster in acetone than in methanol.

Polar Aprotic Solvents

:O: || CH<sub>3</sub>CCH<sub>3</sub> Acetone

Table 6-5

 $CH_3C \equiv N:$ 

Ethanenitrile (Acetonitrile)

:O: ||.. HCN(CH<sub>3</sub>)<sub>2</sub> N,N-Dimethylformamide (DMF)



Dimethyl sulfoxide (DMSO)



Hexamethylphosphoric triamide (HMPA)



Nitromethane

Table 6-6 compares the rates of  $S_N 2$  reactions of iodomethane with chloride in three protic solvents (methanol, formamide, and *N*-methylformamide), and one *aprotic* solvent (*N*,*N*-dimethylformamide, DMF).

Formamide and *N*-methylformamide can form hydrogen bonds by virtue of their polarized N–H linkages.

The rate of reaction in DMF is more than a million times greater than it is in methanol.

Table 6-6	Relative Rates of S <sub>N</sub> 2 Reactions of lodomethane with Chloride Ion in Various Solvents $CH_3I + Cl^- \xrightarrow{Solvent} CH_3Cl + I^-$					
	Solvent					
Formula	Name	Classification	Relative rate $(k_{rel})$			
CH <sub>3</sub> OH	Methanol	Protic	1			
HCONH <sub>2</sub>	Formamide	Protic	12.5			
HCONHCH	I <sub>3</sub> <i>N</i> -Methylformamide	Protic	45.3			
HCON(CH <sub>3</sub>	N,N-Dimethylformamide	Aprotic	1,200,000			

The second consequence of comparatively weaker solvation of anions by aprotic solvents is that the nucleophilicity trend observed in protic solvents inverts.

Thus, while the reactivity of all anions increases, that of the smaller ones *increases more* than that of the others.

For many nucleophiles, including the halide series, base strength overrides solvation.



## Increasing polarizability improves nucleophilic power

The solvation effects are pronounced only for charged nucleophiles, while for *uncharged nucleophiles* solvent effects are much less strong. The degree of nucleophilicity increases down the periodic table, for example,  $H_2Se > H_2S > H_2O$ , and  $PH_3 > NH_3$ .

This factor is the polarizability of the nucleophile. Larger elements have larger, more diffuse, and more polarizable electron clouds. These electron clouds allow for more effective orbital overlap in the  $S_N$ 2 transition state.

The result is a lower transition-state energy and faster nucleophilic substitution.



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## Sterically hindered nucleophiles are poorer reagents

The bulk of the surrounding solvent may adversely affect the power of a nucleophile, another example of steric hindrance.

Such hindrance may also be built into the nucleophile itself in the form of bulky substituents.

The effect on the rate of reaction can be seen in Experiment 7. Sterically bulky nucleophiles react more slowly.

**Experiment 7** 



# Nucleophilic substitutions may be reversible

The halide ions Cl<sup>-</sup>, Br<sup>-</sup>, and l<sup>-</sup> are both good nucleophiles and good leaving groups. Therefore, their  $S_N 2$  reactions are reversible. For example, in acetone, the reactions between lithium chloride and primary bromo- and iodoalkanes form an equilibrium that lies on the side of the chloroalkane products:

 $CH_3CH_2CH_2CH_2I + LiCl \xrightarrow{Acetone} CH_3CH_2CH_2CH_2CH_2CI + LiI$ 

This result correlates with the relative stabilities of the product and starting material, which favor the chloroalkane. However, this equilibrium may be driven in the reverse direction by a simple "trick":

Whereas all of the lithium halides are soluble in acetone, solubility of the *sodium* halides decreases dramatically in the order Nal > NaBr > NaCl, the last being virtually insoluble in this solvent.

The reaction between Nal and a primary or secondary chloroalkane in acetone is *completely* driven to the side of the iodoalkane by the precipitation of NaCI:

$$CH_{3}CH_{2}CH_{2}CH_{2}CI + NaI \xrightarrow{Acetone} CH_{3}CH_{2}CH_{2}CH_{2}I + NaCl \downarrow$$
Insoluble

in acetone

When the nucleophile in an  $S_N^2$  reaction is a strong base (e.g., HO<sup>-</sup> or CH<sub>3</sub>O<sup>-</sup>), it will be incapable of acting as a leaving group. In such cases,  $K_{eq}$  will be very large and displacement will essentially be an irreversible process.

Nucleophilicity is controlled by a number of factors. Increased negative charge and progression from right to left and down (protic solvent) or up (aprotic solvent) the periodic table generally increase nucleophilic power.

Table 6-7 compares the reactivity of a range of nucleophiles relative to that of the very weakly nucleophilic methanol (arbitrarily set at 1).

The use of aprotic solvents improves nucleophilicity, especially of smaller anions, by eliminating hydrogen bonding.

Table 6-7	Relative Rates of Reaction of Vari- ous Nucleophiles with Iodometh- ane in Methanol (Protic Solvent)			
Nucleophile		Relative rate		
CH <sub>3</sub> OH		1		
$NO_3^{-}$		~32		
$F^{-}$		500		
$\begin{array}{c} O \\ \parallel \\ CH_{3}CO^{-} \\ Cl^{-} \\ (CH_{3}CH_{2})_{2}S \\ NH_{3} \\ CH_{3}SCH_{3} \\ N_{3}^{-} \\ Br^{-} \\ CH_{3}SCH_{3} \\ N_{3}^{-} \\ CH_{3}O^{-} \\ CH_{3}SeCH_{3} \\ CN^{-} \\ (CH_{3}CH_{2})_{3}As \\ I^{-} \end{array}$	Increasing nucleophilicity	20,000 23,500 219,000 316,000 347,000 603,000 617,000 1,950,000 2,090,000 5,010,000 7,940,000 26,300,000		
$HS^{-}$		100,000,000		

# STRUCTURE AND $S_N 2$ REACTIVITY: THE SUBSTRATE

Does the structure affect the rate of nucleophilic attack?

#### Branching at the reacting carbon decreases the rate of the S<sub>N</sub>2 reaction

The carbon is surrounded by the incoming nucleophile, the outgoing leaving group, and three substituents.

Although the presence of these five groups increases the crowding about the carbon relative to that in the starting halomethane, the hydrogens do not give rise to serious steric interactions with the nucleophile because of their small size.

However, replacement of one hydrogen by a methyl group, as in a haloethane, creates substantial steric repulsion with the incoming nucleophile, thereby raising the transition-state energy.

This effect significantly retards nucleophilic attack.



If we continue to replace hydrogen atoms with methyl groups, we find that steric hindrance to nucleophilic attack increases dramatically. The two methyl groups in the secondary substrate severely shield the backside of the carbon attached to the leaving group; the rate of reaction diminishes considerably.





Finally, in the tertiary substrate, in which a third methyl group is present, access to the backside of the halide-bearing carbon is nearly blocked; the transition state for  $S_N 2$  substitution is high in energy, and displacement of a tertiary haloalkane by this mechanism is rarely observed.

To summarize,  $S_N 2$  reactivity decreases in the following order:

### **Relative S<sub>N</sub>2 Displacement Reactivity of Haloalkanes**

Methyl	>	primary	>	secondary	$\gg$	tertiary		
Fast		Slower		Very slow		Negligible		
Increasing S <sub>N</sub> 2 reactivity								

If reaction occurs from the most stable *anti* conformer of the substrate, the incoming nucleophile faces severe steric hindrance. However, rotation to a *gauche* conformation before attack gives an  $S_N 2$  transition state.



### Branching next to the reacting carbon also retards substitution



**1-Propyl** (*gauche* CH<sub>3</sub> and Cl)



2-Methyl-1-propyl (two gauche CH<sub>3</sub> and Cl) (High energy transition state: reaction is slower)



- 2,2-Dimethyl-1-propyl
- (All conformations experience severe steric hindrance)





# THE S<sub>N</sub>2 REACTION AT A GLANCE

The factors that affect the energy of the transition state and therefore the rate of the  $S_N 2$  reaction:

**Nucleophilicity** Increases to the left (more basic Nu) and down (more polarizable Nu) the periodic table.

**Solvation** Impedes nucleophilicity by forming a solvent shell around Nu, particularly with protic solvents and for charged, small Nu<sup>-</sup>. Solvation is much attenuated with aprotic solvents.

**Steric hindrance** Slows the reaction through substituents at and adjacent to the reacting center.

**Leaving-group ability** Increases with decreasing basicity of L.

