## **Organic Chemistry I**

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#### The S<sub>N</sub>2 reaction is stereospecific

The reaction of (S)-2-bromobutane with iodide ion. gives (R)-2-iodobutane. This and all other  $S_N 2$  reactions proceed with inversion of configuration.



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#### The transition state of the S<sub>N</sub>2 reaction can be described in an orbital picture

leophile approaches the back lobe of the  $sp^3$  hybrid orbital used by carbon to alogen atom, the rest of the molecule becomes planar at the transition state by ne hybridization at carbon to  $sp^2$ .



As the reaction proceeds to products, the inversion motion is completed and the carbon returns to the tetrahedral  $sp^3$  configuration.



### Synthesize a specific enantiomer by using $S_N 2$ reactions

With optically pure *R* bromide, only *S* thiol is obtained, and none of its *R* enantiomer.



A double inversion sequence of two  $S_N 2$  processes gives a net retention of configuration.

Using Double Inversion to Give Net Retention of Configuration



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In substrates bearing more than one stereocenter, inversion takes place *only* at the carbons that undergo reaction with the incoming nucleophile.

The reaction of (2S,4R)-2-bromo-4-chloropentane with excess cyanide ion results in a meso product.





In these equations, ethanol and acetone are the *solvents* for the indicated transformations. These solvents are polar and particularly good at dissolving salts (the influence of the nature of the solvent on the  $S_N2$  reaction).

Similarly, nucleophilic substitution of a substituted halocycloalkane may change the stereochemical relation between the substituents.

For example, in the disubstituted cyclohexane below, the stereochemistry changes from cis to trans.



## STRUCTURE AND $S_N 2$ REACTIVITY: THE LEAVING GROUP

The relative facility of  $S_N 2$  displacements depends on several factors: the nature of the leaving group, the reactivity of the nucleophile (which is affected by the choice of reaction solvent), and the structure of the alkyl portion of the substrate.

# Leaving-group ability is a measure of the ease of its displacement



Nucleophilic substitution occurs only when the group being displaced, X, is readily able to depart, taking with it the electron pair of the C–X bond.

The relative rate at which it can be displaced, its **leaving-group ability**, can be correlated with its capacity to accommodate a negative charge.

For the halogens, leaving-group ability increases along the series from fluorine to iodine. Thus, iodide is regarded as a "good" leaving group; fluoride is so "poor" that S<sub>N</sub>2 reactions of fluoroalkanes are rarely observed. Leaving-Group Ability

> $I^- > Br^- > Cl^- > F^-$ Best Worst Increasing

Other examples of good leaving groups are sulfur derivatives of the type  $ROSO_3^-$  and  $RSO_3^-$ , such as methyl sulfate ion,  $CH_3OSO_3^-$ , and various sulfonate ions.

Alkyl sulfate and sulfonate leaving groups are used so often that trivial names, such as mesylate, triflate, and tosylate:





## Weak bases are good leaving groups

Leaving-group ability is inversely related to base strength. Weak bases are best able to accommodate negative charge and are the best leaving groups.

Among the halides, iodide is the weakest base and therefore the best leaving group in the series. Sulfates and sulfonates are weak bases as well.

The weaker  $X^-$  is as a base, the stronger is its conjugate acid HX. Therefore, good leaving groups are the conjugate bases of strong acids.

This rule applies to the four halides: HF is the weakest of the conjugate acids, HCl is stronger, and HBr and HI are stronger still.

Basicity $I^- < Br^- < Cl^- < F^-$ LeastMostDecreasing

Table 6-4	Base	Stre	Strengths and Leaving Groups								
Conjugate acid				Leaving group	Conjugate acid		Leaving group				
Strong			pK <sub>a</sub>	Good		Weak		pK <sub>a</sub>	Poor		
HI (stronge	HI (strongest)		-10.0	I <sup>-</sup> (best)	0	HF		3.2	$F^-$	Q	
HBr		-	-9.0	$\mathrm{Br}^-$	no,	CH <sub>3</sub> CO <sub>2</sub> H		4.7	$CH_3CO_2^-$	no,	
HCl		acid	-8.0	$\mathrm{Cl}^-$	l di	HCN	acio	9.2	$NC^{-}$	g gi	
$H_2SO_4$		era	-3.0	$\mathrm{HSO_4}^-$	vinç	CH <sub>3</sub> SH	era	10.0	$CH_3S^-$	vinç	
$H_3O^+$		bug	-1.7	$H_2O$	lea	CH <sub>3</sub> OH	bug	15.5	$CH_3O^-$	lea	
CH <sub>3</sub> SO <sub>3</sub> H		Stre	-1.2	$CH_3SO_3^-$	ier	H <sub>2</sub> O	Stro	15.7	$\mathrm{HO}^{-}$	er	
					<b>3ett</b>	NH <sub>3</sub>		35	$H_2N^-$	<b>3ett</b>	
						H <sub>2</sub> (weakest)		38	$H^{-}(worst)$		

## STRUCTURE AND S<sub>N</sub>2 REACTIVITY: THE NUCLEOPHILE

The nucleophilicity depends on a variety of factors: charge, basicity, solvent, polarizability, and the nature of substituents.

## Increasing negative charge increases nucleophilicity

If the same nucleophilic atom is used, the charge play a role in the reactivity. The species with a negative charge is the more powerful nucleophile.

Of a base and its conjugate acid, the base is always more nucleophilic.

**Experiment 1** 

$$\begin{array}{rcl} CH_{3}\dot{C}l: &+ H\dot{O}:^{-} &\longrightarrow CH_{3}\dot{O}H &+ :\dot{C}l:^{-} & Fast \\ CH_{3}\dot{C}l: &+ H_{2}\dot{O} &\longrightarrow CH_{3}\dot{O}H_{2}^{+} &+ :\dot{C}l:^{-} & Very \ slow \end{array}$$

**Experiment 2** 

$$\begin{array}{cccc} CH_{3}\dot{C}l^{\textstyle :} + H_{2}\dot{N}^{\textstyle :}^{-} \longrightarrow CH_{3}\dot{N}H_{2} & + :\dot{C}l^{\textstyle :}^{-} & \text{Very fast} \\ CH_{3}\dot{C}l^{\textstyle :} + H_{3}N^{\textstyle :} & \longrightarrow CH_{3}NH_{3}^{+} & + :\dot{C}l^{\textstyle :}^{-} & \text{Slower} \end{array}$$

### Nucleophilicity decreases to the right in the periodic table

The more basic species is the more reactive nucleophile. Therefore, in the progression from the left to the right of the periodic table, nucleophilicity decreases.



**Experiment 3** 

$$CH_{3}CH_{2}\dot{B}r: + H_{3}N: \longrightarrow CH_{3}CH_{2}NH_{3}^{+} + \dot{B}r:^{-} Fast$$

$$CH_{3}CH_{2}\dot{B}r: + H_{2}\dot{O} \longrightarrow CH_{3}CH_{2}\dot{O}H_{2}^{+} + \dot{B}r:^{-} Very slow$$

**Experiment 4** 

$$CH_{3}CH_{2}Br: + H_{2}N:^{-} \longrightarrow CH_{3}CH_{2}NH_{2} + Br:^{-} Very fast$$

$$CH_{3}CH_{2}Br: + HO:^{-} \longrightarrow CH_{3}CH_{2}OH + Br:^{-} Slower$$

#### Should basicity and nucleophilicity be correlated?

Strong bases typically make good nucleophiles. However, a fundamental difference between the two properties is based on how they are measured.

Basicity is a *thermodynamic* property, measured by an equilibrium constant:

$$A^- + H_2O \rightleftharpoons^K AH + HO^- K = equilibrium constant$$

Nucleophilicity is a *kinetic* phenomenon, quantified by comparing rates of reactions:

$$Nu^- + R - X \xrightarrow{k} Nu - R + X^ k = rate constant$$

Despite these inherent differences, we have observed good correlation between basicity and nucleophilicity in the cases of charged versus neutral nucleophiles along a row of the periodic table.