Salahaddin University- Erbil
College of Education
Chemistry Department

Organic Reaction Mechanism

For 3rd stage

By Lecturer

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Reaction mechanisms and their importance

The microscopic steps in a chemical reaction which reflect how the reactant molecules interact (collide) with each other to lead to the formation of the product molecules are defined as the **mechanism** of the reaction. ***The mechanism*** *of a reaction reveals detailed process of bond breaking in reactants and bond formation in products. It is a microscopic view of a chemical reaction at molecular, atomic, and/or even electronic level*. The structure of most organic compounds is well established by X-ray crystallography and various spectroscopic methods with the accuracy of measurement in bond distances and angles being the nearest to 0.01 °A and 1o, respectively

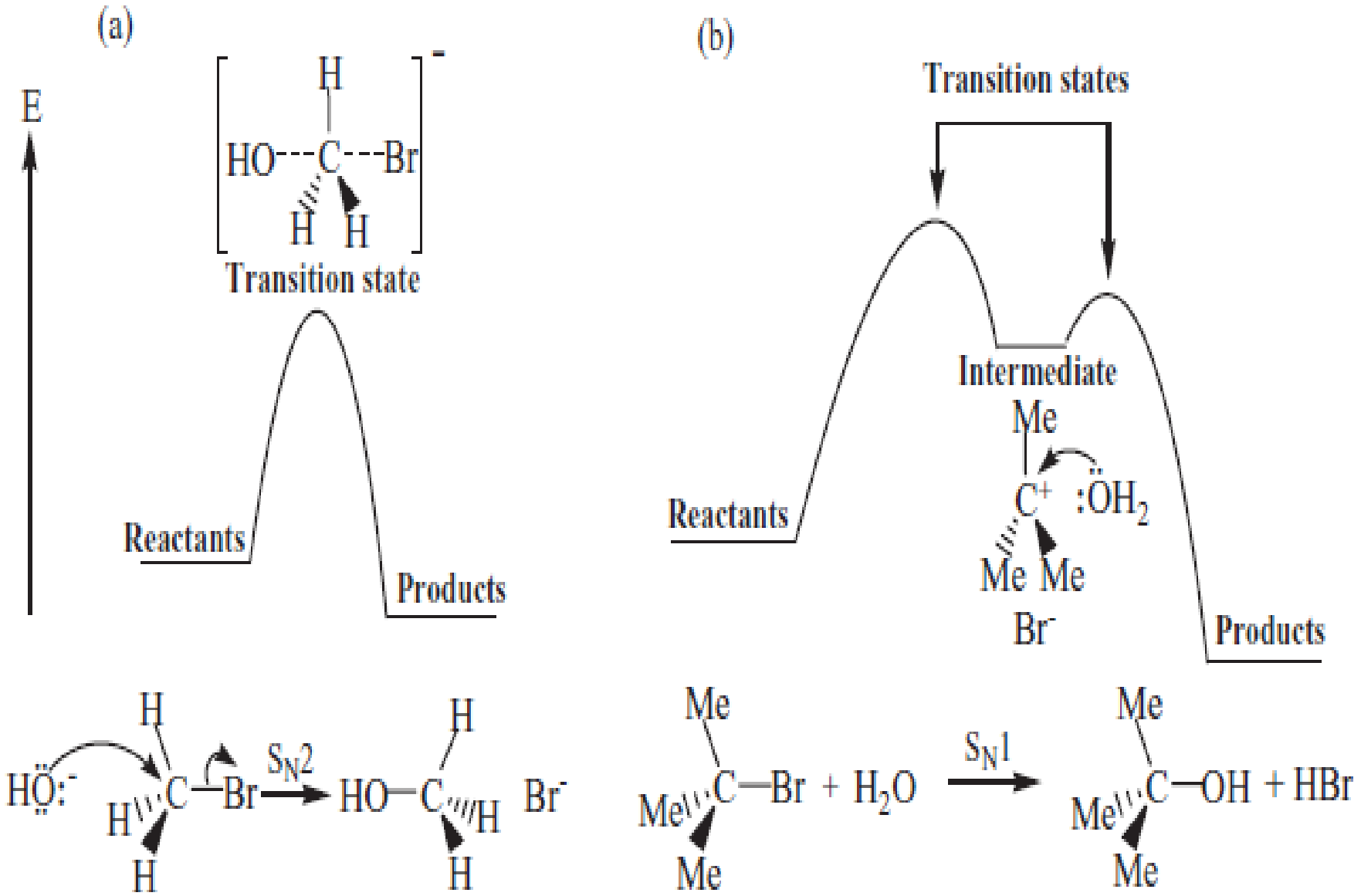
Reaction mechanisms play very important roles in the study of organic chemistry. The importance of mechanisms lies in that they not only facilitate understanding of various chemical phenomena, but also can provide guideline for exploring new chemistry and developing new synthetic methods for various useful substances, drugs, and materials. On this regard, mechanistic studies will allow ***synthetic chemists*** to vary reaction conditions, temperatures, and proportions of chemical reagents to maximize yields of targeted pure products.

For ***industrial chemists***, mechanistic knowledge allows the prediction of new reagents and reaction conditions which may affect desired transformations. It also allows the optimization of yields, reducing the costs on raw materials and waste disposals. **For *biochemists* and *medicinal chemists***, the microscopic view of organic reactions can help them better understand how the metabolic processes in living organisms work at molecular level, how diseases affect metabolism, and how to develop appropriate drug molecules to assist or prevent particular biochemical reactions.

Elementary (concerted) and stepwise reactions

Some chemical reactions only involve *one microscopic step*. In these reactions, the effective molecular collision, the collision of reactant molecules with sufficient energy in appropriate orientation, leads to *simultaneous* breaking of old bonds in reactants and formation of new bonds in products. This type of reactions is defined as **elementary (or concerted) reactions.** An elementary (concerted) reaction proceeds via **a single transition state**. The transition state is a short-lived (transient) activated complex in which the old bonds are being partially broken and new bonds are being partially formed concurrently. It possesses the maximum energy level in the reaction profile (energy profile).

Many other chemical reactions involve *many microscopic elementary* (*concerted*) *steps* in the course of the overall reactions. These reactions are defined as **stepwise or multistep**) **reactions.** A stepwise reaction proceeds via **more than one transition state.** Each microscopic concerted step proceeds through one transition state, giving a distinct product which is referred to as an **intermediate**. Each intermediate formed in the course of a reaction is metastable and usually highly reactive, possessing a relatively high energy level. Once formed, the intermediate undergoes a subsequent reaction eventually leading to the formation of the final product.

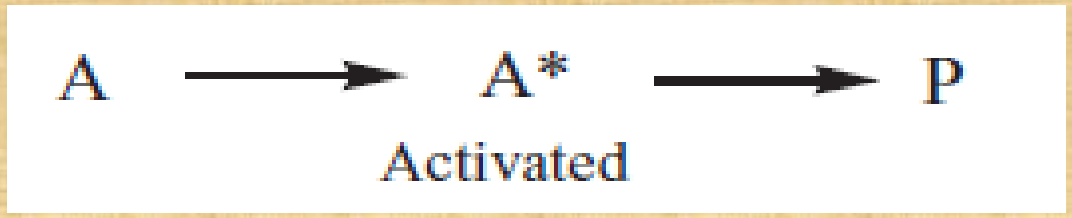

(a)
E
HO---C---Br
H
H
H
Transition state
Reactants
Products
(b)
Transition states
Intermediate
Reactants
Products
Me
C+
:OH2
Me
Me
Br-
HO:-
H
C
Br
SN2
HO
C
H
Br-
Me
C
Br + H2O
Me
Me
SN1
Me
C
OH + HBr
Me
Me

Molecularity

The number of molecules contained in the transition state of a *concerted reaction* is called the **molecularity** of the reaction. Clearly, the molecularity is determined by the number of reactant molecules that are involved in the mechanism (microscopic step) of a concerted reaction.

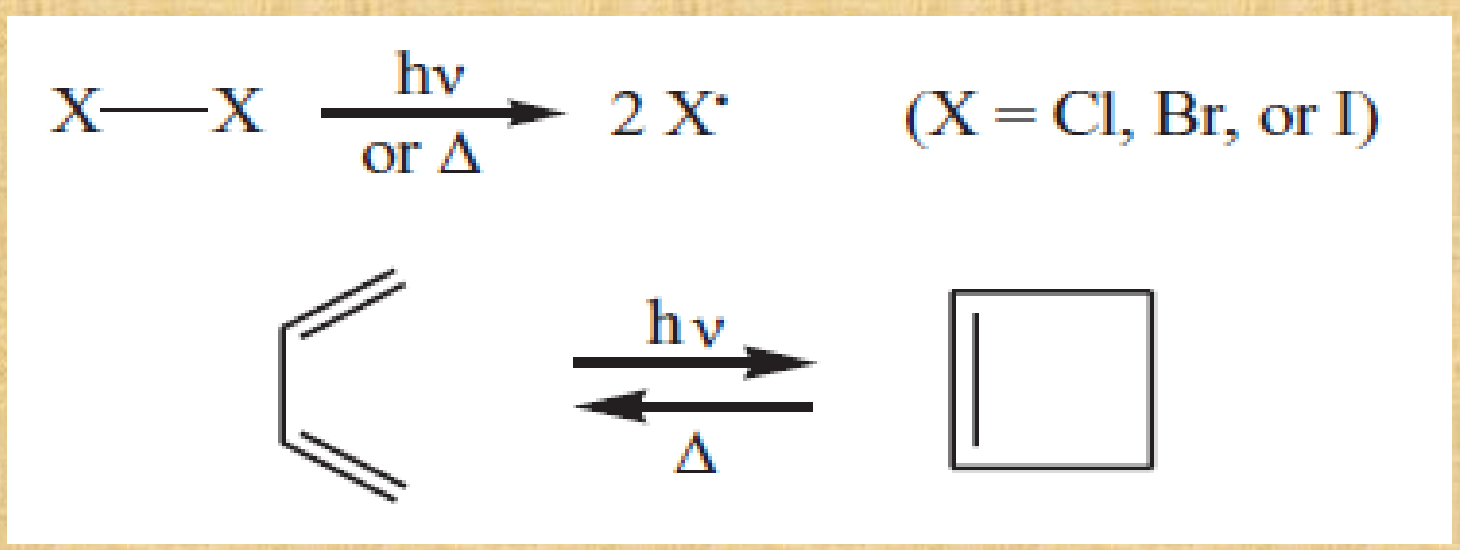
Unimolecular Reactions

The microscopic steps of many concerted chemical reactions only involve a single reactant molecule. Such a concerted reaction whose mechanism involves only *one reactant molecule* is defined as a **unimolecular reaction**. It is generalized as follows



A, A*, and P represent a reactant molecule, an activated reactant molecule (transition state), and a product molecule, respectively. *In a unimolecular reaction, a reactant molecule can possibly gain energy and then is activated by several means, including collision of the reactant molecule with a solvent molecule or with the wall of the reactor, thermally induced vibration of the reactant molecule, and photochemical excitation of the reactant molecule*. After the molecule is activated, some simultaneous bond-breaking and bond-formation processes will take place in A* intramolecularly.

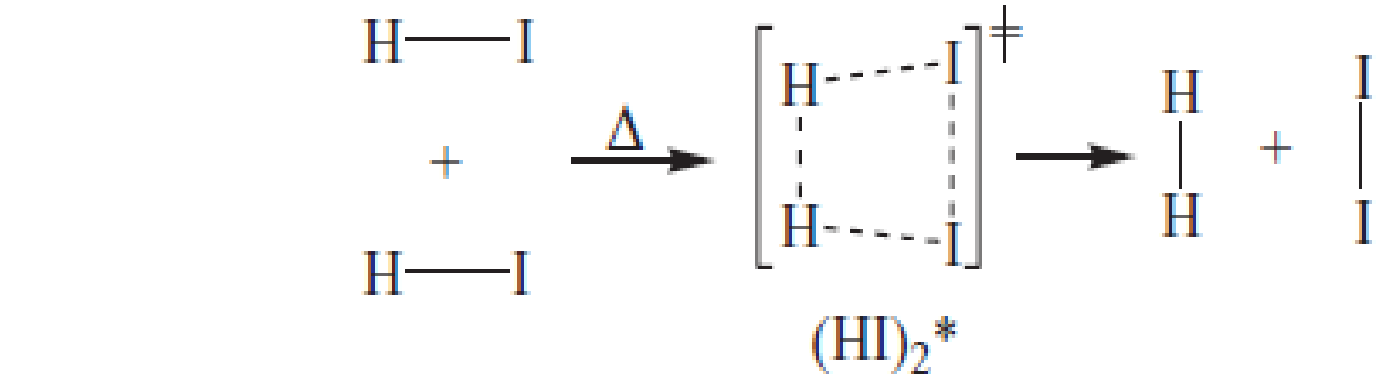
As a result, the reactant molecule A will be transformed into one or more product molecules. Common examples of unimolecular reactions are *thermal or photochemical dissociation of a halogen molecule and intramolecular ring-opening and ring-closure reactions.*



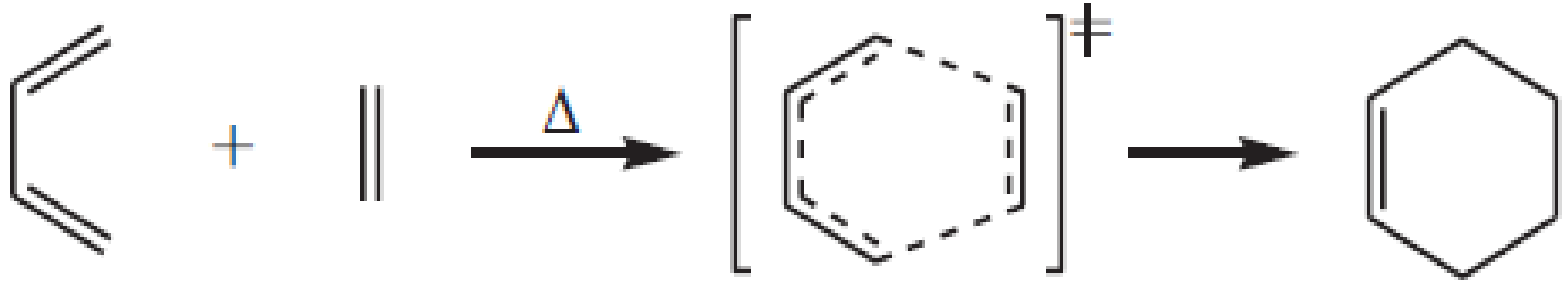
Bimolecular Reactions

For most of the concerted chemical reactions, their microscopic steps (mechanisms) involve effective collisions between two reactant molecules. Such a concerted reaction that is effected by collision of two reactant molecules to directly lead to the formation of products is defined as a bimolecular reaction. *A bimolecular reaction can be effected by collision of two molecules of a same compound or two molecules of different compounds*

As a result, simultaneous bond breaking and bond formation take place within the activated complex (transition state) A2 ∗ or [AB]∗. This leads to spontaneous collapse of the activated complex (transition state) giving product molecules. Common examples of bimolecular reactions are thermal decomposition of hydrogen iodide (HI) to elemental iodine (I_2) and hydrogen (H_2), the S_N2 reaction of hydroxide with bromomethane, and Diels–Alder reaction of 1,3-butadiene and ethylene:

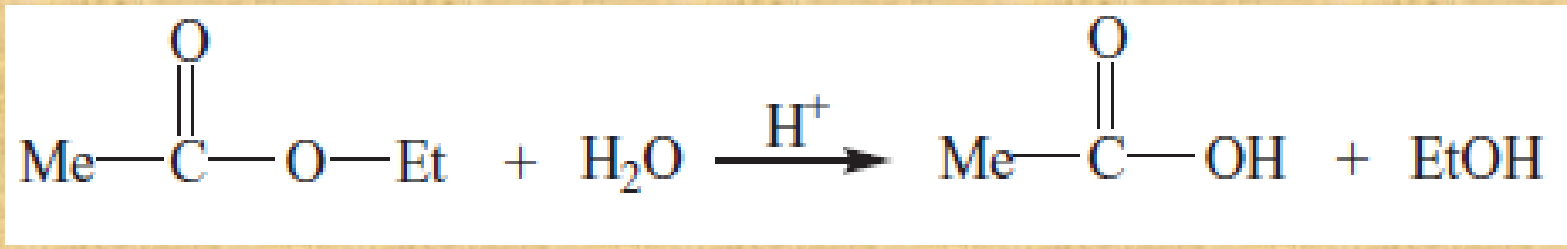

H—I
+
H—I
Δ
H
H
I
I
+
(HI)2*


HO⁻ + CH3—Br
[HO----CH3----Br]⁻
HO—CH3 + Br⁻


+
Δ

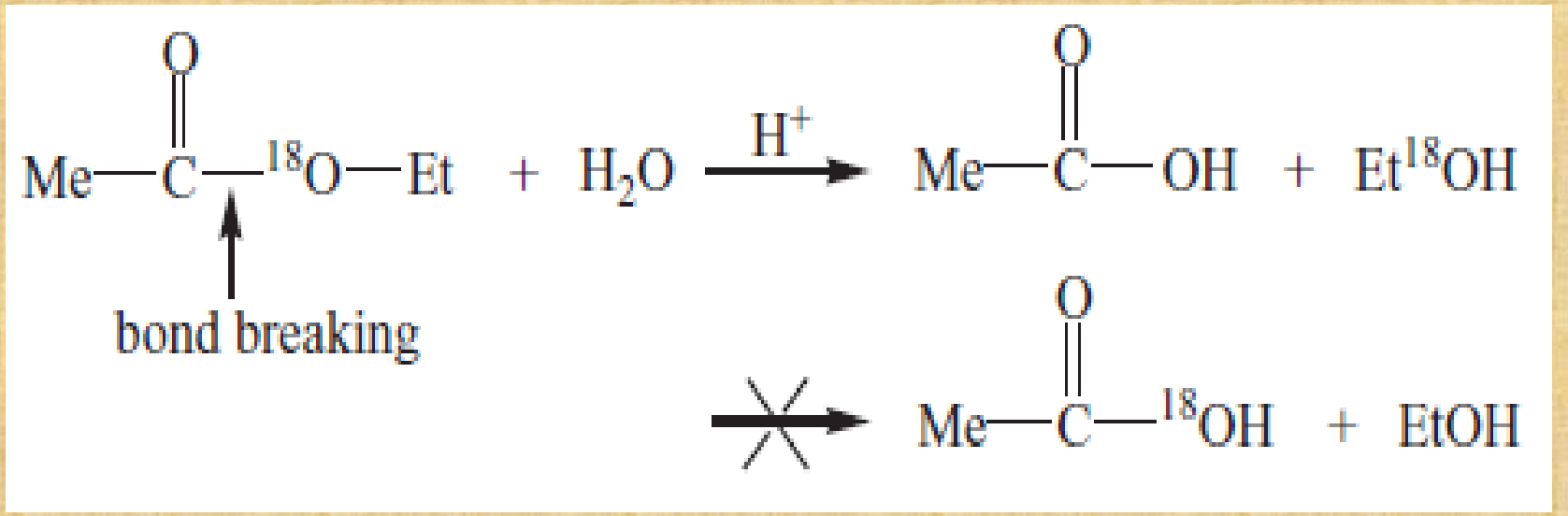
Isotope labeling

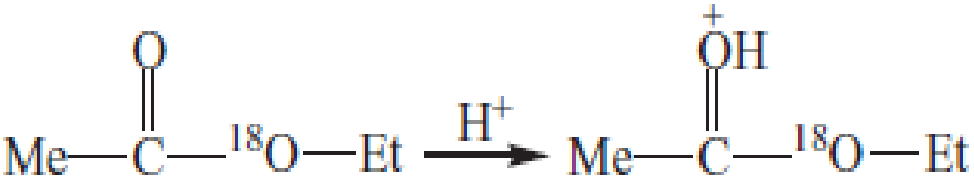
The enrichment of specific isotope of an element for an atom in a compound molecule is called **isotope labeling**. It is a very useful technique for studying kinetics and mechanisms for organic reactions. For example, let us first consider the acid-catalyzed hydrolysis of esters such as ethyl acetate.

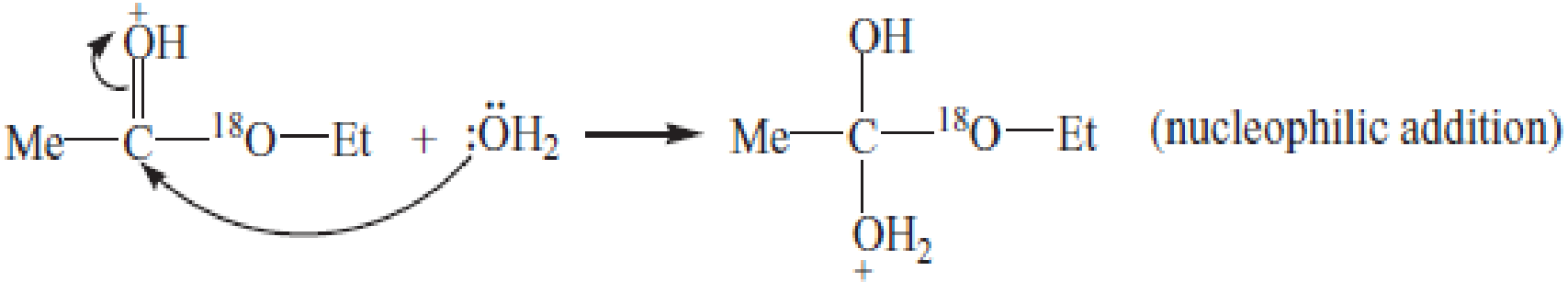


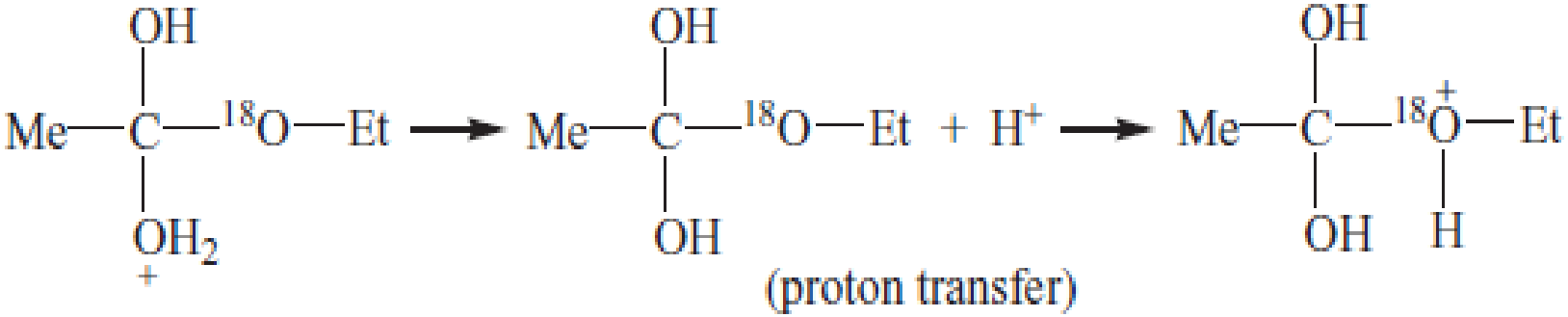
From the overall reaction, *it is not clear what bond, the acyl-oxygen bond or the alkyl-oxygen bond, is broken*. Cleavage of either bond could lead to the formation of the products

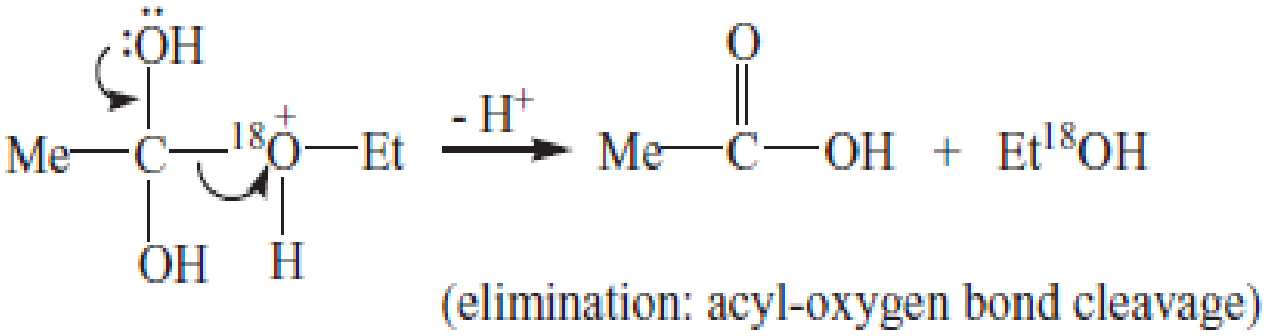
In order to establish the mechanism for the reaction, the oxygen atom of the alkoxide group (–OEt) in the ester is labeled (enriched) with the oxygen-18 isotope (^{18}O) and the hydrolysis of the ^{18}O-labeled ester is conducted in the same condition.






(nucleophilic addition)


(proton transfer)


(elimination: acyl-oxygen bond cleavage)

Nucleophilic substitution

Is a fundamental class of substitution reaction in which an "electron rich" nucleophile selectively bonds with or attacks the positive or partially positive charge of an atom attached to a group or atom called the leaving group; the positive or partially positive atom is referred to as an electrophile. In 1930s, chemists 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. *The two main mechanisms are the* ***S_N1 reaction*** *and the* ***S_N2 reaction***. ***S*** *stands for chemical substitution,* ***N*** *stands for nucleophilic, and the* ***number*** *represents the kinetic order of the reaction*

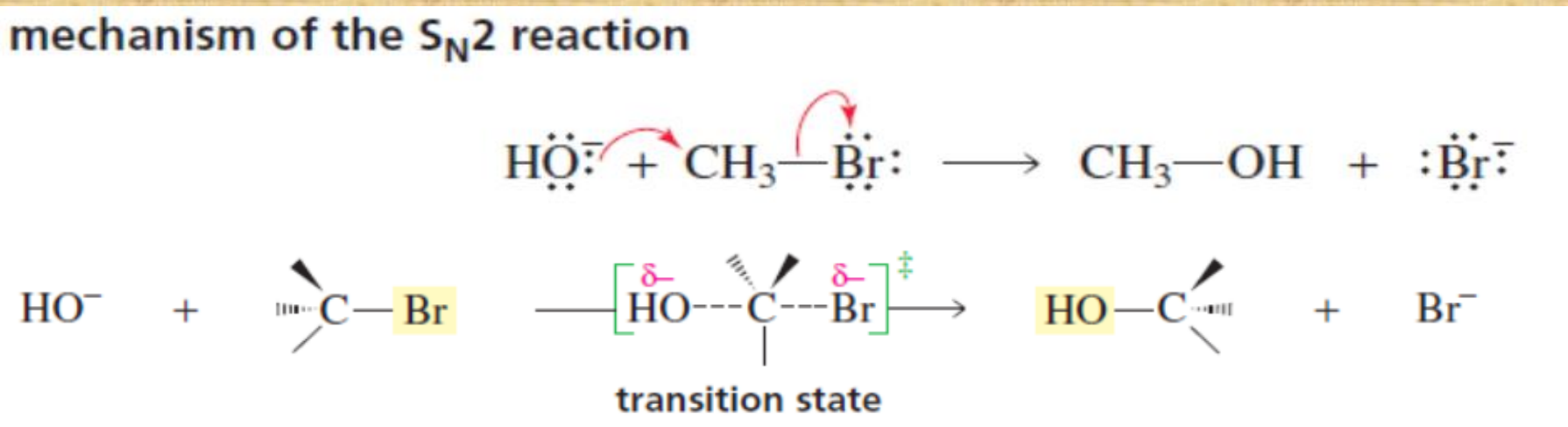
The most general form for the reaction may be given as:

Nuc**:** + R-LG → R-Nuc + LG**:** R: electrophile

The nucleophile may be electrically neutral or negatively charged, whereas the substrate is typically neutral or positively charged. There are several mechanisms or types of nucleophilic substitution reactions such as: **S_N1, S_N2, S_Ni, S_N1', S_N2' and S_Ni'.** The most common of these mechanisms are S_N1& S_N2 reactions

S_N2 reaction

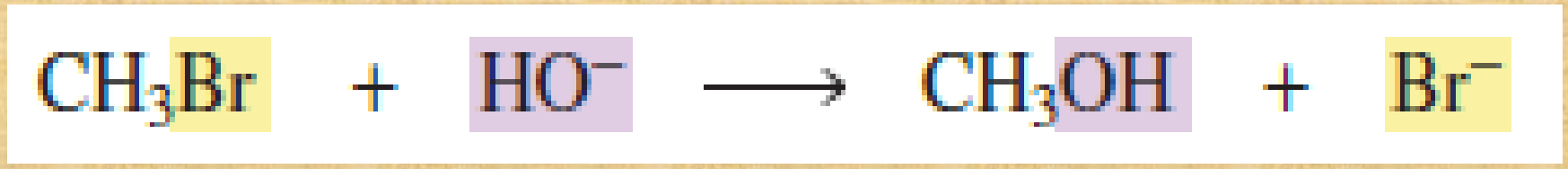
The **S_N2 reaction** (also known as **bimolecular nucleophilic substitution** or as **backside attack**) (why), where a lone pair from a nucleophile attacks an electron deficient electrophilic center and bonds to it, expelling another group called a leaving group. Thus the incoming group replaces the leaving group in one step. Since two reacting species are involved in the slow, rate-determining step of the reaction, this leads to the name bimolecular nucleophilic substitution, or S_N2. The reaction of methyl bromide with hydroxide ion is an example of **S_N2 reaction.** In 1937, Edward Hughes and Christopher Ingold proposed a mechanism for an S_N2 reaction.



Hughes and Ingold proposed that an S_N2 reaction is a concerted reaction it takes place in a single step, so no intermediates are formed. The nucleophile attack the carbon bearing the leaving group on the opposite side to the leaving group, the carbon is said to undergo **back-side attack**, and displaces the leaving group. ***Why does the nucleophile attack from the back side?*** *The simplest explanation is that the leaving group blocks the approach of the nucleophile to the front side of the molecule*.

Experimental Evidence for the Mechanism of an S_N2 Reaction

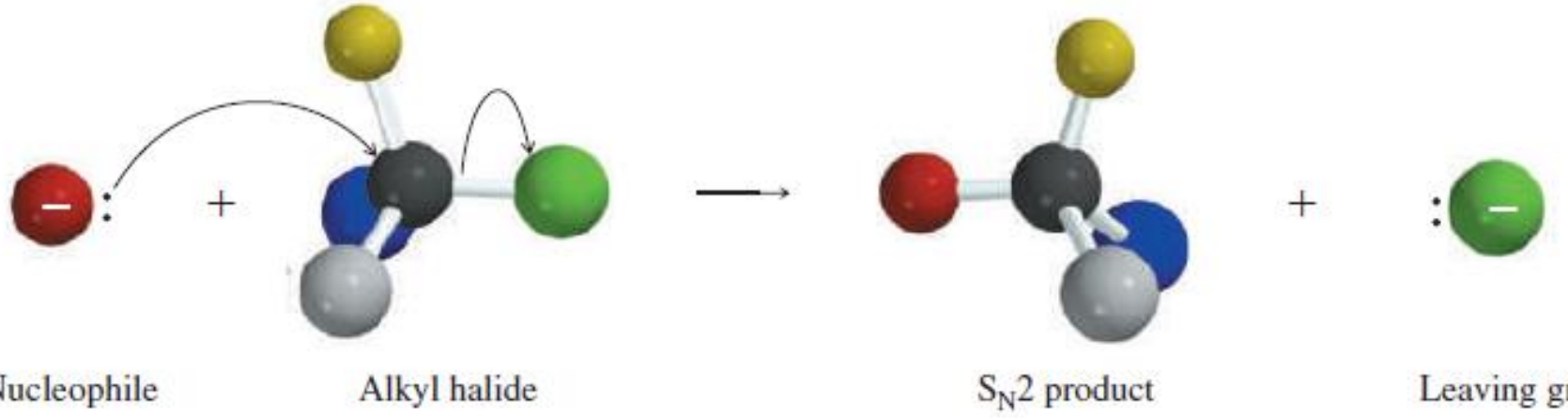
1- Kinetic: We can learn a great deal about a reaction's mechanism by studying its **kinetics**, the factors that affect the rate of the reaction. For example, the rate of the following nucleophilic substitution reaction depends on the concentrations of both reactants.

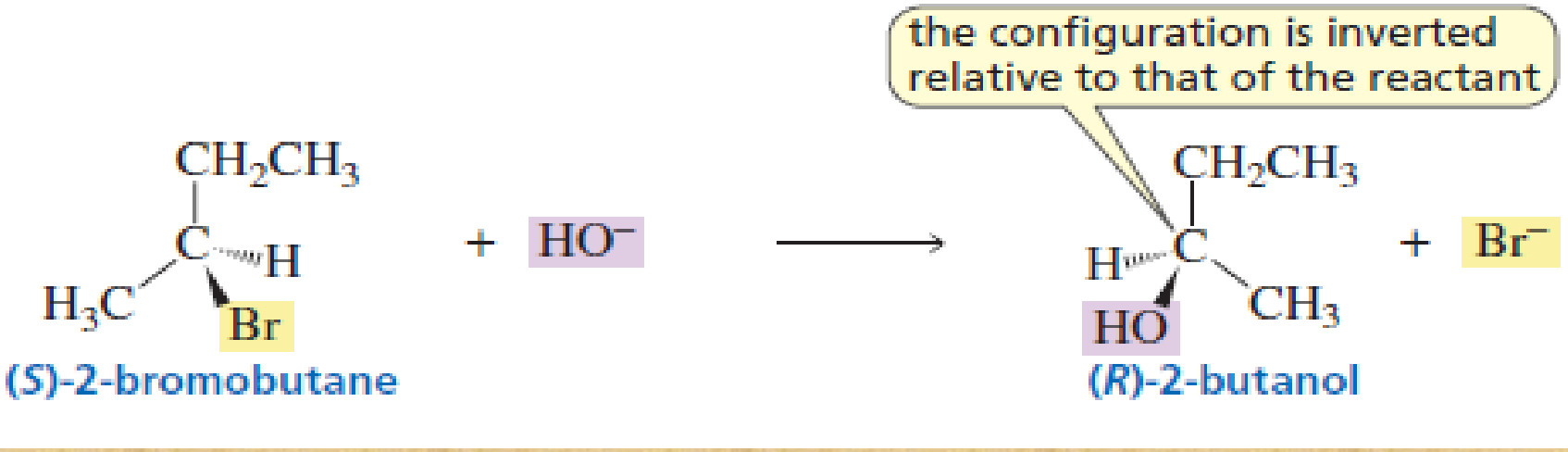


- Doubling the concentration of the alkyl halide (CH_3Br) doubles the rate of the reaction.
- Doubling the concentration of the nucleophile (HO^-) doubles the rate of the reaction.
- Doubling the concentration of both reactants quadruples the rate of the reaction.

we can write a **rate law** for the reaction: **rate** α [**alkyl halide**][**nucleophile**] The proportionality sign (α) can be replaced by an equal sign and a proportionality constant (*k*). This is a **second-order reaction** because its rate depends linearly on the concentration of each of the two reactants.

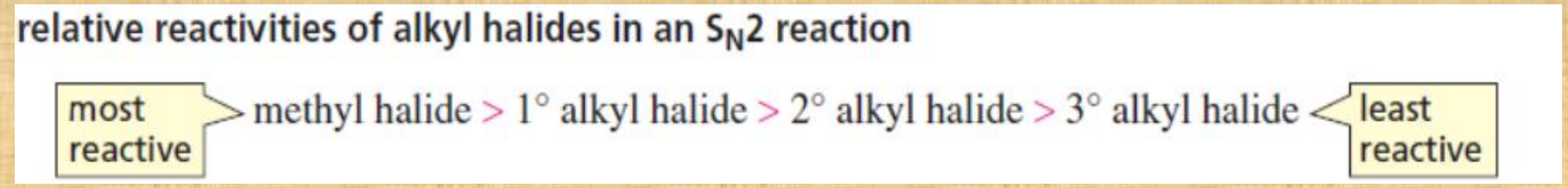
2- Stereochemistry: The reaction leads to the formation of only one stereoisomer with **inversion of configuration,** this stereochemical outcome is often called a **Walden inversion**, named after Paul Walden, the German chemist who first observed it. The requirement for inversion of configuration means that the nucleophile can only attack from the back side (the side opposite the leaving group) and never from the front side.



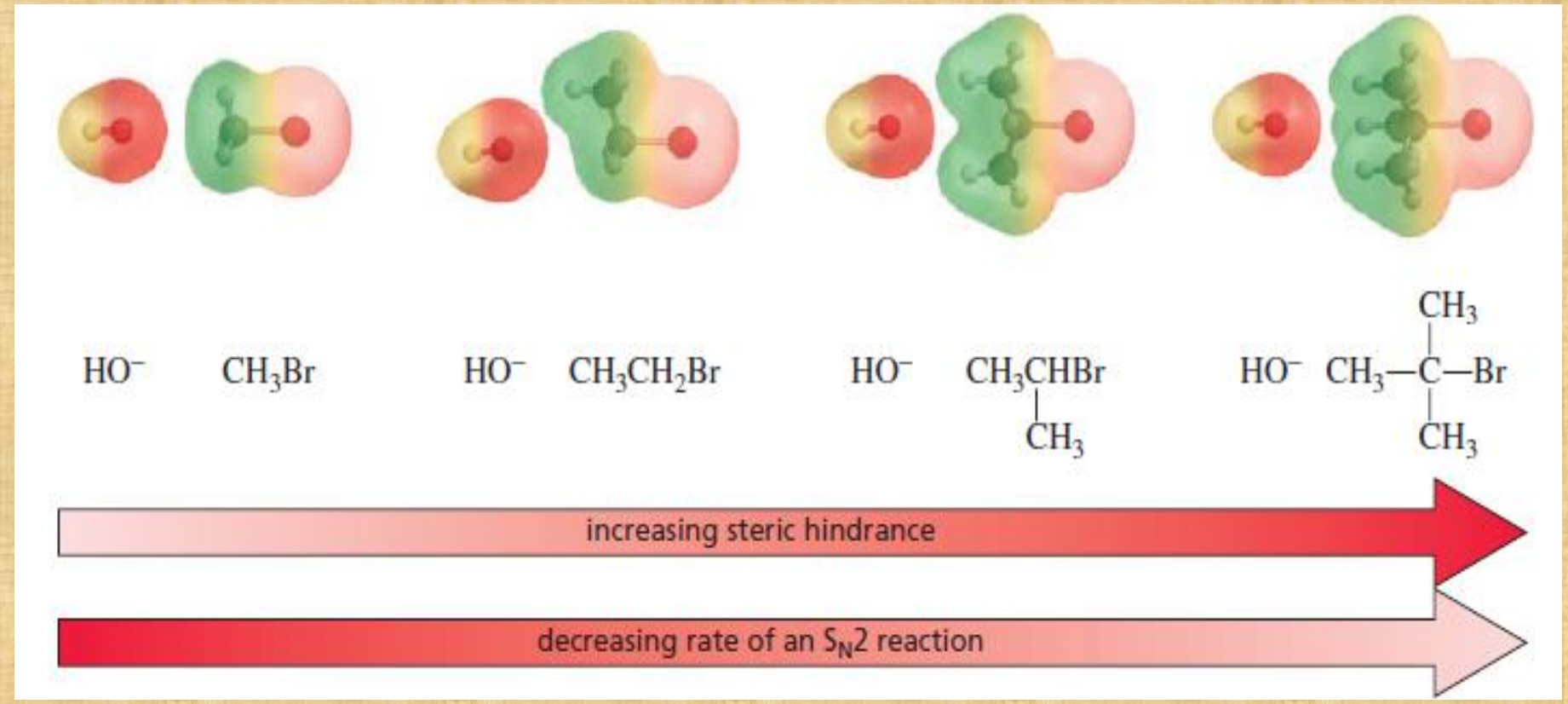


This reaction is said to be stereospecific, because the configuration of the product is *dependent on the configuration of the starting material*.

3- Steric factor: The rate of the reaction with a given nucleophile becomes as follows:

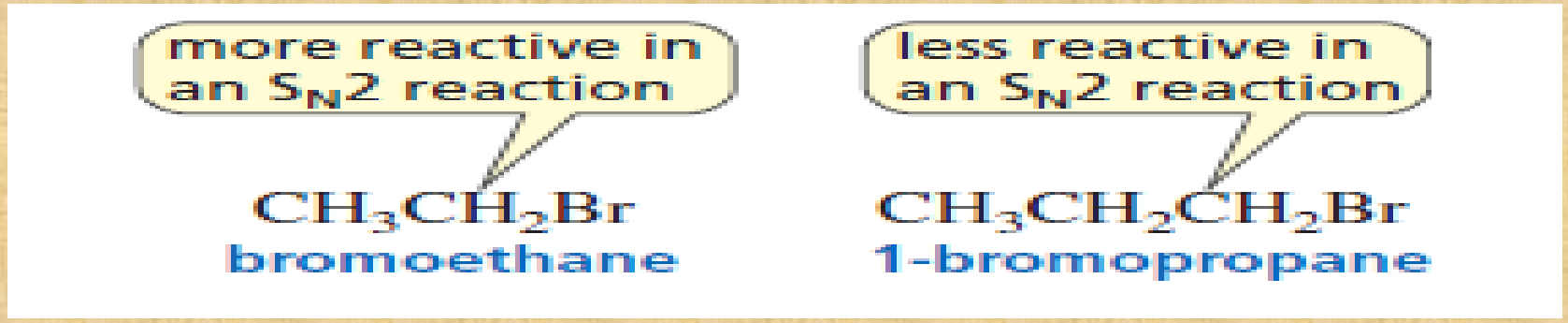


Because the nucleophile attacks the back side of the carbon that is bonded to the halogen, **bulky substituents** attached to this carbon will make it harder for the nucleophile to get to that side and will therefore decrease the rate of the reaction. This explains why tertiary and secondary alkyl halides slow the rate of the substitution reaction. **Steric effects** are caused by groups occupying a certain volume of space. A steric effect that decreases reactivity is called **steric hindrance**.

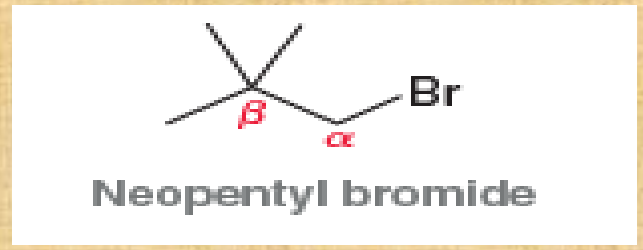


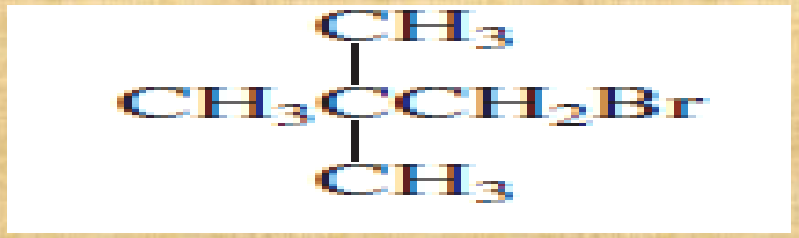
In fact, the three alkyl groups of a tertiary alkyl halide make it impossible for the nucleophile to come within bonding distance of the tertiary carbon, so tertiary alkyl halides are unable to undergo S_N2 reactions.

The rate of an S_N2 reaction depends not only on the *number* of alkyl groups attached to the carbon that is undergoing nucleophilic attack but also on their size. For example, bromoethane and 1-bromopropane are both primary alkyl halides, but bromoethane is more than twice as reactive in an S_N2 reaction (why), because the bulkier alkyl group on the carbon undergoing nucleophilic attack in 1-bromopropane provides greater steric hindrance to back-side attack.



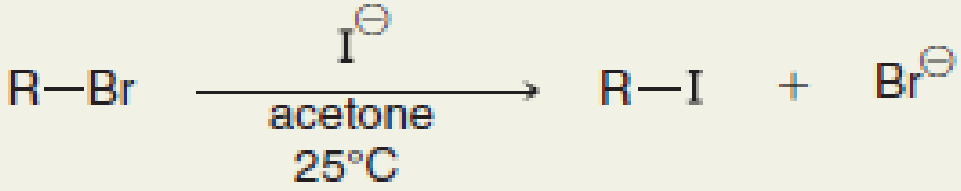
An S_N2 process will also not occur when the starting alkyl halide has three substituents connected to a β position. As an example, we revisit the structure of neopentyl bromide

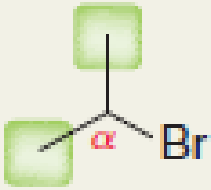
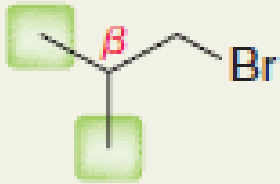
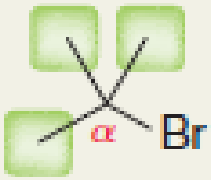
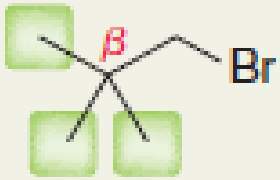




This compound is a primary alkyl halide, but it has three methyl groups attached to the β position, as a result, the rate of S_N2 is too slow to be useful. This is an interesting example, because the substrate is a primary alkyl halide that essentially does not undergo an S_N2 reaction. *This example illustrates why it is best to understand concepts in organic chemistry rather than memorize rules without knowing what they mean.*

TABLE 7.2 EFFECT OF SUBSTITUENTS ON THE RATES OF S_N2 REACTIONS

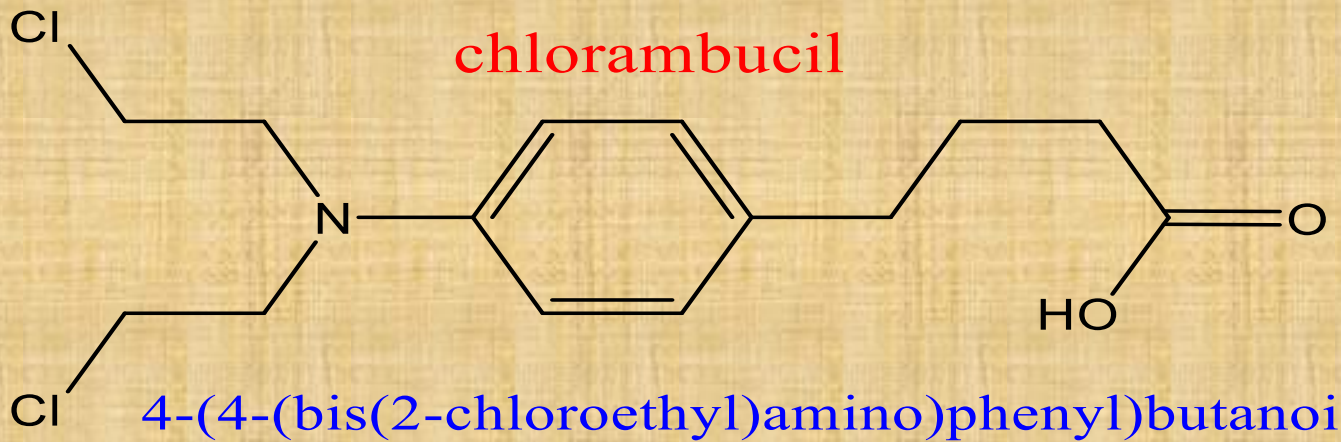


Effect of α-Substituents		Effect of β-Substituents	
Structure	Relative rate*	Structure	Relative rate*
H_3C^{α}—Br	145		1
	1		0.8
	0.008		0.04
	Negligible		0.00001

*All rates are relative to the rate of reaction between ethyl bromide and iodide in acetone at 25°C.

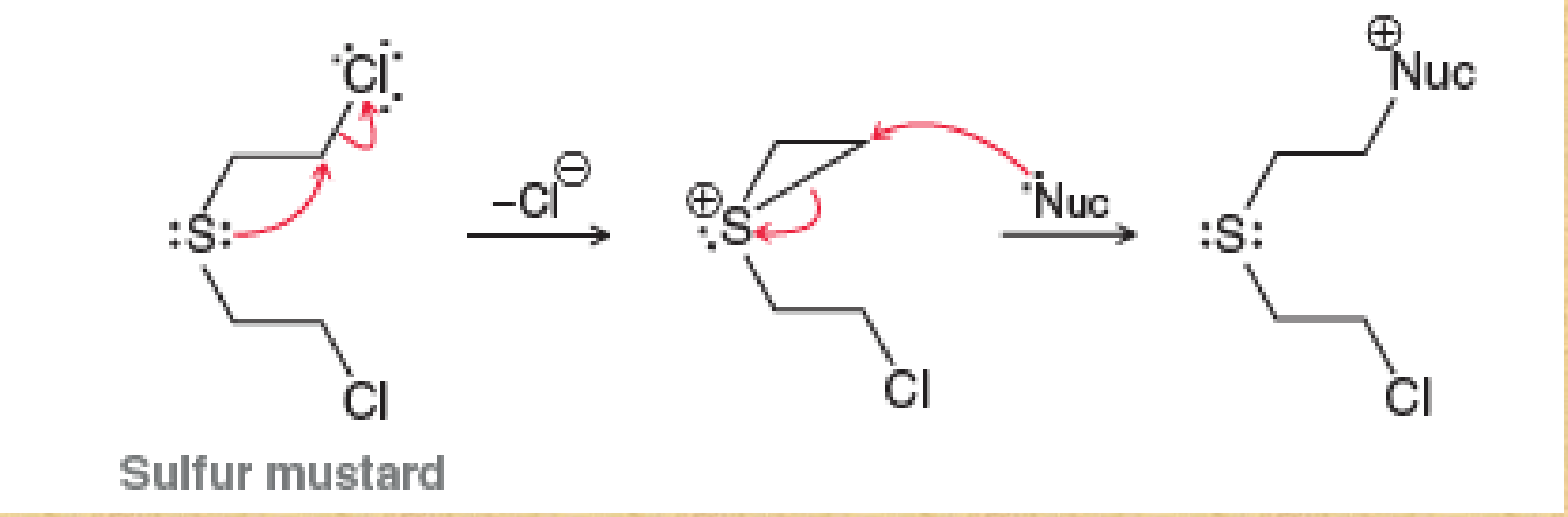
Medically Speaking Pharmacology and Drug Design

Pharmacology is the study of how drugs interact with biological systems, including the mechanisms that explain drug action. Pharmacology is a very important field of study because it serves as the basis for the design of new drugs. In this section, we will explore one specific example, the design and development of chlorambucil, an antitumor agent:

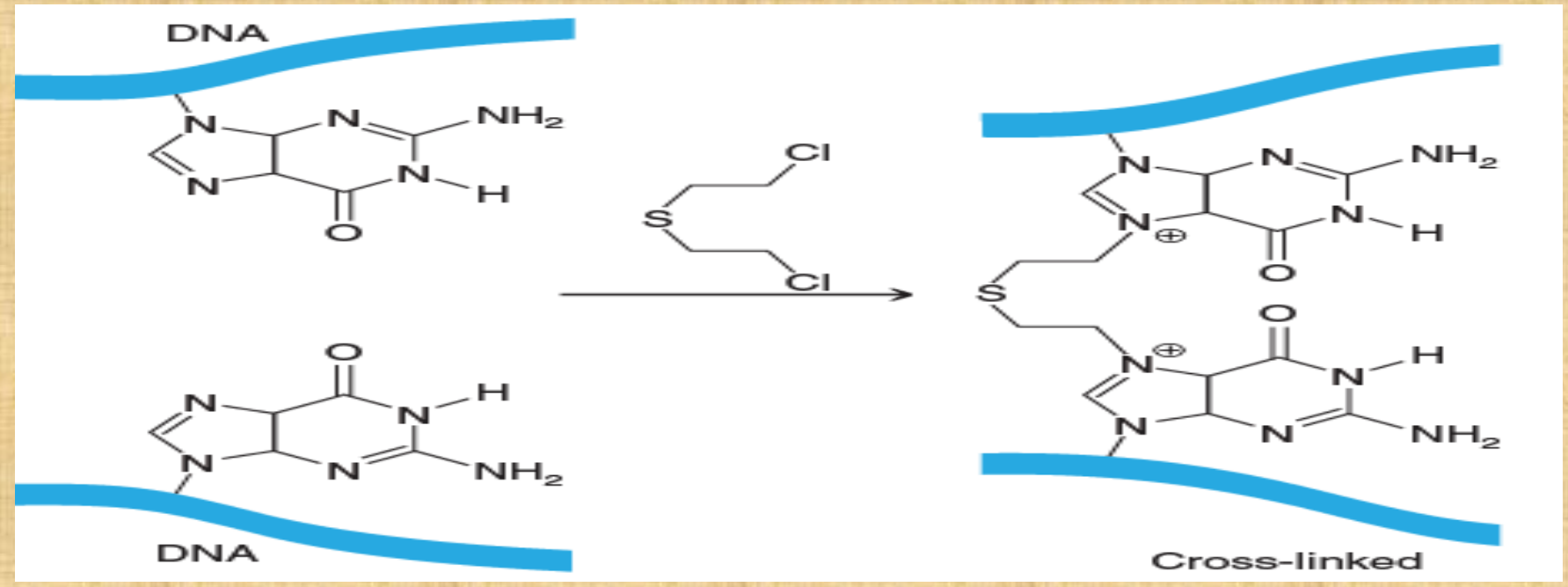


4-(4-(bis(2-chloroethyl)amino)phenyl)butanoic acid

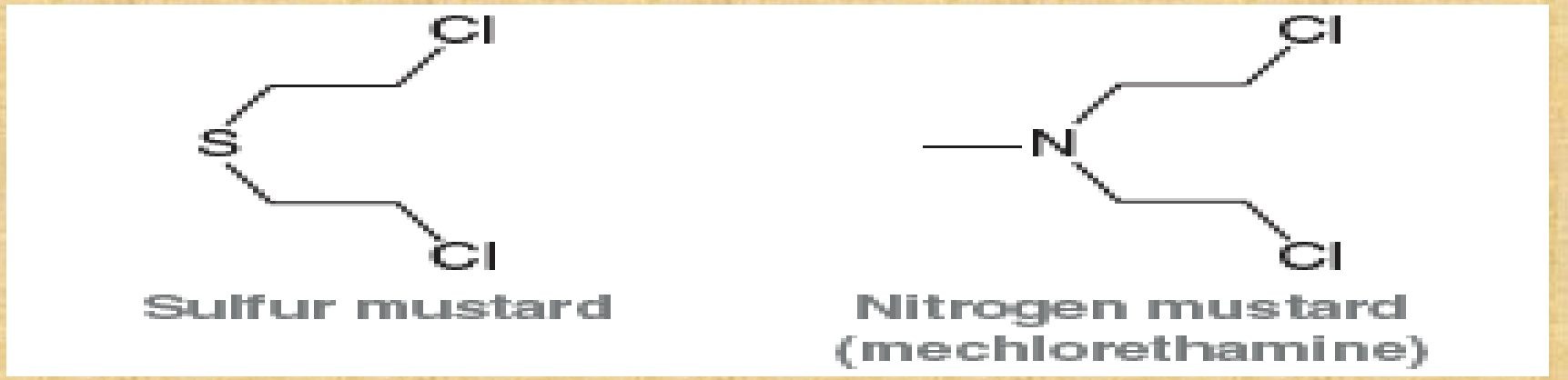
The story of chlorambucil begins with a toxic compound called sulfur mustard. This compound was first used as a chemical weapon in World War I. It was sprayed as an aerosol mixture with other chemicals and exhibited a characteristic odor similar to that of mustard plants, thus the name mustard gas. Sulfur mustard is a *powerful alkylating agent. The mechanism of alkylation involves a sequence of two substitution reactions:*



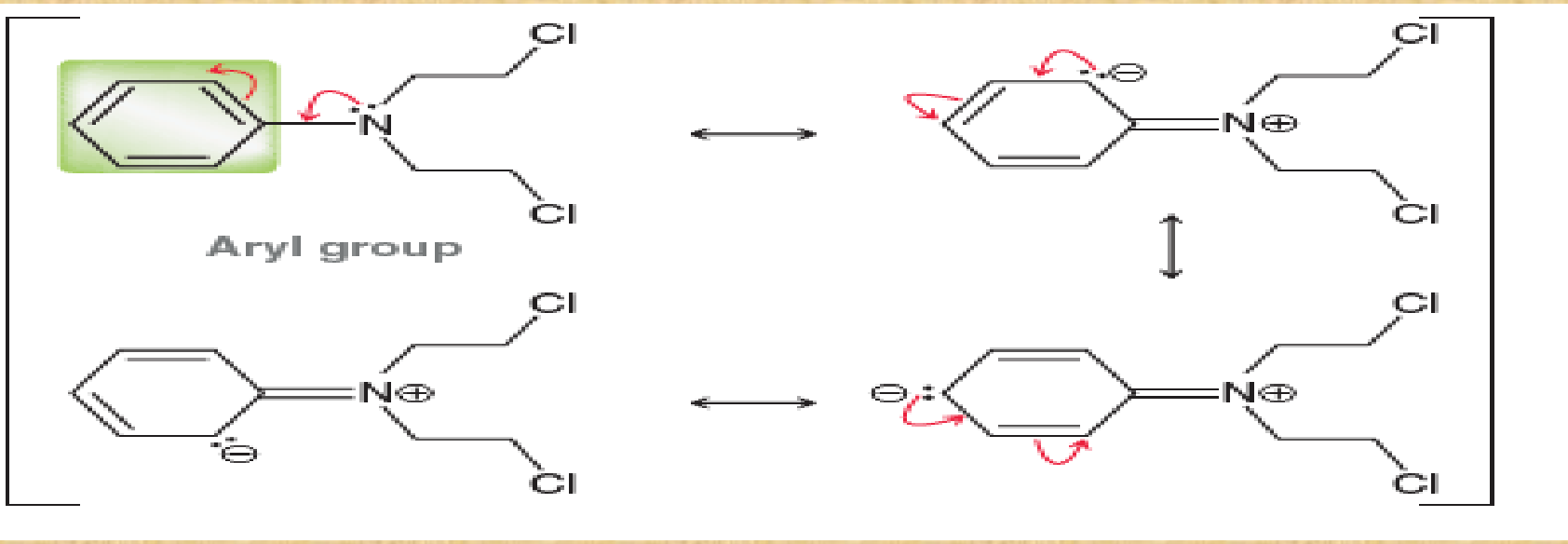
Sulfur mustard



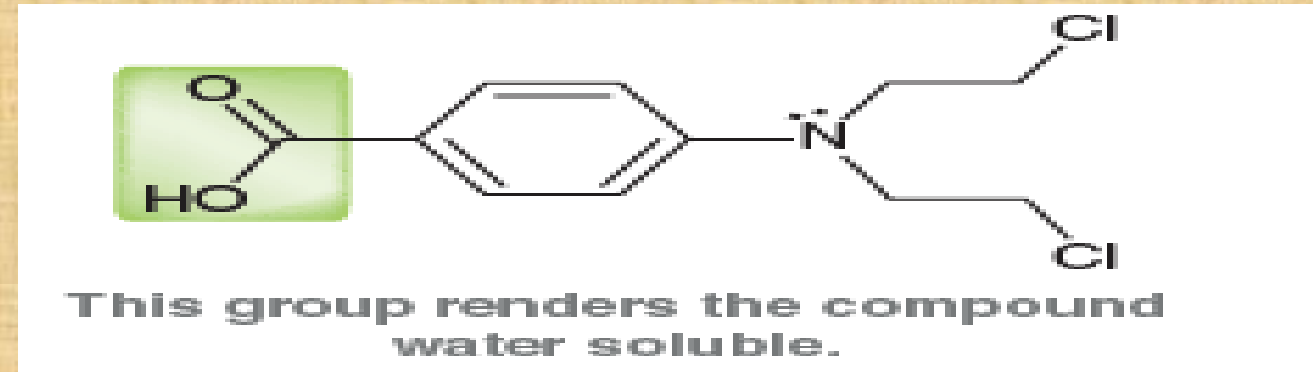
In 1931, sulfur mustard was injected directly into tumors with the intention of stopping tumor growth by interrupting the rapid division of the cancerous cells. Ultimately, sulfur mustard was found to be too toxic for clinical use, and the search began for a similar, less toxic, compound. The first such compound to be produced was a nitrogen analogue called mechlorethamine (nitrogen mustard)



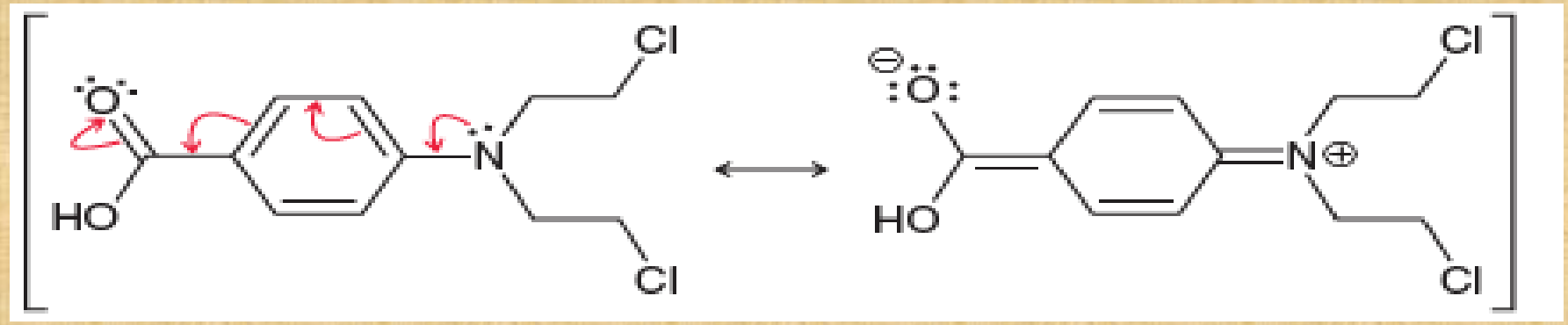
Mechlorethamine is still in use today, in combination with other agents, for the treatment of advanced Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL). The use of mechlorethamine is limited, though, by its high rate of reactivity with water. This limitation led to a search for other analogues. Specifically, it was found that replacing the methyl group with an aryl group had the effect of delocalizing the lone pair through resonance, rendering the lone pair less nucleophilic



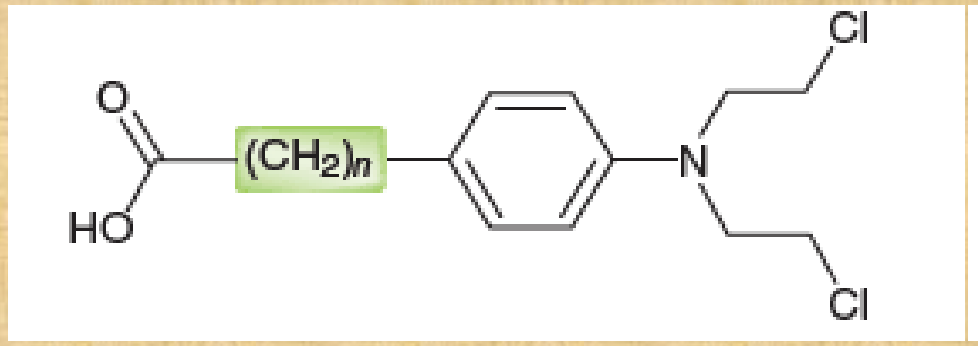
Introduction of the aryl group (in place of the methyl group) might have solved one problem, but it created another problem. Specifically, this new compound was not water soluble, which prevented intravenous administration. This problem was solved by introducing a carboxylate group, which rendered the compound water soluble:

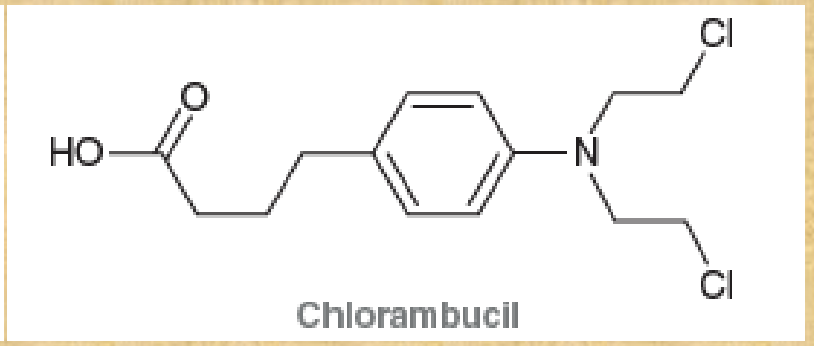


But, once again, solving one problem created another. Now, the lone pair on the nitrogen atom was too delocalized, because of the following resonance structure:



The lone pair on the nitrogen atom was not sufficiently nucleophilic to provide anchimeric assistance. Solving all these problems required a way to maintain water solubility without overly stabilizing the lone pair on the nitrogen atom. This was achieved by placing methylene groups (CH_2 groups) between the carboxylate group and the aryl group:





FACTORS THAT AFFECT S_N2 REACTIONS

We will now look at how the nature of the leaving group and the nature of the nucleophile affect an S_N2 reaction.

- The Leaving Group in an S_N2 Reaction

If an alkyl iodide, an alkyl bromide, an alkyl chloride, and an alkyl fluoride with the same alkyl group were allowed to react with the same nucleophile under the same conditions, we would find that the alkyl iodide is the most reactive and the alkyl fluoride is the least reactive.

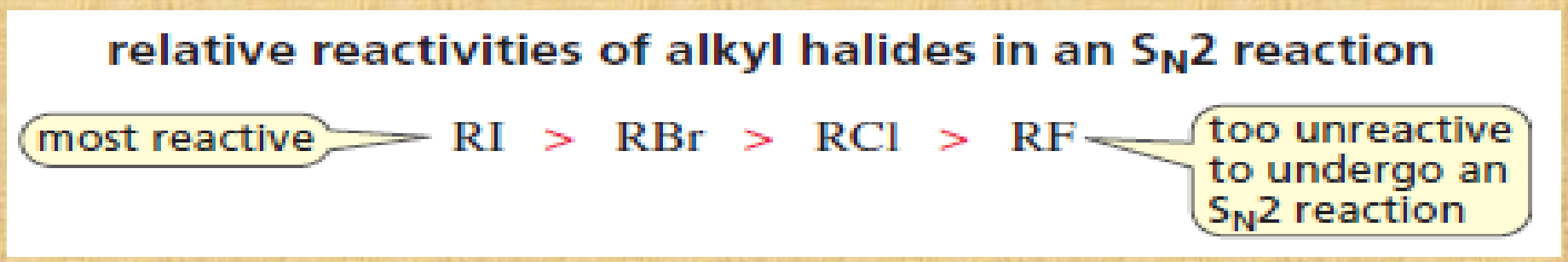
	relative rates of reaction	pK_a values of HX
$HO^- + RCH_2I \longrightarrow RCH_2OH + I^-$	30,000	–10
$HO^- + RCH_2Br \longrightarrow RCH_2OH + Br^-$	10,000	–9
$HO^- + RCH_2Cl \longrightarrow RCH_2OH + Cl^-$	200	–7
$HO^- + RCH_2F \longrightarrow RCH_2OH + F^-$	1	3.2

The only difference between these four reactions is the leaving group. From the relative reaction rates, we see that iodide ion is the best leaving group and fluoride ion is the worst. This brings us to an important rule in organic chemistry that you will encounter frequently: when comparing bases of the same type.

the weaker the basicity of a group, the better is its leaving propensity

Leaving propensity depends on basicity because weak bases are stable bases; they readily bear the electrons they formerly shared with a proton. Therefore, they do not share their electrons well. Thus, a weak base is not bonded as strongly to the carbon as a strong base would be, and a weaker bond is more easily broken.

In fact, the fluoride ion is such a strong base that alkyl fluorides essentially do not undergo S_N2 reactions



The Nucleophile in an S_N2 Reaction

When we talk about atoms or molecules that have lone-pair electrons, sometimes we call them bases and sometimes we call them nucleophiles. What is the difference between a base and a nucleophile?

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

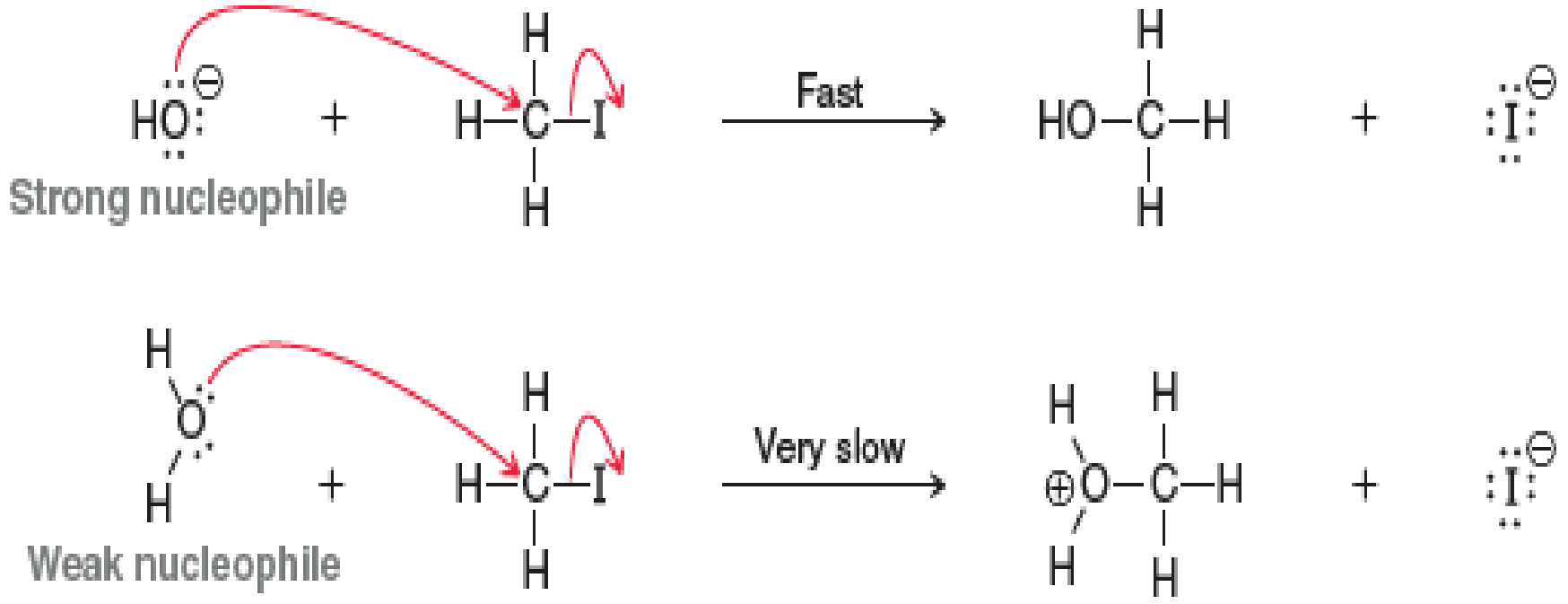
*Relative reactivity is k(nucleophile)/k(methanol) for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

- **Basicity** is a measure of how well a compound (a **base**) shares its lone pair with a proton. The stronger the base, the better it shares its electrons. Basicity is measured by an *equilibrium constant* (the acid dissociation constant, *K*a) that indicates the tendency of the conjugate acid of the base to lose a proton.
- **Nucleophilicity:** The term "nucleophilicity" refers to the rate at which a nucleophile will attack a suitable electrophile. A strong nucleophile will give a relatively fast S_N2 reaction, while a weak nucleophile will give a relatively slow S_N2 reaction. For this reason, a strong nucleophile is generally required in order for an S_N2 reaction to be efficient and practical.

Note that a species with a negative charge is a stronger base *and* a better nucleophile than a species that has the same attacking atom but is neutral. Thus, HO^- is a stronger base and a better nucleophile than H_2O. Also note that bases are described as being strong or weak, whereas nucleophiles are described as being good or poor.

Indeed, hydroxide is over a million times more reactive than water toward an S_N2 reaction with methyl iodide:

stronger base, better nucleophile		weaker base, poorer nucleophile
HO^-	>	H_2O
CH_3O^-	>	CH_3OH
$^-NH_2$	>	NH_3
$CH_3CH_2NH^-$	>	$CH_3CH_2NH_2$

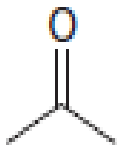
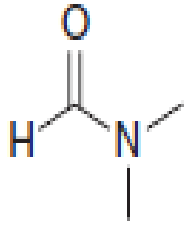
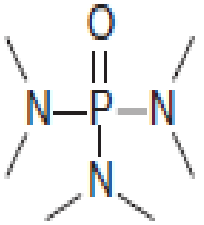
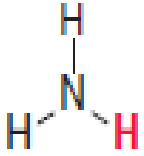
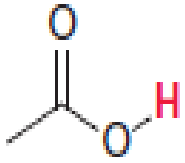


The connection between basicity and nucleophilicity holds when comparing atoms in the *same row* of the periodic table. Thus, HO^- is more basic and more nucleophilic than F^-, and NH_3 is more basic and more nucleophilic than H_2O

It does not hold when proceeding down a column in the periodic table. In that case, polarizability involving the distortion of the electron density surrounding an atom or ion comes into play. The more easily distorted the electron distribution, the more nucleophilic the atom or ion. Among the halide ions, for example, I^- is the least basic but the most nucleophilic, F^- the most basic but the least nucleophilic. In the same vein, phosphines (R_3P) are more nucleophilic than amines (R_3N), and thioethers (R_2S) more nucleophilic than their oxygen counterparts (R_2O).

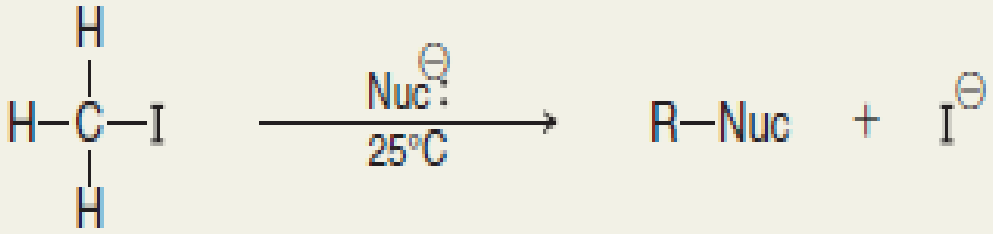
Solvent Effects in S_N2 Reactions

For S_N2 reactions, the nucleophile is generally ionic, as is the leaving group, so a polar solvent is required in order to solvate these ionic species. Furthermore, the transition state also has ionic character, so a polar solvent helps stabilize the transition state as well. For these reasons, S_N2 reactions generally cannot be performed in nonpolar solvents, such as benzene, unless special techniques are employed. Polar solvents are broadly classified into two categories: protic and aprotic. **Protic solvents** contain a hydrogen atom connected directly to an electronegative atom, while **polar aprotic solvents** lack such a hydrogen atom. Several examples are shown for each category:

Protic solvents	Polar aprotic solvents
 Water	 Acetone
 Methanol	 Dimethylformamide (DMF)
 Ethanol	 Hexamethyl-phosphoramide (HMPA)
 Ammonia	 Dimethylsulfoxide (DMSO)
 Acetic acid	 Acetonitrile

Indeed, the effect of polar aprotic solvents on the rate of S_N2 reactions can be very significant, as seen in below.

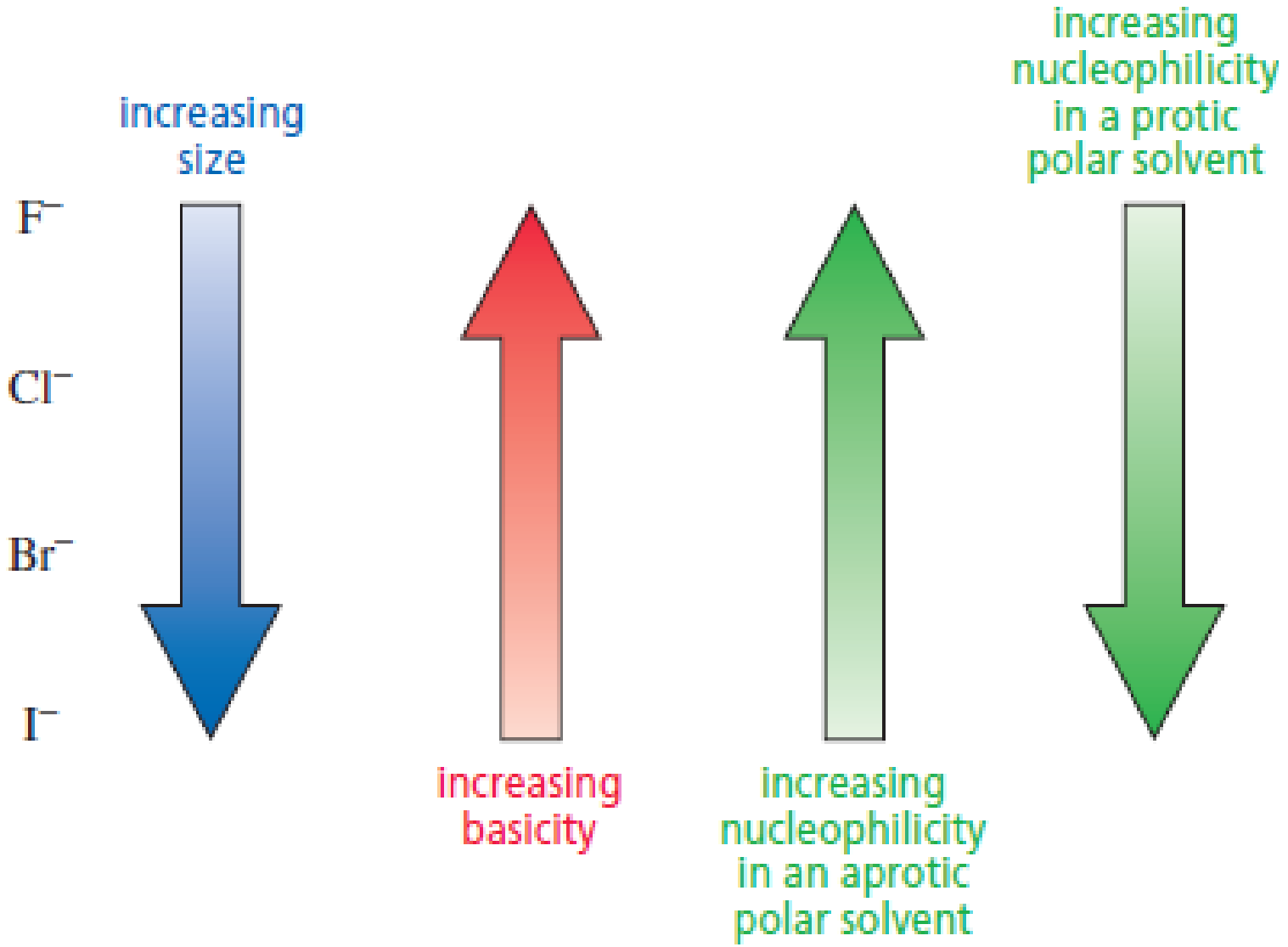
TABLE 7.3 EFFECT OF SOLVENTS ON THE RATES OF S_N2 REACTIONS



Nucleophile	Relative rate in MeOH* (protic solvent)	Relative rate in DMF* (polar aprotic solvent)	Increase in rate (due to polar aprotic solvent)
I^-	43**	6,500**	× 150
Br^-	1	21,000	× 21,000
Cl^-	0.04	41,000	× 1,030,000
F^-	0.0006	49,000	× 82,000,000

* All rates are relative to the rate of reaction between methyl iodide and bromide at 25°C.

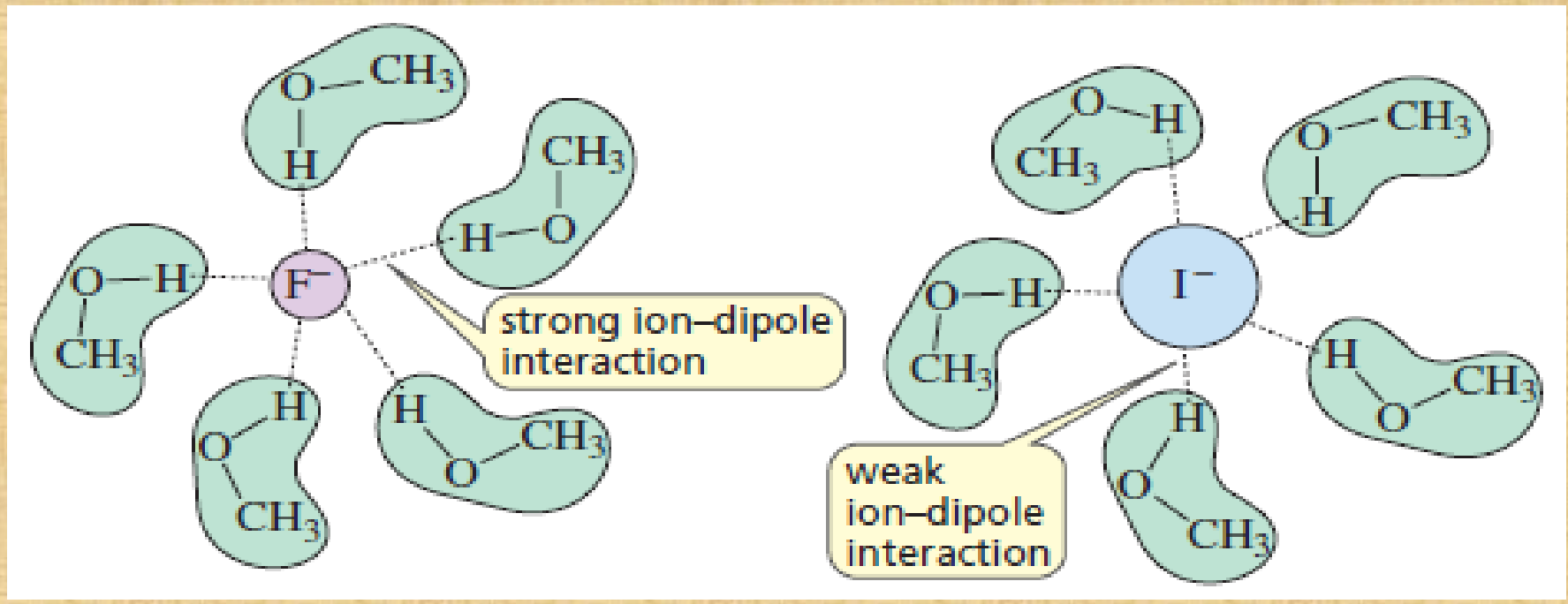
** Rate of reaction is measured by using an isotope of iodine and then tracking its location.


increasing
size
F⁻
Cl⁻
Br⁻
I⁻
increasing
basicity
increasing
nucleophilicity
in an aprotic
polar solvent
increasing
nucleophilicity
in a protic
polar solvent

Why Is the Nucleophilicity Affected by the Solvent?

Why, in a protic solvent, is the smallest atom the poorest nucleophile even though it is the strongest base? *How does a protic solvent make strong bases less nucleophilic?*

Protic solvents are hydrogen bond donors. Therefore, when a negatively charged species is placed in a protic solvent, the solvent molecules arrange themselves with their partially positively charged hydrogens pointing toward the negatively charged species. *The interaction between the ion and the dipole of the protic solvent is called an* ***ion–dipole interaction*****.**



Because the solvent shields the nucleophile, at least one of the ion–dipole interactions must be broken before the nucleophile can participate in an S_N2 reaction. Weak bases interact weakly with protic solvents, whereas strong bases interact strongly because they are better at sharing their electrons