

# Δομή και Δραστικότητα στην Οργανική Χημεία

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## Επισκόπηση Κεφαλαίων

- Οξέα και Βάσεις (Brønsted /Lewis)
- $pK_a$ ,  $pK_b$ ,  $pK_{BH^+}$
- Παράγοντες που επηρεάζουν την οξύτητα και τη βασικότητα
- Πυρηνοφιλία, ομοιότητες και διαφορές από τη βασικότητα
- Η αντίδραση  $S_{N2}$
- Παράγοντες που επηρεάζουν την αντίδραση  $S_{N2}$
- Στεreoχημεία στις αντιδράσεις  $S_{N2}$
- Η αντίδραση  $E_2$
- Παράγοντες που επηρεάζουν την αντίδραση  $E_2$
- Στεreoχημεία στις αντιδράσεις  $E_2$

## 6.1 Definitions of Acids and Bases

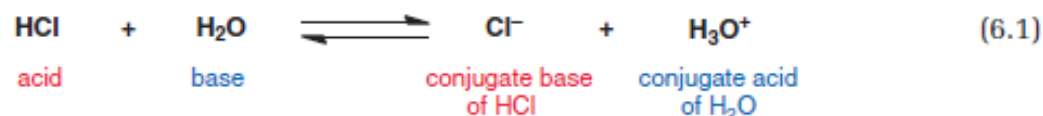
### 6.1.1 Brønsted acids and bases

As defined by Brønsted in Denmark in the early part of the twentieth<sup>1</sup> century, *an acid is a compound which donates a proton ( $H^+$ ) and a base is a compound which can accept a proton*; such compounds are now often called **Brønsted acids** (or sometimes proton acids) and bases.

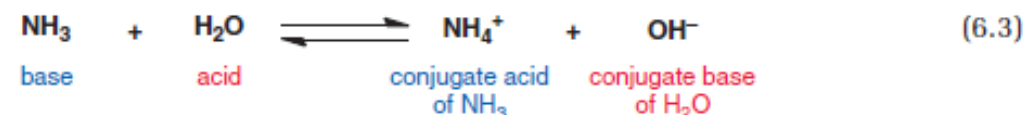
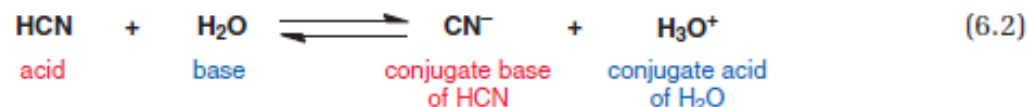
Gaseous hydrogen chloride, HCl, dissolves in water and immediately reacts by **proton transfer** in a typical Brønsted acid–base reaction, to give hydrochloric acid. In this *acid dissociation reaction*, HCl donates a proton to a water molecule so HCl is an acid and  $H_2O$  is a base (eqn 6.1). In principle, this reaction is reversible and, in the reverse direction, the chloride accepts a proton from the oxonium ion  $H_3O^+$  (also called hydronium ion);  $Cl^-$  is now a base (the **conjugate base** of HCl) and  $H_3O^+$  is an acid (the **conjugate acid** of  $H_2O$ ). In practice, however, no covalent HCl molecules can be detected at equilibrium in dilute aqueous solution (it is an example of a **strong acid**, see later).



Johannes N. Brønsted

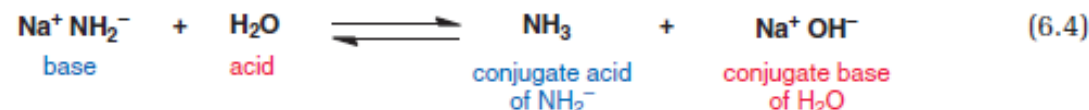


Gaseous hydrogen cyanide, HCN, also dissolves in water and reacts as an acid, but the reaction does not proceed to completion; HCN (the solute) is a **weak acid** (see later) and covalent HCN molecules coexist in aqueous solution with the dissociated acid (eqn 6.2).

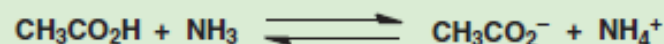


The reaction of eqn 6.3, however, like that of eqn 6.2, does not proceed to completion; in fact, in dilute aqueous solution, most of the ammonia remains unprotonated because it is only a **weak base**.

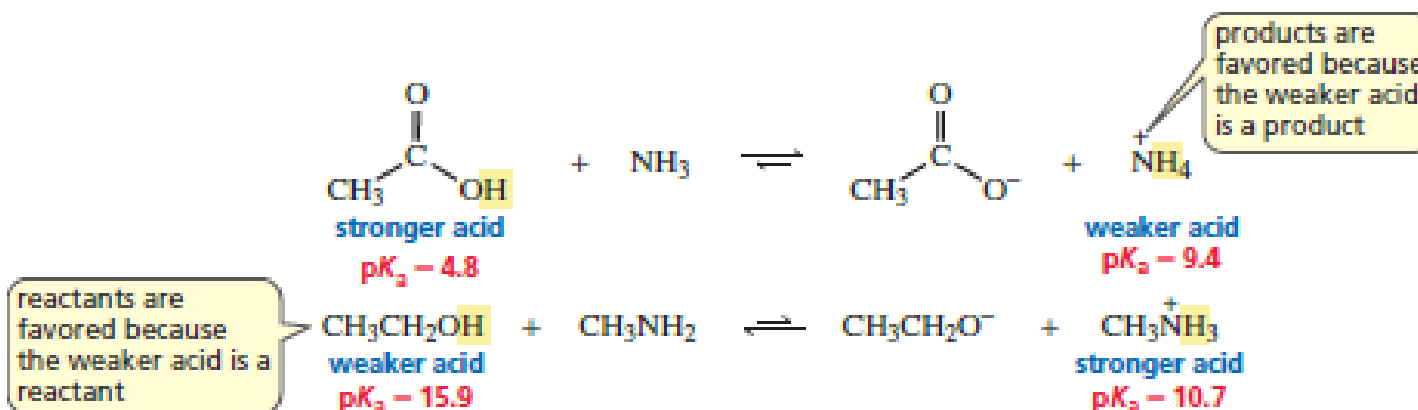
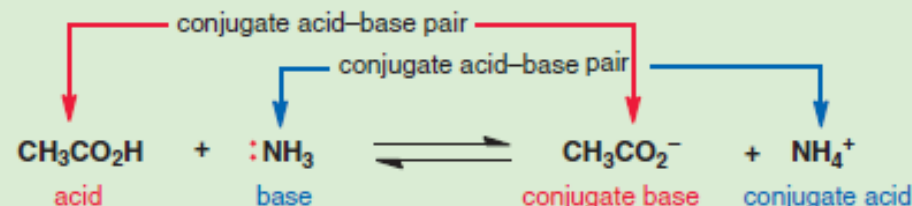
In contrast, there is an immediate and virtually complete proton transfer reaction when sodium amide is added to water (even though it is still written as an equilibrium in eqn 6.4):  $NH_2^-$  is a **strong base** in water.



Correlate acid with its conjugate base and base with its conjugate acid in the following acid–base reaction.



**Solution**



The strength of an acid is determined by the stability of the conjugate base that forms when the acid loses its proton: the more stable the conjugate base, the stronger the acid. (The reason for this is explained in Section 5.7.)

A stable base readily bears the electrons it formerly shared with a proton. In other words, stable bases are weak bases—they do not share their electrons well. Thus, we can say:

*The weaker the base, the stronger its conjugate acid.*

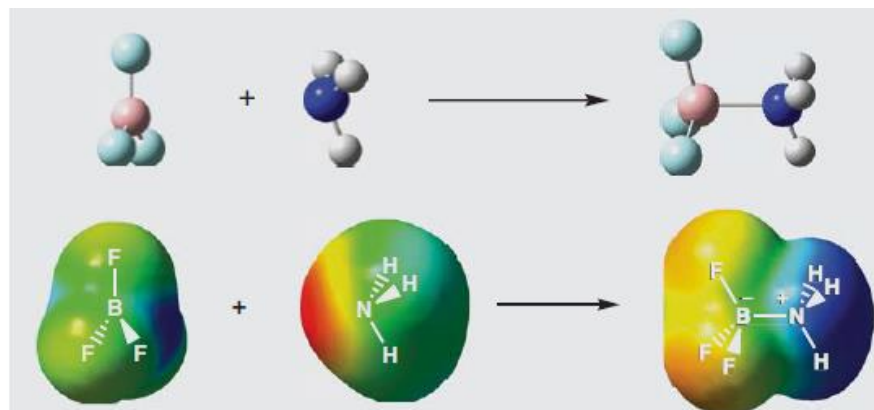
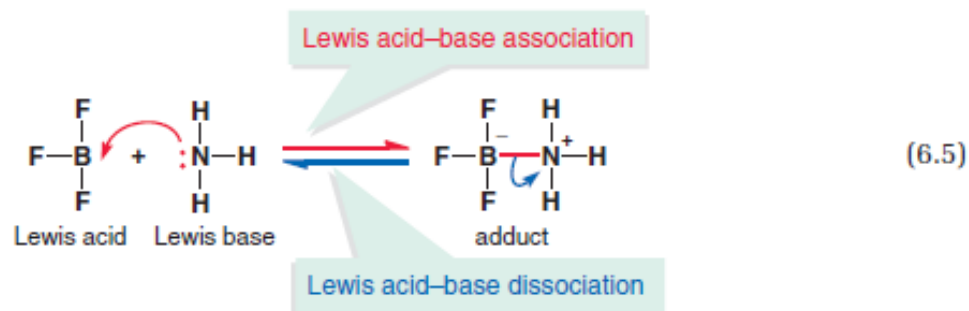
or

*The more stable the base, the stronger its conjugate acid.*

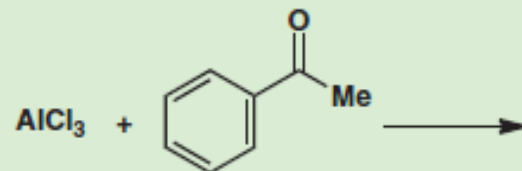
Now let's look at two factors that affect the stability of a base—its electronegativity and its size.

## 6.1.2 Lewis acids and bases

A more general definition of acids and bases was proposed by Lewis in 1923 with the focus on the electron pair of the base rather than the proton of the acid; a *Lewis base is an electron pair donor* and a *Lewis acid is an electron pair acceptor*. The central atom in a Lewis acid is able to accept the lone pair of a base into its valence shell and thereby form a covalent bond between them. Typical Lewis acids include  $\text{AlCl}_3$ ,  $\text{FeBr}_3$ ,  $\text{ZnCl}_2$ , and  $\text{BF}_3$ . For example,  $\text{BF}_3$  with only six valence electrons on the boron reacts with ammonia, which has a lone pair on the nitrogen, to form an adduct, as shown in eqn 6.5. In this way, the valence needs of both B and N are satisfied when a covalent bond is formed between them. The shared electron pair of the bond, however, comes wholly from the N, so there is a transfer of charge and the adduct is dipolar.

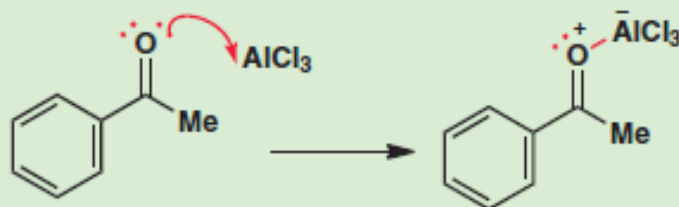


Complete the following Lewis acid–base reaction by showing the electron pairs involved.



**Solution**

The ketone is a Lewis base and  $\text{AlCl}_3$  is a Lewis acid in this reaction. Movement of the electron pair to give the dipolar adduct is represented by a curly arrow.



Classify each of the following as a Lewis acid or base.

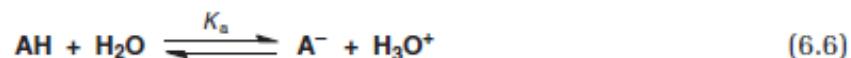
- (a)  $(\text{CH}_3)_2\text{O}$     (b)  $\text{FeCl}_3$     (c)  $(\text{CH}_3)_2\text{NH}$     (d)  $\text{B}(\text{CH}_3)_3$     (e)  $\text{CH}_3^+$

Complete the following two Lewis acid–base reactions by showing the structures of the products.

- (a)  $\text{BF}_3 + (\text{CH}_3)_2\text{O} \longrightarrow$                       (b)  $\text{CH}_3\text{CH}_2\text{Cl} + \text{AlCl}_3 \longrightarrow$

## 6.2.1 Acid dissociation constants and $pK_a$

Dissociation of a Brønsted acid in aqueous solution is an acid–base reaction with a solvent water molecule acting as the base as shown in eqn 6.6 for a generic acid, AH. A proton transfers from acid AH to  $H_2O$  to give the conjugate base  $A^-$  and  $H_3O^+$  (oxonium ion).

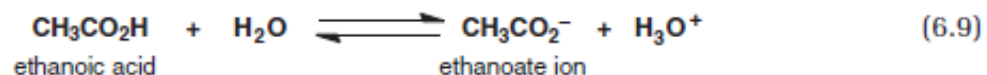


The extent of proton transfer when the system achieves equilibrium is expressed by an equilibrium constant,  $K_a$ , defined in the conventional way by eqn 6.7, where  $[AH]$ ,  $[A^-]$ , and  $[H_3O^+]$  stand for the equilibrium concentrations of AH,  $A^-$ , and  $H_3O^+$ .<sup>\*</sup> The equilibrium constant,  $K_a$ , is called the **acid dissociation constant** (or **acidity constant**), and provides a measure of the acid strength (or acidity) of a compound, i.e. its effectiveness as a proton donor.

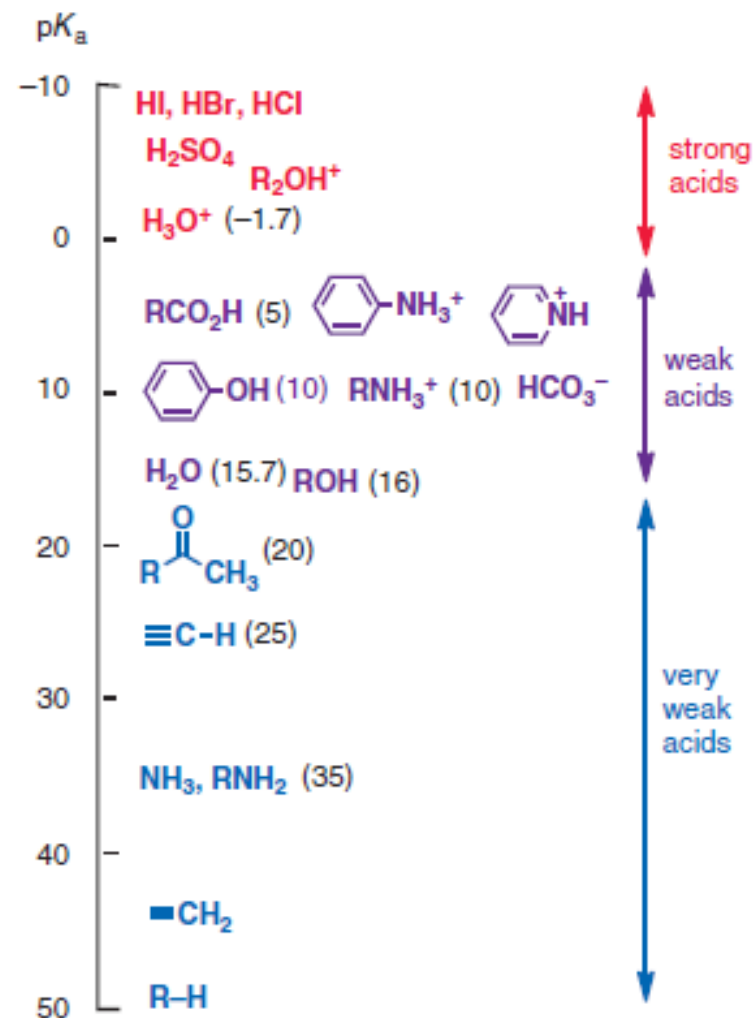
$$K_a = \frac{[A^-][H_3O^+]}{[AH]} \quad (6.7)$$

Organic acids are generally weak and  $K_a$  is correspondingly small. In order to deal conveniently with a wide range of very small numbers, a logarithmic scale is used and  $pK_a$  is defined as the *negative* logarithm of the numerical value of  $K_a$  (eqn 6.8). It follows that *the stronger an acid, the smaller its  $pK_a$*  (acids as strong as HCl or  $H_2SO_4$  have negative  $pK_a$  values). For the dissociation of ethanoic (acetic) acid, a typical weak organic acid,  $K_a = 1.74 \times 10^{-5} \text{ mol dm}^{-3}$  (eqn 6.9).

$$pK_a = -\log K_a \quad (6.8)$$



$$K_a = 1.74 \times 10^{-5} \text{ mol dm}^{-3} \quad \text{and} \quad pK_a = 4.76$$



## Ranking the Factors That Affect the Stability of Negative Charges

We have thus far examined four factors that affect the stability of negative charges. We must now consider their order of priority—in other words, which factor takes precedence when two or more factors are present?

Generally speaking, the order of priority is the order in which the factors were presented:

1. *Atom*. Which atom bears the charge? (How do the atoms compare in terms of electronegativity and size? Remember the difference between comparing atoms in the same row vs. atoms in the same column.)
2. *Resonance*. Are there any resonance effects that make one conjugate base more stable than the other?
3. *Induction*. Are there any inductive effects that stabilize one of the conjugate bases?
4. *Orbital*. In what orbital do we find the negative charge for each conjugate base?

A helpful way to remember the order of these four factors is to take the first letter of each factor, giving the following mnemonic device: *ARIO*.

As an example, let's compare the protons shown in the following two compounds:



## Electronegativity

The atoms in the second row of the periodic table are all *similar in size*, but they have very *different electronegativities*, which increase across the row from left to right. Of the atoms shown, carbon is the least electronegative and fluorine is the most electronegative.

relative electronegativities



most  
electronegative

If we look at the acids formed by attaching hydrogens to these elements, we see that the most acidic compound is the one that has its hydrogen attached to the most electronegative atom. Thus, HF is the strongest acid and methane is the weakest acid.

*When atoms are similar in size,  
the strongest acid has its hydrogen attached to the most electronegative atom.*

relative acidities



strongest  
acid

If we look at the stabilities of the conjugate bases of these acids, we find that they, too, increase from left to right, because the more electronegative the atom, the better it bears its negative charge. Thus, *the strongest acid has the most stable (weakest) conjugate base*.

relative stabilities



most  
stable

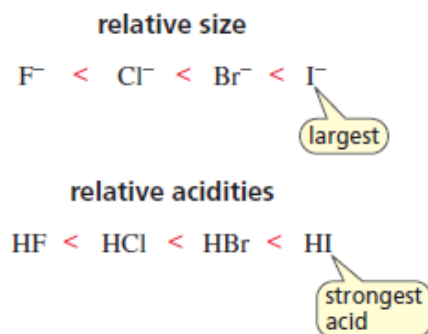
The effect that the electronegativity of the atom bonded to a hydrogen has on the compound's acidity can be appreciated when the  $\text{p}K_\text{a}$  values of alcohols and amines are compared. Because oxygen is more electronegative than nitrogen, an alcohol is more acidic than an amine.



## Size

When comparing atoms that are very different in size, the *size* of the atom is more important than its *electronegativity* in determining how well it bears its negative charge. For example, as we proceed down a column in the periodic table, the atoms get larger and the *stability* of the anions *increases* even though the electronegativity of the atoms *decreases*. Because the stability of the bases increases going down the column, the strength of their conjugate acids *increases*. Thus, HI is the strongest acid of the hydrogen halides (that is,  $\text{I}^-$  is the weakest, most stable base), even though iodine is the least electronegative of the halogens (Table 2.2).

*When atoms are very different in size,  
the strongest acid has its hydrogen attached to the largest atom.*



Why does the size of an atom have such a significant effect on stability that it more than overcomes any difference in electronegativity?

The valence electrons of  $\text{F}^-$  are in a  $2sp^3$  orbital, the valence electrons of  $\text{Cl}^-$  are in a  $3sp^3$  orbital, those of  $\text{Br}^-$  are in a  $4sp^3$  orbital, and those of  $\text{I}^-$  are in a  $5sp^3$  orbital. The volume of space occupied by a  $3sp^3$  orbital is significantly larger than the volume of space occupied by a  $2sp^3$  orbital because a  $3sp^3$  orbital extends out farther from the nucleus. Because its negative charge is spread over a larger volume of space,  $\text{Cl}^-$  is more stable than  $\text{F}^-$ .

Thus, as a halide ion increases in size (going down the column of the periodic table), its stability increases because its negative charge is spread over a larger volume of space. As a result, HI is the strongest acid of the hydrogen halides because  $\text{I}^-$  is the most stable halide ion. The potential maps shown in the margin illustrate the large difference in size of the hydrogen halides.

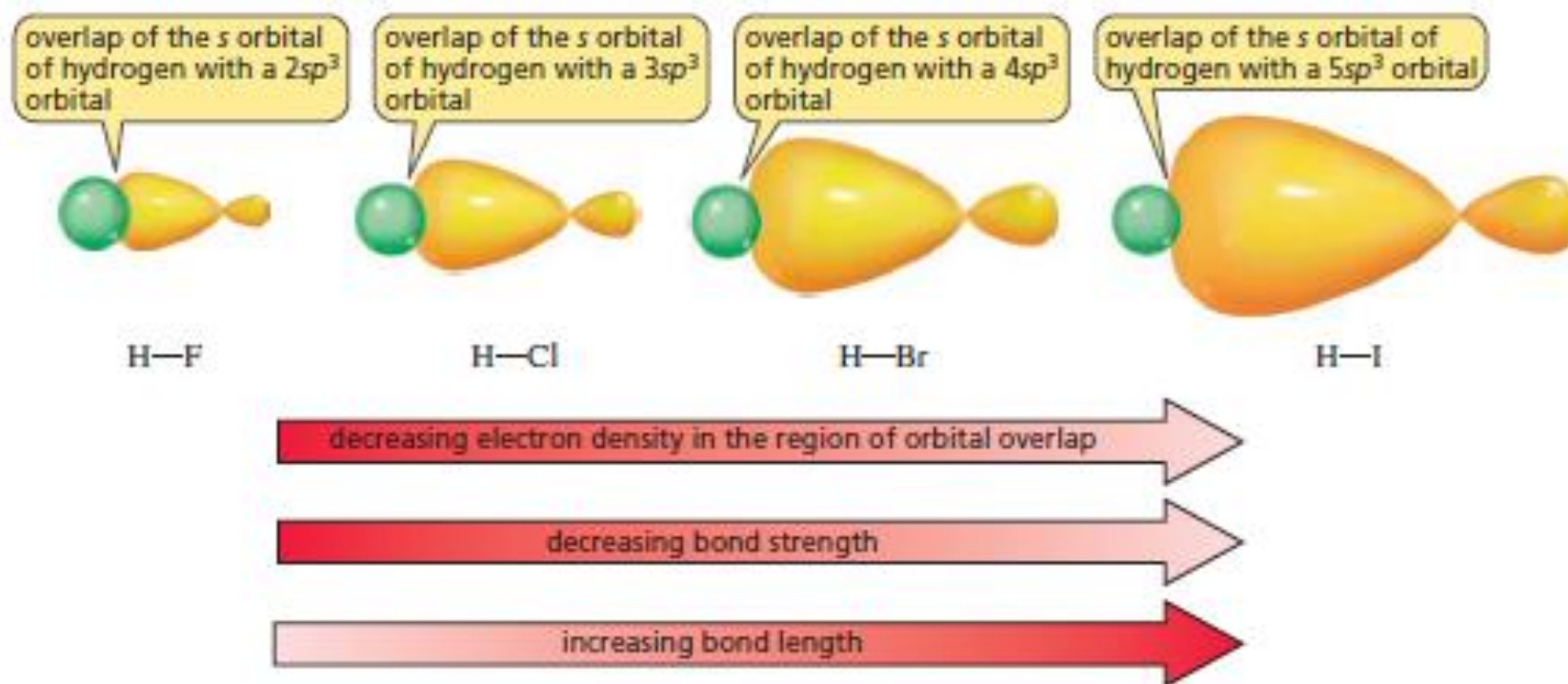
**Size overrides electronegativity  
when determining relative acidities.**

**Table 2.2** The  $pK_a$  Values of Some Simple Acids

$\text{CH}_4$ $pK_a = 60$	$\text{NH}_3$ $pK_a = 36$	$\text{H}_2\text{O}$ $pK_a = 15.7$	$\text{HF}$ $pK_a = 3.2$
		$\text{H}_2\text{S}$ $pK_a = 7.0$	$\text{HCl}$ $pK_a = -7$
			$\text{HBr}$ $pK_a = -9$
			$\text{HI}$ $pK_a = -10$

In summary:

- atomic size does not change much as we move from left to right across a row of the periodic table, so the atoms' orbitals have approximately the same volume. Thus, electronegativity determines the stability of the base and, therefore, the acidity of its conjugate acid.
- atomic size increases as we move down a column of the periodic table, so the volume of the orbitals increases. The volume of an orbital is more important than electronegativity in determining the stability of a base and, therefore, the acidity of its conjugate acid.



**Table 1.6** Hydrogen–Halogen Bond Lengths and Bond Strengths

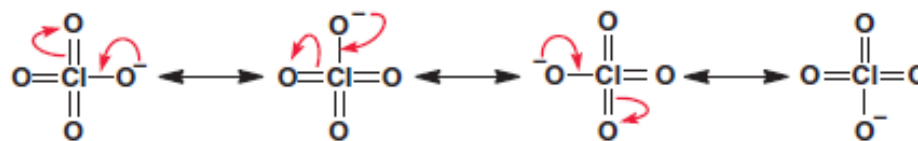
Hydrogen halide		Bond length (Å)	Bond strength (kcal/mol)
H—F		0.917	136
H—Cl		1.275	103
H—Br		1.415	87
H—I		1.609	71

### 6.3.2 Charge delocalization in anions

Anions are stabilized by dispersion (delocalization) of negative charge (or electrons). The relative acidities of the oxy-acids of chlorines are typical:

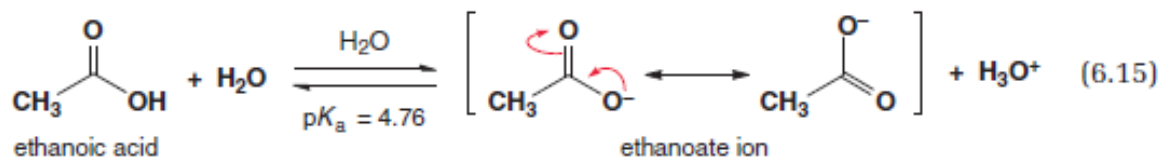
Acid:	HClO	HClO <sub>2</sub>	HClO <sub>3</sub>	HClO <sub>4</sub>
p <i>K</i> <sub>a</sub> :	7.5	2	-1	-10

The acidity of the oxy-acids increases with the increasing number of oxygen atoms bonded to the central Cl as these are able to delocalize the negative charge in the anionic conjugate bases. This is illustrated below by the four equivalent resonance forms of the highly stabilized tetrahedral perchlorate anion, ClO<sub>4</sub><sup>-</sup>: perchloric acid is a very strong acid.



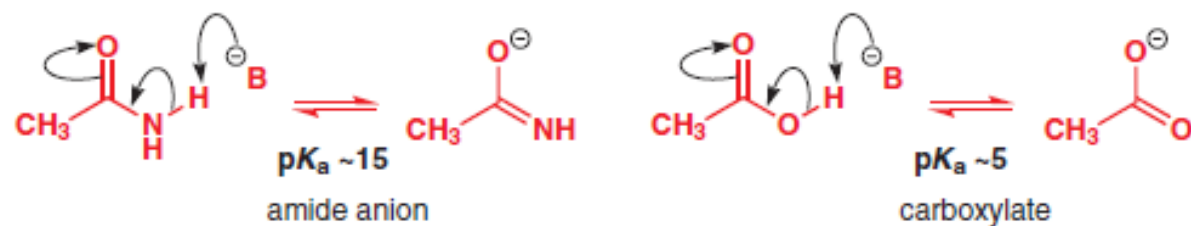
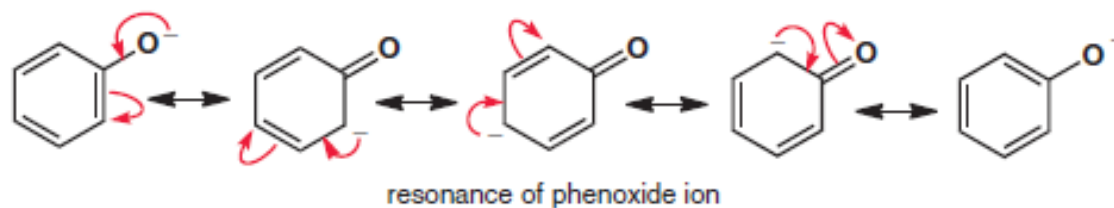
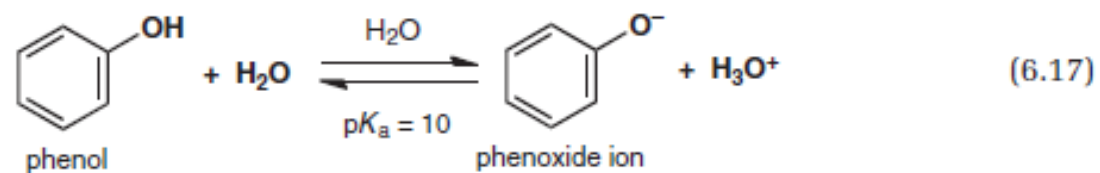
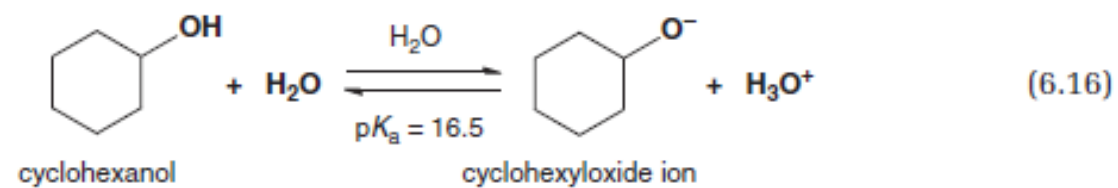
Resonance stabilization of the perchlorate ion

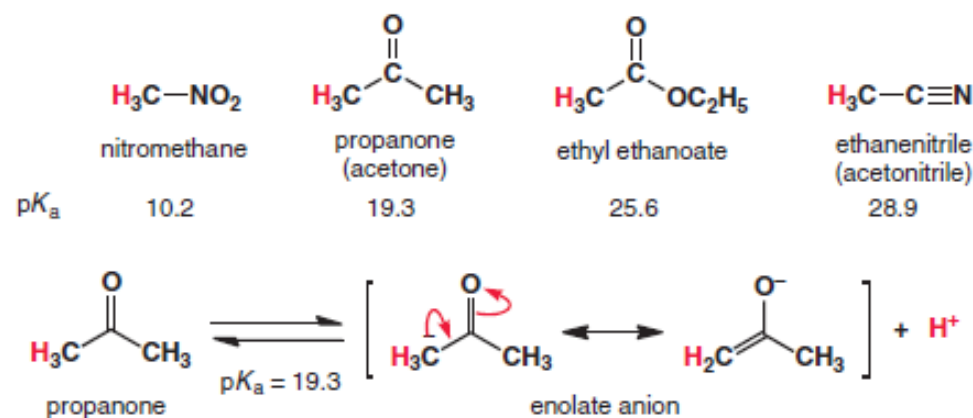
The higher acidity of carboxylic acids (p*K*<sub>a</sub> of AcOH = 4.76) compared with alcohols (p*K*<sub>a</sub> of ethanol = 15.9) is also explained by electron delocalization in the conjugate base of the acid. The negative charge of ethoxide, EtO<sup>-</sup> is localized on a single O atom whereas the charge of the carboxylate anion is delocalized symmetrically, and the two oxygen atoms become equivalent (eqn 6.15).



The electron-withdrawing effect of the carbonyl group also contributes to the acidity of a carboxylic acid being greater than that of an alcohol.

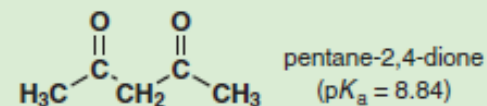
Phenol (p*K*<sub>a</sub> -10) is considerably more acidic than cyclohexanol (p*K*<sub>a</sub> -16, i.e. about the same as ethanol); see eqns 6.16 and 6.17. This is principally because the phenoxide





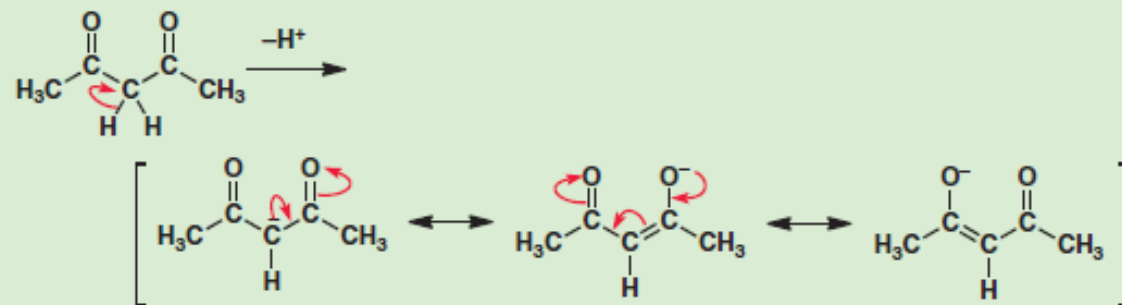
Carbon acids become stronger (i.e. their conjugate bases become more stable) if two or even three EWGs are bonded to the C bearing the acidic H. The conjugate bases of carbon acids are important as reactive intermediates, and reactions involving them will be covered in Chapter 17.

The  $pK_a$  of pentane-2,4-dione (acetylacetone) is 8.84. Of the two kinds of hydrogen, which is the more acidic, and why is this compound much more acidic than propanone?



#### Solution

The hydrogens on C3 of pentane-2,4-dione are the more acidic, and deprotonation from this position gives a resonance stabilized conjugate base as illustrated below with the negative charge delocalized mainly onto the two oxygen atoms (as opposed to onto just one as in the enolate from propanone).

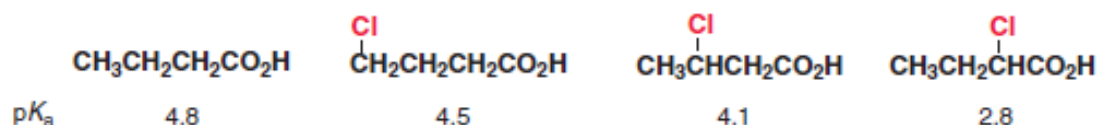




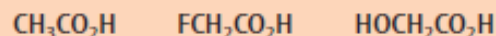
### 6.3.3 Substituent effects

When a hydrogen atom on a carbon in a molecule is replaced by another atom or group, the atom or group introduced is called a *substituent* and its effects on properties of other parts of the molecule, especially a functional group, are called **substituent effects**. We saw in Chapter 3 that organic compounds are classified according to the functional group, which is that distinctive part of the molecule responsible for the characteristic chemical properties of the compound. Such a property is often modulated by a substituent elsewhere in the molecule without qualitatively changing the *nature* of the property. Two kinds of substituent effects have been recognized which affect not only the acidity of a compound but other chemical and physical properties as well. This ability to attribute a quantitative change in a property of a functional group to a systematic change elsewhere in the molecule is a major unifying feature of mechanistic organic chemistry.

Inductive effects are transmitted through the  $\sigma$  bonds of a molecule and weaken rapidly as the number of  $\sigma$  bonds between a substituent and the reaction site increases.<sup>3</sup> This tendency can be seen in a series of chlorobutanoic acids:

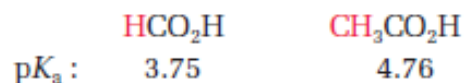


Predict the relative acidities of the following carboxylic acids.



Exercise 6.12

Methyl and other alkyl groups are **electron donating** (electron releasing), although the effect is small, so ethanoic acid is less acidic than methanoic (formic) acid.



## a. Inductive effects

When a proton is abstracted from an acidic functional group of an uncharged molecule, the conjugate base becomes an anion and, in the absence of any special effect, the charge resides as a lone pair localized on the functional group. An **electron-withdrawing (electron-attracting)** group elsewhere in the molecule will stabilize the anion by dispersing the negative charge and thereby enhance the acidity of the molecule. The highly electronegative chlorine, for example, is a substituent which stabilizes an anion by attracting electron density.

The  $pK_a$  values of chloroethanoic acids given below illustrate this effect:

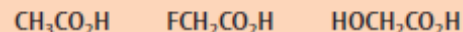
	$\text{CH}_3\text{CO}_2\text{H}$	$\text{ClCH}_2\text{CO}_2\text{H}$	$\text{Cl}_2\text{CHCO}_2\text{H}$	$\text{Cl}_3\text{CCO}_2\text{H}$
$pK_a$ :	4.76	2.86	1.35	-0.5

When the methyl hydrogen atoms of ethanoic acid are replaced by chlorine atoms one by one, the acid becomes increasingly stronger. The origin of this **inductive effect** is the strong polarization of the C–Cl  $\sigma$  bond.

Inductive effects are transmitted through the  $\sigma$  bonds of a molecule and weaken rapidly as the number of  $\sigma$  bonds between a substituent and the reaction site increases.<sup>3</sup> This tendency can be seen in a series of chlorobutanoic acids:

	$\text{CH}_3\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	$\overset{\text{Cl}}{\underset{ }{\text{CH}_2}}\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$	$\text{CH}_3\overset{\text{Cl}}{\underset{ }{\text{CH}}}\text{CH}_2\text{CO}_2\text{H}$	$\text{CH}_3\text{CH}_2\overset{\text{Cl}}{\underset{ }{\text{CH}}}\text{CO}_2\text{H}$
$pK_a$	4.8	4.5	4.1	2.8

Predict the relative acidities of the following carboxylic acids.



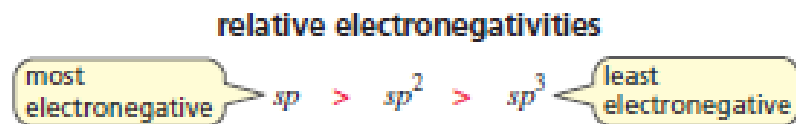
Exercise 6.12

Methyl and other alkyl groups are **electron donating (electron releasing)**, although the effect is small, so ethanoic acid is less acidic than methanoic (formic) acid.

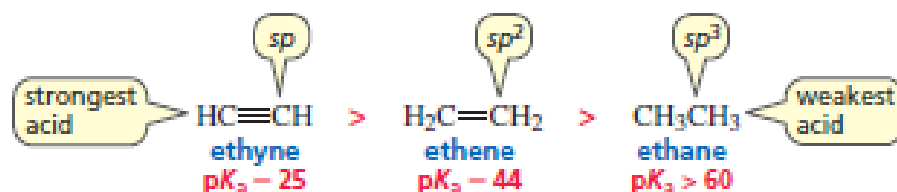
	$\text{HCO}_2\text{H}$	$\text{CH}_3\text{CO}_2\text{H}$
$pK_a$ :	3.75	4.76

## Hybridization

Because hybridization affects electronegativity and electronegativity affects acidity, the hybridization of an atom affects the acidity of the hydrogen bonded to it. An  $sp$  hybridized atom is more electronegative than the same atom that is  $sp^2$  hybridized, which is more electronegative than the same atom that is  $sp^3$  hybridized.



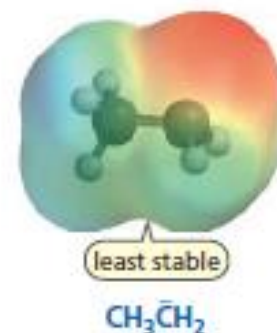
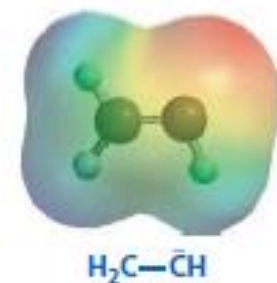
Therefore, ethyne is a stronger acid than ethene and ethene is a stronger acid than ethane, because the most acidic compound is the one with its hydrogen attached to the most electronegative atom.



Why does the hybridization of the atom affect its electronegativity? Electronegativity is a measure of the ability of an atom to pull the bonding electrons toward itself. Thus, the most electronegative atom is the one with its bonding electrons closest to the nucleus. The average distance of a  $2s$  electron from the nucleus is less than the average distance of a  $2p$  electron from the nucleus. Therefore, an  $sp$  hybridized atom with 50%  $s$  character is the most electronegative, an  $sp^2$  hybridized atom (33.3%  $s$  character) is next, and an  $sp^3$  hybridized atom (25%  $s$  character) is the least electronegative.

Pulling the electrons closer to the nucleus stabilizes the carbanion. Once again we see that the stronger the acid, the more stable (the weaker) its conjugate base. Notice that the electrostatic potential maps show that the strongest base (the least stable) is the most electron-rich (the most red).

An  $sp$  carbon is more electronegative than an  $sp^2$  carbon, which is more electronegative than an  $sp^3$  carbon.





## b. Conjugative effects

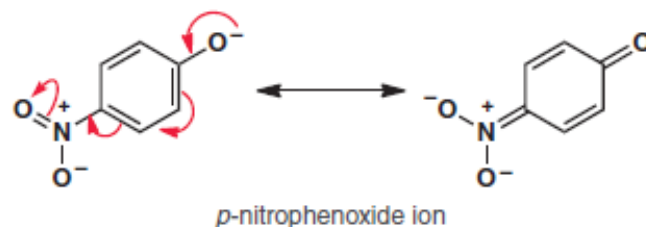
Substituents can also affect the electron distribution within a molecule, and hence its properties, by conjugation. Such effects of substituents are known as **conjugative** (or **resonance**) **effects** and are found in molecules (or ions) containing  $\pi$  electron systems; they can be represented by drawing the contributing resonance forms.

The effect is exemplified by the acidity of nitrophenols. A *m*-nitro group enhances the acidity of phenol through its inductive effect but a *p*-nitro group enhances the acidity even more strongly even though it is further away from the reaction site.

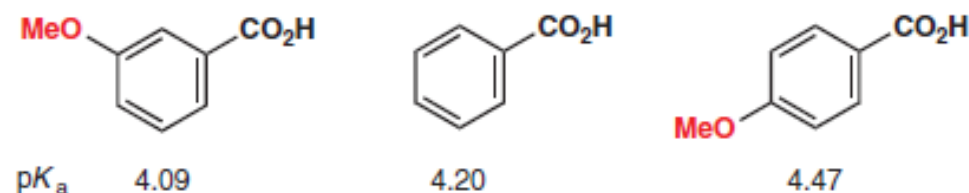


The negative charge of *p*-nitrophenoxide ion is delocalized over the molecule as illustrated by a resonance contributor with direct conjugation between the anionic oxygen

and the nitro group through the  $\pi$  system of the benzene ring. Although a lone pair on the OH of un-ionized *p*-nitrophenol can also be delocalized by resonance into the  $\text{NO}_2$ , this leads to charge separation which is absent in the corresponding delocalization in the *p*-nitrophenoxide. Consequently, resonance stabilization is greater in *p*-nitrophenoxide than in the *p*-nitrophenol, and *p*-nitrophenol is a stronger acid than phenol. For the *m*-nitro derivative, such direct conjugation is impossible, and only the inductive electron-withdrawing effect of the nitro group stabilizes the *m*-nitrophenoxide ion relative to the un-ionized *m*-nitrophenol.



A *p*-methoxy substituent is an example of an electron-donating group (EDG) by resonance, in contrast to the electron-withdrawing inductive effect of the methoxy group (oxygen is an electronegative element). These opposing properties of the methoxy group are illustrated by the acidities of the methoxybenzoic acids: *p*-methoxybenzoic acid is weaker than the unsubstituted benzoic acid, whereas the *m*-methoxy analogue is stronger than both.

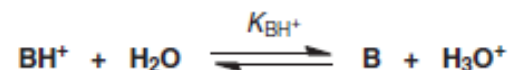
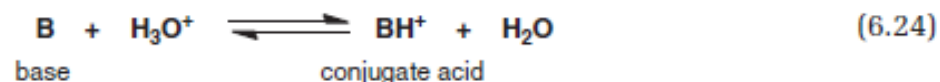


The *m*-methoxy group can only attract electrons through  $\sigma$  bonds, and this effect is stronger in the anionic conjugate base than in the carboxylic acid. In contrast, a *p*-methoxy group can conjugate with the carboxy group of benzoic acid through the  $\pi$  system of the benzene ring (a lone pair of the methoxy is delocalized to some degree into the carbonyl of the carboxy group). And because this resonance effect is greater in the carboxylic acid than in the carboxylate anion, the acid is stabilized with respect to its conjugate base so the acidity is decreased by the *p*-methoxy substituent.

## 6.5 Basicity of Organic Compounds

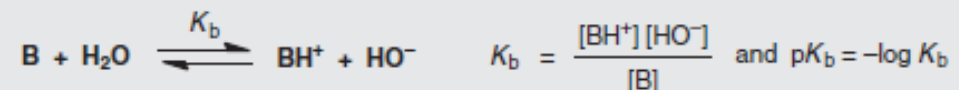
### 6.5.1 Definition of base strengths

A Brønsted base is always related to its conjugate acid, so the  $pK_a$  of the conjugate acid can be used as a quantitative measure of the basicity of a base (see Sub-section 6.2.1). However, when a compound (B) is uncharged and the focus is on its base strength with the reaction written as eqn 6.24, we usually refer to the  $pK_{BH^+}$  of B rather than the  $pK_a$  of  $BH^+$  (eqn 6.25), but the numerical value is, of course, the same. We see, therefore, that the larger the value of the  $pK_{BH^+}$ , the more basic compound B is.



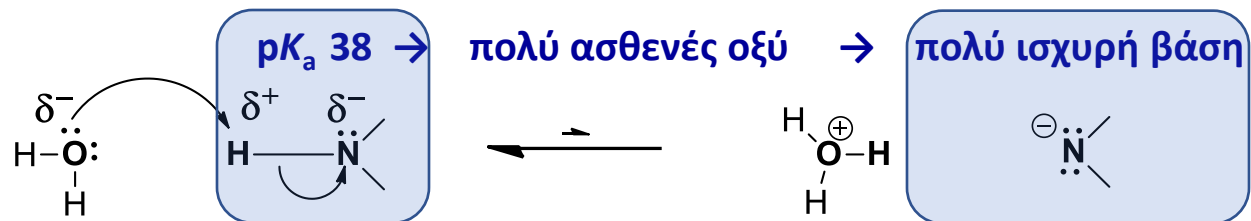
$$K_{BH^+} = \frac{[\text{B}][\text{H}_3\text{O}^+]}{[\text{BH}^+]} \quad (6.25)$$

An alternative definition of base strength used in older books is based on the reaction of the base with water:



Since the autoprotolysis constant (ionic product) of water is defined as  $K_w = [\text{H}_3\text{O}^+][\text{HO}^-] = 10^{-14}$ , we can work out that  $pK_b + pK_{BH^+} = 14$ .

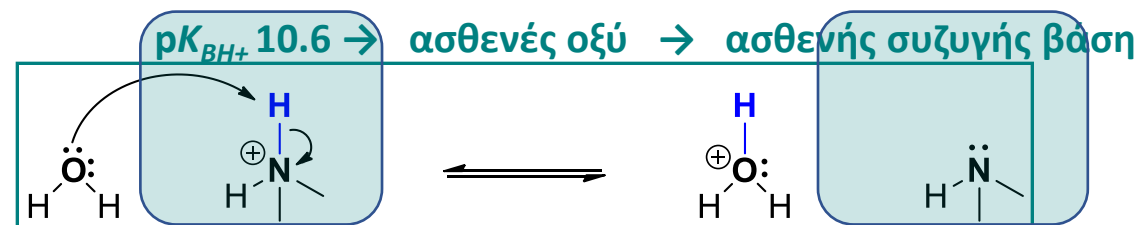
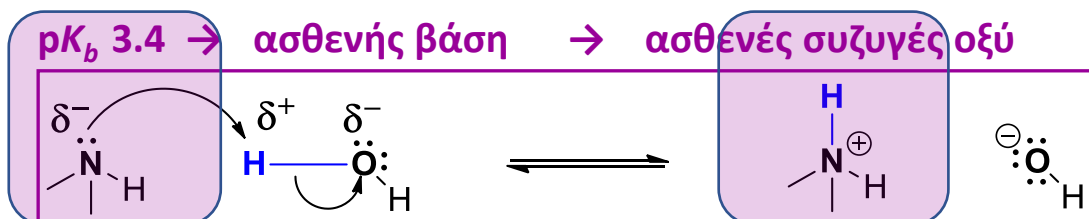
$pK_a, pK_b, pK_{BH+}$



Η  $pK_a$  μίας ένωσης αντανακλά την οξύτητά της δηλαδή την τάση της να απωλέσει ένα πρωτόνιο με ταυτόχρονη δημιουργία της συζυγούς της βάσης. Εδώ η υψηλή  $pK_a$  μαρτυρά ότι η διμεθυλαμίνη δεν έχει καμία τέτοια διάθεση (δεν είναι καθόλου όξινη) κυρίως διότι η συζυγής της βάση είναι ένα ανιόν ( $\text{Me}_2\text{N}^-$ ) που δεν σταθεροποιείται επαρκώς δηλαδή πρόκειται για μία ισχυρή βάση. Αν αυτό ( $\text{Me}_2\text{N}^-$ ) σχηματιστεί θα αποσπάσει άμεσα ένα πρωτόνιο (από οτιδήποτε με  $pK_a < 38$ ) προς δημιουργία διμεθυλαμίνης.

**Άρα η  $pK_a$  μίας ένωσης αντανακλά όχι μόνο την οξύτητά της αλλά και τη βασικότητα της συζυγούς βάσης της.**

Κατά αντιστοιχία Η  $pK_b$  μίας ένωσης αντανακλά τη βασικότητά της (ικανότητα να αποσπά ένα πρωτόνιο) αλλά και την οξύτητα του συζυγούς οξέος της,  $pK_{BH+}$  (τάση να αποδίδει ένα πρωτόνιο) Επειδή μιλάμε για οξύτητα έχει επικρατήσει να αναφέρεται και η  $pK_{BH+}$  ως  $pK_a$ .

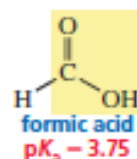
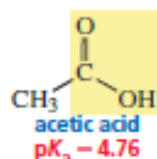


Άρα για να εκτιμήσουμε τη βασικότητα ( $pK_b$ ) μίας ένωσης B μπορούμε να εξετάσουμε την οξύτητα ( $pK_{BH+}$ ) του συζυγούς της οξέος. Η διμεθυλαμίνη είναι ασθενής βάση είτε μετρήσει κάποιος την ικανότητά της να αποσπά πρωτόνιο από το νερό ή την ικανότητα του νερού να αποσπά πρωτόνιο από το κατιόν διμεθυλοαμμωνίου (πρωτονιοδοτική ικανότητα του συζυγούς της οξέος)

Η οξύτητα (ή **βασικότητα**) μιας ένωσης μπορεί να περιγραφεί τόσο από την  $pK_a$  (ή  $pK_b$ ) της ίδιας όσο και από την  $pK_b$  της συζυγούς της βάσης της (ή  $pK_{BH+}$  του συζυγούς της οξέος). Κατά σύμβαση χρησιμοποιούμε την  $pK_{a/BH+}$  τόσο για να προσδιορίζουμε οξύτητα όσο και βασικότητα.

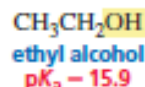
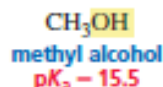
## Carboxylic Acids

The most common organic acids are carboxylic acids—compounds that have a COOH group. Acetic acid and formic acid are examples of carboxylic acids. Carboxylic acids have  $pK_a$  values ranging from about 3 to 5, so they are weak acids. The  $pK_a$  values of a wide variety of organic compounds are listed in Appendix I.



## Alcohols

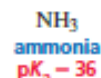
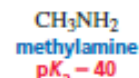
Alcohols—compounds that have an OH group—are much weaker acids than carboxylic acids, with  $pK_a$  values close to 16. Methyl alcohol and ethyl alcohol are examples of alcohols. We will see why carboxylic acids are stronger acids than alcohols in Section 2.8.



$pK_a < 0$	$pK_a \sim 5$	$pK_a \sim 10$	$pK_a \sim 15$
<p>protonated alcohol</p> <p>protonated carboxylic acid</p> <p>protonated water</p>	<p>carboxylic acid</p>	<p>protonated amine</p>	<p>alcohol</p> <p>water</p>

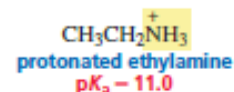
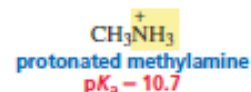
## Amines

Amines are compounds that result from replacing one or more of the hydrogens bonded to ammonia with a carbon-containing substituent. Amines and ammonia have such high  $pK_a$  values that they rarely behave as acids—they are more likely to act as bases. In fact, they are the most common organic bases. We will see why alcohols are stronger acids than amines in Section 2.6.

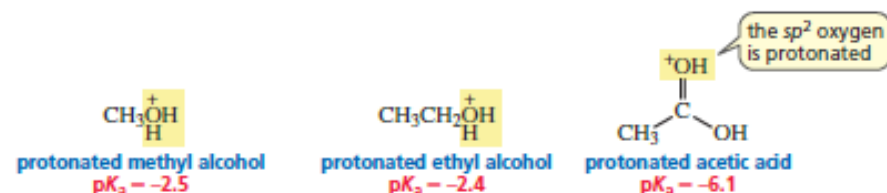


## Protonated Compounds

We can assess the strength of a base by considering the strength of its conjugate acid—remembering that *the stronger the acid, the weaker its conjugate base*. For example, based on their  $pK_a$  values, protonated methylamine (10.7) is a stronger acid than protonated ethylamine (11.0), which means that methylamine is a weaker base than ethylamine. (A protonated compound is a compound that has gained an additional proton.) Notice that the  $pK_a$  values of protonated amines are about 11.

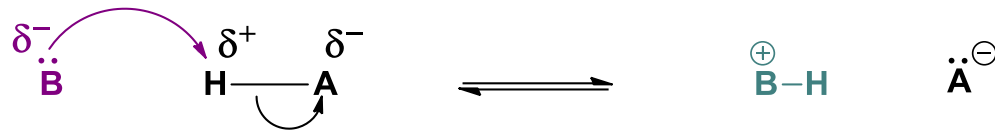


Protonated alcohols and protonated carboxylic acids are very strong acids, with  $pK_a$  values  $< 0$ .



Notice that it is the doubly bonded oxygen of the carboxylic acid that is protonated (meaning that it acquires the proton). You will see why this is so when you read the Problem-Solving Strategy on p. 68.

**Βασικότητα = Η ικανότητα ενός ζεύγους  $e^-$  ενός ατόμου αποσπά ένα πρωτόνιο από μία ένωση**



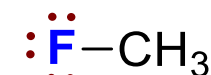
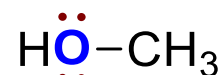
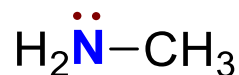
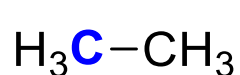
Η αξιολόγηση της βασικότητας ενός ουδέτερου μορίου B μπορεί να γίνει  
είτε βάσει της διαθεσιμότητας του ζεύγους  $e^-$   
ή βάσει της σταθερότητας του κατιόντος  $(B-H)^+$  που προκύπτει (συζυγές οξύ της βάσης)

Εξυπακούεται ότι η μετατόπιση της ισορροπίας προς τα δεξιά (δηλ. η βασικότητα) θα ευνοείται εάν  
το  $(B-H)^+$  μπορεί να σταθεροποιείται επαρκώς /  
η ηλεκτρονιακή πυκνότητα του μη-δεσμικού ζεύγους  $e^-$  του B είναι σχετικά υψηλή και εντοπισμένη  
(όσο πιο  $\delta^-$  τόσο βασικότερο)

Σε κάθε περίπτωση εξετάζονται οι ίδιοι παράγοντες που αναφέρθηκαν παραπάνω  
**(Μέγεθος/ηλεκτραρνητικότητα ατόμου, συντονισμός, επαγωγικά φαινόμενα, υβριδισμός)**

για το συμπληρωματικό τμήμα αυτής της διαδικασίας,  
δηλαδή τη διάσπαση του δεσμού A-H και το σχηματισμό του ανιόντος  $A^-$   
είδαμε ότι ευνοείται όταν ο δεσμός A-H είναι ασθενής/το ανιόν  $A^-$  είναι σχετικά σταθερό

## Ηλεκτραρνητικότητα ατόμου



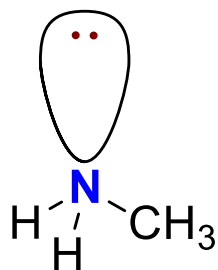
Δεν έχει μη  
δεσμικό ζεύγος e-  
Δεν είναι βάση

Αύξηση ηλεκτραρνητικότητας

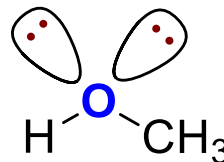
Όσο αυξάνεται η ηλεκτραρνητικότητα ενός ατόμου μειώνεται η βασικότητά του

Σύγκριση αντίστοιχων ενώσεων N, O, F, με τα ετεροάτομα σε  $sp^3$  υβριδισμό

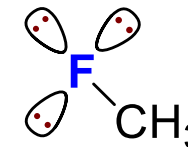
1x ζεύγος e- που δεν  
έλκεται υπερβολικά  
από τον πυρήνα N.  
Μπορεί να  
διοχετευθεί εύκολα  
προς ένα H  
Αρκετά βασικό μόριο



2x ζεύγη e- που έλκονται αρκετά από τον πυρήνα O.  
Μπορούν να διοχετευθούν με δυσκολία προς ένα H  
Ελάχιστα βασικό μόριο



3x ζεύγη e- που  
έλκονται πολύ ισχυρά  
από τον πυρήνα F.  
Αδύνατο να  
διοχετευθούν προς  
ένα H  
Καθόλου βασικό  
μόριο



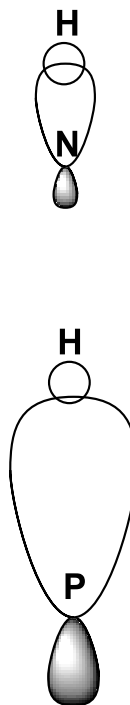
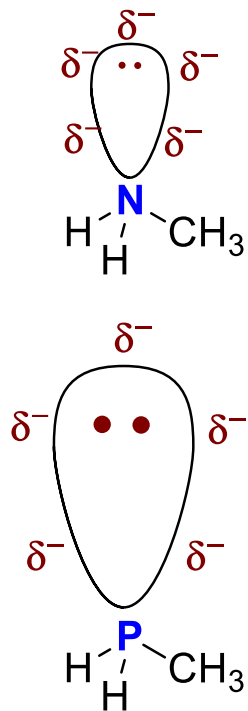
Διαθεσιμότητα ζεύγους e- για σύναψη δεσμού με H



## Μέγεθος ατόμου

Αυξανόμενου του μεγέθους ενός ατόμου, αυξάνεται και το μέγεθος/επιφάνεια των τροχιακών που βρίσκεται το μη-δεσμικό ζεύγος με συνέπεια το  $\delta^-$  αυτού να διασπείρεται και να χάνει σε ένταση.

(Βλέπε αργότερα για σκληρά/μαλακά)



Επιπλέον ο δεσμός που σχηματίζει ένα άτομο H με μεγαλύτερα άτομα είναι ασθενέστερος λόγω της μικρότερης / λιγότερο αποτελεσματικής αλληλοεπικάλυψης των εμπλεκόμενων τροχιακών



## Υβριδισμός ατόμου

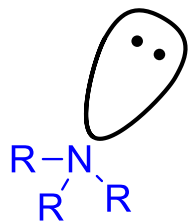
Η βασικότητα ενός ατόμου εξαρτάται από τον υβριδισμό του.

Αυξανόμενου του 's' χαρακτήρα μειώνεται η βασικότητα

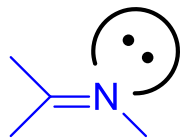
διότι ο 's' χαρακτήρας συρρικνώνει τη στοιβάδα γύρω από τον πυρήνα

Με τα ηλεκτρόνια να συγκρατούνται ισχυρότερα γύρω από αυτόν και

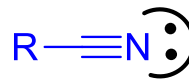
να καθίστανται λιγότερο διαθέσιμα να διοχετευθούν προς άλλα άτομα συνάπτοντας δεσμό π.χ. με ένα  $H^+$



**sp<sup>3</sup>**



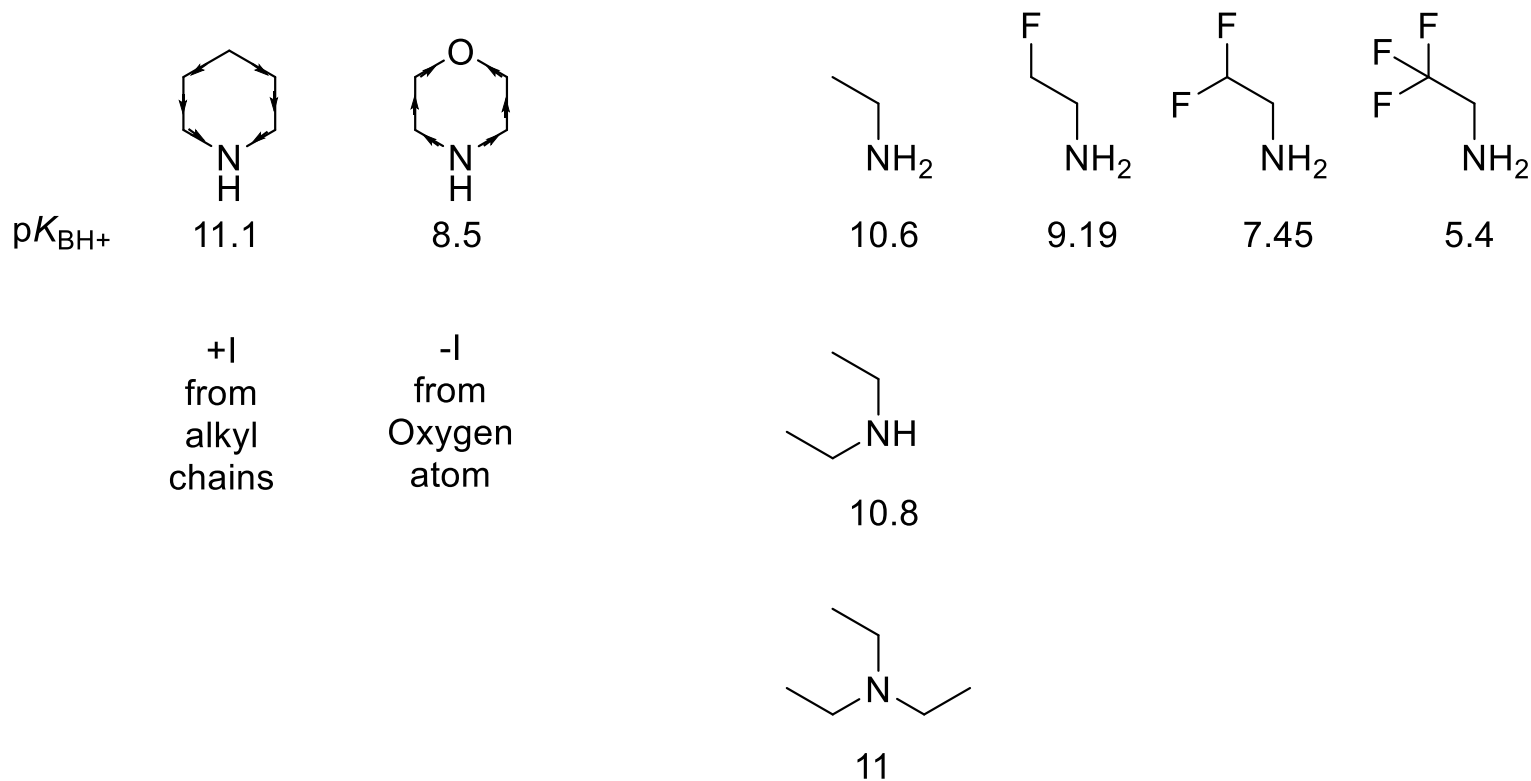
**sp<sup>2</sup>**



**sp**

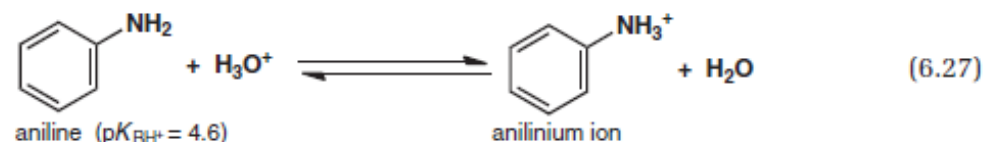
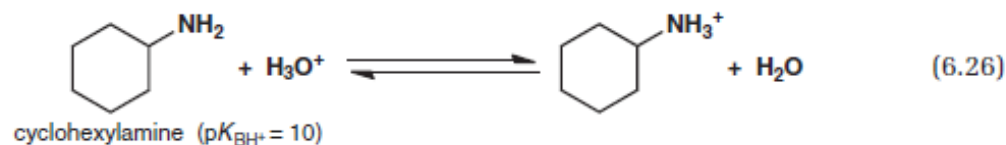
## Επαγωγικό φαινόμενο

Δεδομένου ενός ατόμου με διαθέσιμο ζεύγος, ομάδες που εξασκούν σε αυτό  $-I$  αποδυναμώνουν την ηλεκτρονιακή πυκνότητα σε αυτό συνεπώς μειώνουν τη βασικότητά του. Αντιθέτως ομάδες που εξασκούν  $+I$  ενισχύουν την ηλεκτρονιακή πυκνότητα σε αυτό συνεπώς το καθιστούν βασικότερο.

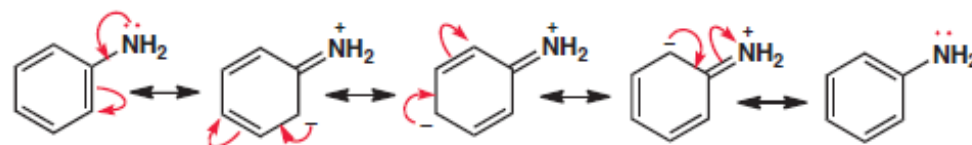


## Φαινόμενα συντονισμού – ελάττωση της βασικότητας

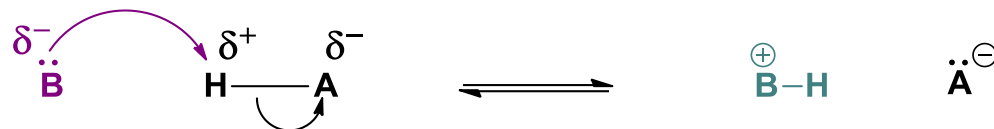
Amines are the most commonly encountered organic bases. For most typical alkylamines,  $pK_{BH^+}$  is about 10 (e.g. eqn 6.26), but arylamines are much weaker ( $pK_{BH^+}=4.6$  for aniline, eqn 6.27). This relationship is similar to the one between an alcohol and a phenol (see eqns 6.16 and 6.17 in Sub-section 6.3.2) except that some degree of delocalization is possible for the phenol as well as phenoxide.



Aniline is isoelectronic with phenoxide and the benzyl anion. The lone pair on the nitrogen of aniline is delocalized into the benzene ring as the resonance forms below show. But this is not possible for the protonated form, the anilinium ion, so appreciable resonance stabilization is lost upon protonation.

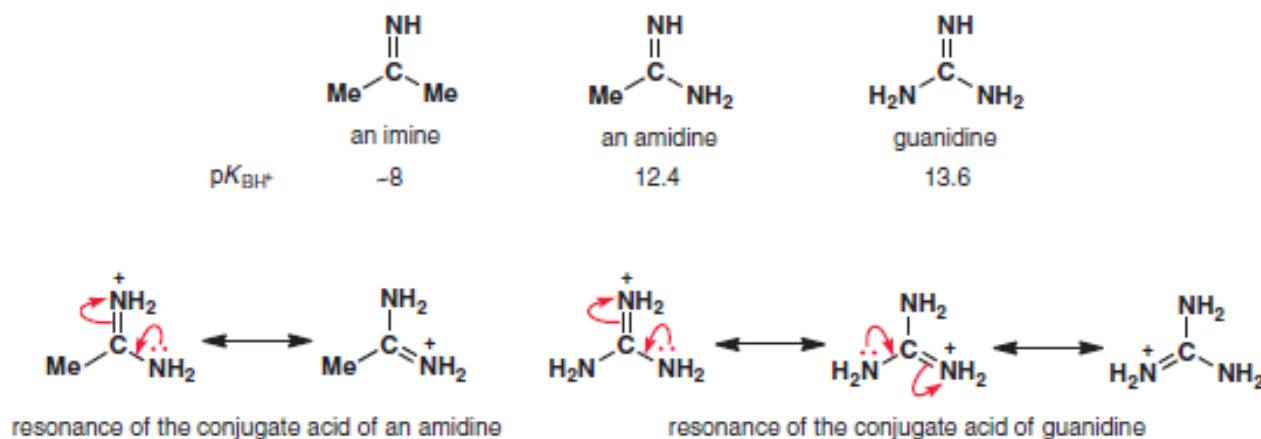


## Φαινόμενα συντονισμού – ενίσχυση της βασικότητας (Αμιδίνες και γουανιδίνες)

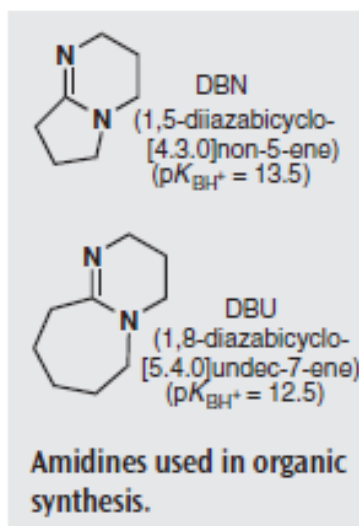


Θυμηθείτε ότι η βασικότητα ενός **ουδέτερου** μορίου B εξαρτάται από **τη διαθεσιμότητα του ζεύγους e<sup>-</sup> του και τη σταθερότητα του κατιόντος (B-H)<sup>+</sup> που προκύπτει (συζυγές οξύ της βάσης)**

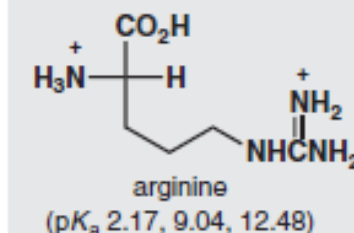
Amines are often used as bases in synthetic reactions and, when a simple alkylamine is not sufficiently basic, modified versions are available. The  $\text{p}K_{\text{BH}^+}$  values of acetamidine and guanidine are 12.4 and 13.6, respectively, so they are quite strong as neutral bases in spite of the hybridization of the nitrogen ( $\text{sp}^2$  compared with  $\text{sp}^3$  of the N in simple alkylamines). The high basicity of these amines compared with the analogous imines is attributable to the extra resonance stabilization of their conjugate acids.



If still stronger bases are needed for organic syntheses, anionic bases such as alkoxides  $\text{RO}^-$  ( $\text{p}K_{\text{BH}^+} \sim 16$ ) or amides  $\text{R}_2\text{N}^-$  ( $\text{p}K_{\text{BH}^+} \sim 35$ ) have to be used.



The conjugate acid of an  $\alpha$ -amino acid containing a guanidine group:



## Επιρροή του διαλύτη σε οξεοβασικές αντιδράσεις - Το εξισορροπητικό φαινόμενο του (διαλύτη) νερού

### 6.7.1 The levelling effect of water

We saw above that water is amphoteric. For example, it can accept a proton from HCl to give  $\text{H}_3\text{O}^+$  or, in a different solution, it can donate a proton to  $\text{NH}_3$  to give  $\text{HO}^-$ . Only a limited range of acids and bases can be used in an amphoteric solvent; in water, the range is from acids with  $\text{p}K_{\text{a}} > -2$  to bases with  $\text{p}K_{\text{BH}^+} < -16$ . This is because an acid

which is more acidic than the conjugate acid of the solvent is completely deprotonated by the solvent, while a base which is more basic than the conjugate base of the solvent becomes completely protonated by the solvent. In other words, the strongest acid and base which can exist in a solvent are the conjugate acid and conjugate base of the solvent, respectively. It follows that  $\text{H}_2\text{SO}_4$  ( $\text{p}K_{\text{a}} = -3$ ) and HCl ( $\text{p}K_{\text{a}} = -7$ ) cannot be distinguished as acids in water ( $\text{p}K_{\text{BH}^+} = -1.7$ ); both dissociate completely in dilute aqueous solution to give  $\text{H}_3\text{O}^+$ . This property of a solvent is called its *levelling effect*. So, if we

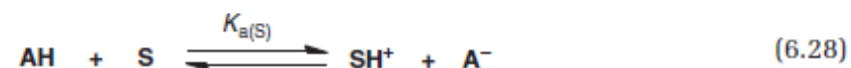
want to exploit the greater acidity of HCl compared with  $\text{H}_3\text{O}^+$ , for example, we need to use a solvent less basic than water. Ethanoic acid is a commonly used weakly basic solvent and we can even use  $\text{H}_2\text{SO}_4$  as an extremely weakly basic (and strongly acidic) medium.

Correspondingly, in order to use bases stronger than  $\text{OH}^-$ , e.g.  $\text{NH}_2^-$  or  $\text{H}^-$  as their sodium salts which would simply deprotonate water to give NaOH, we need to use a solvent less acidic than water. Liquid ammonia ( $\text{p}K_{\text{a}} = 35$ , bp =  $-33^\circ\text{C}$ ), which is also appreciably basic as we have already seen ( $\text{p}K_{\text{BH}^+} = 9.25$ ), or dimethyl sulfoxide (DMSO,  $\text{p}K_{\text{a}} = 33$ ), which is only weakly basic and a good solvent for organic compounds, are such solvents used in organic synthesis.

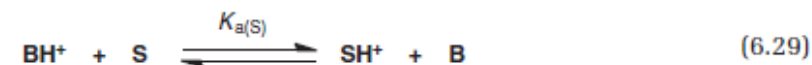
## Οξεοβασικές αντιδράσεις σε μη-υδατικά διαλύματα

Previously, we have been concerned mainly with acids and bases in aqueous solution even though some *aqueous*  $pK_a$  values have been estimated from results in other solvents (because they cannot be measured in aqueous solution when water is either too acidic or too basic). However, acids and bases are widely used, e.g. as catalysts, for organic reactions in non-aqueous solvents, especially so-called *polar aprotic solvents*, e.g. dimethyl sulfoxide, so measures of relative acidity (and basicity) in such solvents are desirable.

Some  $pK_a$  values in water and DMSO are compared in Table 6.1 where  $K_{a(S)}$  of acid AH in solvent (S) is defined as  $K_{a(S)} = [SH^+][A^-]/[AH]$  (eqn 6.28):



We expect the  $K_{a(S)}$  value of an acid to depend on the basicity of the solvent S because the acid donates a proton to the solvent in its dissociation (see Sub-section 6.7.1). However, water and DMSO are similarly basic ( $pK_{BH^+}$  values  $-1.7$  and  $-1.5$ , respectively, in water) and yet we find interesting differences. The most distinctive feature in the data of Table 6.1 is that the neutral acids (HCl and  $MeCO_2H$ ) are much *less* dissociated (larger  $pK_a$  values) in DMSO than in water whereas cationic acids ( $NH_4^+$  and  $Et_3NH^+$ ) are similarly dissociated (similar  $pK_a$  values) in these two solvents. This is because dissociation of the neutral acids results in charge separation (eqn 6.28), while dissociation of the cations does not (eqn 6.29), and solvents exert a strong effect upon acid–base behaviour only when proton transfer changes the ionic states of the compounds involved. The charge-separated state is more stable in a more polar solvent, so neutral acids dissociate more readily in water than in a less polar solvent.



In addition to a general medium effect, specific solvation of  $H_3O^+$  and of anionic conjugate bases, e.g.  $Cl^-$ , by hydrogen bonding is much more effective in water than in DMSO (Figure 6.5).

$pK_a$ values of some acids in $H_2O$ and DMSO		
Acid	$H_2O$	DMSO
HCl	$-7$	2.0
$MeCO_2H$	4.76	12.6
$NH_4^+$	9.24	10.5
$Et_3NH^+$	10.75	9.0

## Inorganic Compounds

H <sub>2</sub> O	15.74
H <sub>3</sub> O <sup>+</sup>	-1.74
HI	-10*
HBr	-9*
HCl	-7*
HF	3.17
HClO <sub>4</sub>	-10*
H <sub>2</sub> SO <sub>4</sub>	-3*
HSO <sub>4</sub> <sup>-</sup>	1.99
HNO <sub>3</sub>	-1.64
HNO <sub>2</sub>	3.29
H <sub>3</sub> PO <sub>4</sub>	1.97
H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	6.82
HPO <sub>4</sub> <sup>2-</sup>	12.3
H <sub>2</sub> CO <sub>3</sub>	6.37
HCO <sub>3</sub> <sup>-</sup>	10.33
HOOH	11.6
H <sub>2</sub> S	7.0
NH <sub>4</sub> <sup>+</sup>	9.24
HONH <sub>3</sub> <sup>+</sup>	6.0
H <sub>2</sub> NNH <sub>3</sub> <sup>+</sup>	8.07
NH <sub>3</sub>	35*

## Organic Compounds

### Carboxylic acids

HCO <sub>2</sub> H	3.75
CH <sub>3</sub> CO <sub>2</sub> H	4.76
(CH <sub>3</sub> ) <sub>3</sub> CCO <sub>2</sub> H	5.03
HOCH <sub>2</sub> CO <sub>2</sub> H	3.46
CF <sub>3</sub> CO <sub>2</sub> H	-0.6
H <sub>3</sub> <sup>+</sup> NCH <sub>2</sub> CO <sub>2</sub> H	2.35
CH <sub>2</sub> =CHCO <sub>2</sub> H	4.25
C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	4.20
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	3.44
HO <sub>2</sub> CCH <sub>2</sub> CO <sub>2</sub> H	2.85
<sup>-</sup> O <sub>2</sub> CCH <sub>2</sub> CO <sub>2</sub> H	5.70

### Sulfonic acids

C <sub>6</sub> H <sub>5</sub> SO <sub>3</sub> H	-2.8
CH <sub>3</sub> SO <sub>3</sub> H	-1.9
CF <sub>3</sub> SO <sub>3</sub> H	-5.5

### Hydroperoxy compounds

CH <sub>3</sub> C(O)O <sub>2</sub> H	8.2
CH <sub>3</sub> OOH	11.5
(CH <sub>3</sub> ) <sub>3</sub> COOH	12.8

### Alcohols

CH <sub>3</sub> OH	15.5
CH <sub>3</sub> CH <sub>2</sub> OH	15.9
(CH <sub>3</sub> ) <sub>2</sub> CHOH	17.1
(CH <sub>3</sub> ) <sub>3</sub> COH	19.2
HOCH <sub>2</sub> CH <sub>2</sub> OH	15.4
CF <sub>3</sub> CH <sub>2</sub> OH	12.4
(CF <sub>3</sub> ) <sub>2</sub> CHOH	9.3
(CF <sub>3</sub> ) <sub>3</sub> COH	5.1

### Phenols

C <sub>6</sub> H <sub>5</sub> OH	9.99
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	7.14
2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OH	4.1
2,4,6-(NO <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> OH	0.3

### Thiols and thioacids

CH <sub>3</sub> SH	10.33
C <sub>6</sub> H <sub>5</sub> SH	6.61
CH <sub>3</sub> C(O)SH	3.43
CH <sub>3</sub> C(S)SH	2.57

### Conjugate acids of miscellaneous organic compounds

CH <sub>3</sub> <sup>+</sup> OH <sub>2</sub>	-2.05
(CH <sub>3</sub> ) <sub>2</sub> <sup>+</sup> OH	-2.48
(CH <sub>3</sub> ) <sub>2</sub> <sup>+</sup> SH	-6.99
<sup>+</sup> OH    CH <sub>3</sub> CCH <sub>3</sub>	-3.06
<sup>+</sup> OH    CH <sub>3</sub> COMe	-3.90
<sup>+</sup> OH    CH <sub>3</sub> CNMe <sub>2</sub>	-0.21
<sup>+</sup> OH    CH <sub>3</sub> SCH <sub>3</sub>	-1.54
CH <sub>3</sub> - <sup>+</sup> N(=O)   OH	-12*
Ph <sub>2</sub> C= <sup>+</sup> NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	7*
CH <sub>3</sub> -C≡N <sup>+</sup> -H	-10*

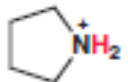
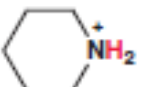
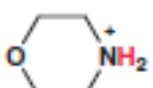
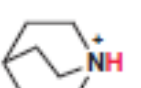
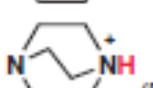


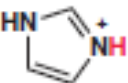
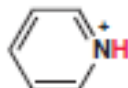
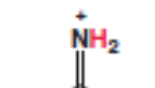
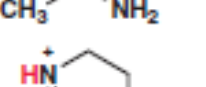
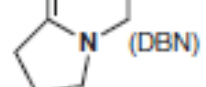
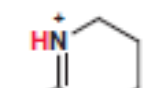
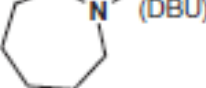

## Amines and amides

$(\text{Me}_2\text{CH})_2\text{NH}$	38 <sup>b</sup>
$\text{C}_6\text{H}_5\text{NH}_2$	27.7
$\text{CH}_3\text{CONH}_2$	15.1


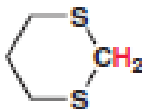
## Ammonium ions

$\text{CH}_3\text{NH}_3^+$	10.64
$(\text{CH}_3)_2\text{NH}_2^+$	10.73
$(\text{C}_2\text{H}_5)_3\text{NH}^+$	10.75
$(\text{CH}_3)_3\text{NH}^+$	9.75
$\text{C}_6\text{H}_5\text{NH}_3^+$	4.60
$p\text{-NO}_2\text{C}_6\text{H}_4\text{NH}_3^+$	0.99
$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{NH}_3^+$	-4.31
$2,4,6\text{-(NO}_2)_3\text{C}_6\text{H}_2\text{NH}_3^+$	-10.04

	11.30
	11.12
	8.4
	11.0
	8.4

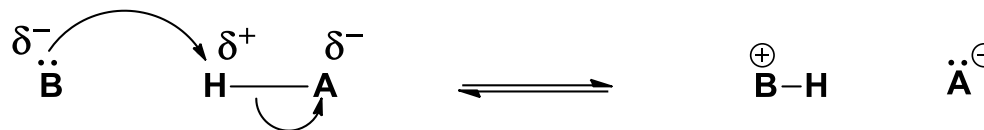
	6.99
	5.25
	12.4
	13.5*
	12.5*
	13.6
	12.1
	16.3

## Carbon acids

$\text{HC}\equiv\text{N}$	9.1
$\text{HC}\equiv\text{CH}$	25*
$\text{H}_2\text{C}=\text{CH}_2$	44*
$\text{H}_3\text{C}-\text{CH}_3$	50*
$\text{H}_2\text{C}=\text{CHCH}_3$	43*
$\text{C}_6\text{H}_5\text{CH}_3$	41*
	16
$\text{CH}_3\text{C}(=\text{O})\text{CH}_3$	19.3
$\text{CH}_3\text{C}(=\text{O})\text{OEt}$	25.6
$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{CH}_3$	8.84
$\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{OEt}$	10.7
$\text{EtOC}(=\text{O})\text{CH}_2\text{C}(=\text{O})\text{OEt}$	13.3
$\text{CH}_3\text{CN}$	28.9
$\text{CH}_3\text{NO}_2$	10.2
	31*
$\text{CH}_3\text{S}(=\text{O})\text{CH}_3$	33*
$\text{CHCl}_3$	24*



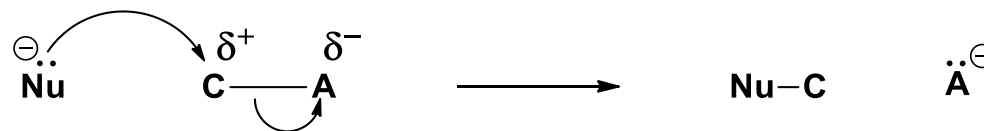
# Πυρηνοφιλία vs Βασικότητα



Βασικότητα είναι η τάση ενός ατόμου ( $\delta^-$ ) να προσβάλει/αποσπά ένα πρωτόνιο (ηλεκτρονιόφιλο άτομο  $\delta^+$ )

Πυρηνοφιλία είναι η τάση ενός ατόμου ( $\delta^-$ ) να προσβάλει ένα ηλεκτρονιόφιλο άτομο ( $\delta^+$ )  $\neq$  του πρωτονίου δηλαδή μεγαλύτερα άτομα.

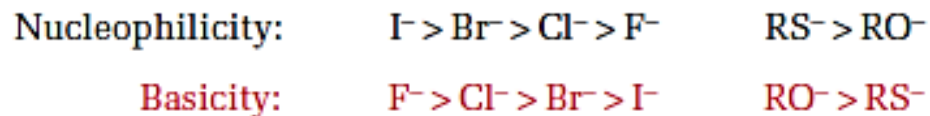
Εδώ θα ασχοληθούμε με την προσβολή πυρηνόφιλων αντιδραστηρίων ( $\delta^-$ ) σε ηλεκτρονιόφιλα άτομα άνθρακα C ( $\delta^+$ ).



Σημειώστε ότι η οξύτητα/βασικότητα αφορά σε μία ισορροπία δηλαδή ένα θερμοδυναμικό φαινόμενο

Η πυρηνοφιλία αφορά κατά κανόνα (υπάρχουν εξαιρέσεις) σε μία μη-αντιστρεπτή αντίδραση δηλαδή ένα κινητικό φαινόμενο.

Λόγω αυτής της διαφοράς η βασικότητα δεν παραλληλίζεται πάντα με την πυρηνοφιλία και όπως θα εξηγήσουμε αργότερα...

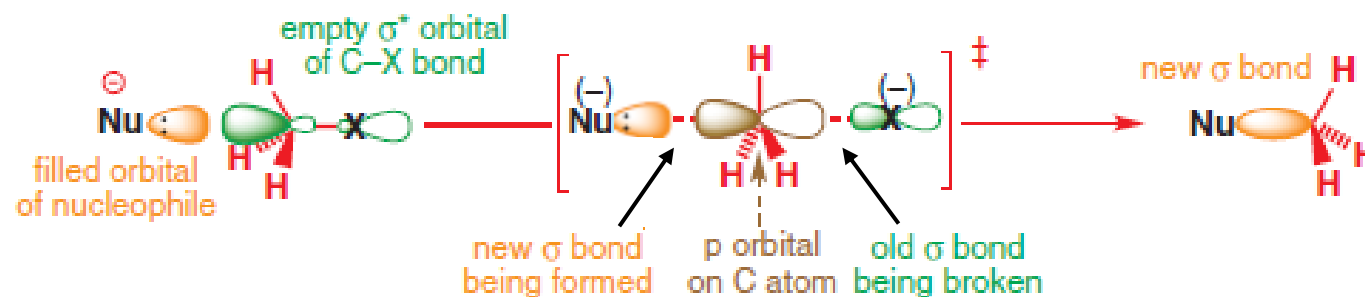
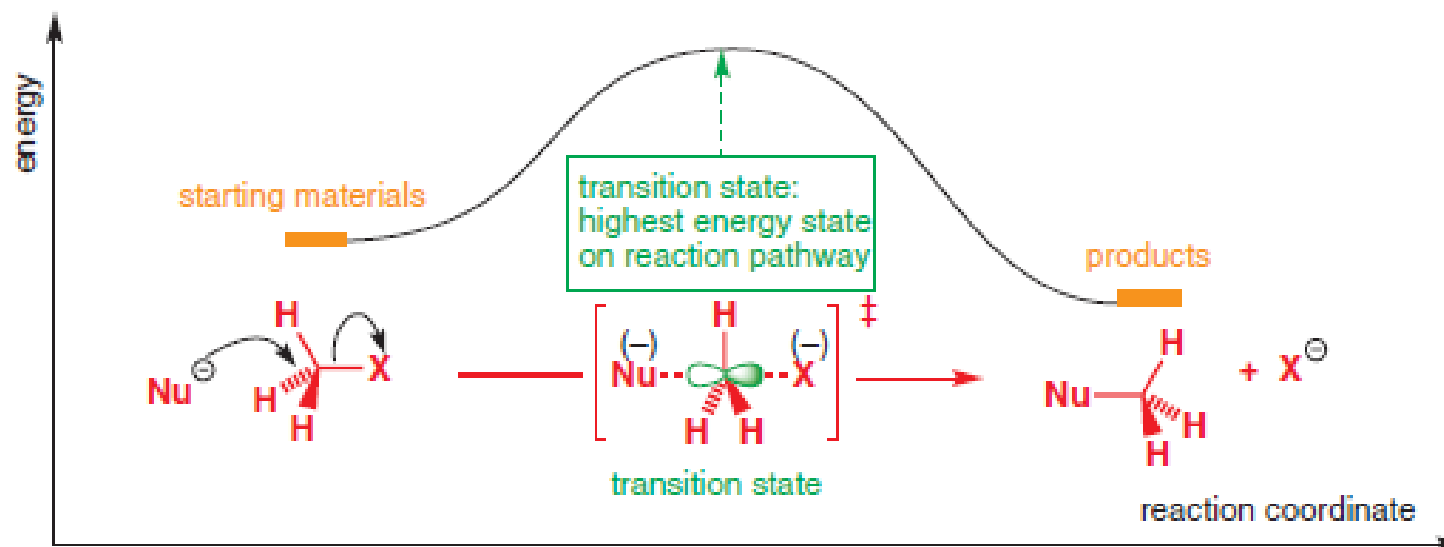


## Η αντίδραση $S_{N2}$ – Γεωμετρική προϋπόθεση / Μεταβατικό στάδιο

The transition state is the highest energy point on the reaction pathway. In the case of an  $S_{N2}$  reaction it will be the point where the new bond from the nucleophile is partially formed while the old bond to the leaving group is partially broken. It will look something like this:

The dashed bonds in the transition state indicate partial bonds (the C–Nu bond is partly formed and the C–X bond partly broken) and the charges in brackets indicate substantial partial charges (about half a minus charge each in this case). Transition states are often shown in square brackets and marked with the symbol  $\ddagger$ .

Another way to look at this situation is to consider the orbitals. The nucleophile must have available lone-pair electrons (HOMO), which will interact with the  $\sigma^*$  orbital of the C–X bond (LUMO).



## Experimental Evidence for the Mechanism for an S<sub>N</sub>2 Reaction

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<sub>3</sub>Br) doubles the rate of the reaction.
- Doubling the concentration of the nucleophile (HO<sup>−</sup>) doubles the rate of the reaction.
- Doubling the concentration of both reactants quadruples the rate of the reaction.

Because we know the relationship between the rate of the reaction and the concentration of the reactants, we can write a **rate law** for the reaction:

$$\text{rate} \propto [\text{alkyl halide}][\text{nucleophile}]$$

The proportionality sign ( $\propto$ ) 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.

$$\text{rate} = k [\text{alkyl halide}][\text{nucleophile}]$$

the rate constant

The **rate law** tells us which molecules are involved in the transition state of the rate-determining step of the reaction. Thus, the rate law for this substitution reaction tells us that *both* the alkyl halide and the nucleophile are involved in the rate-determining transition state.

The proportionality constant is called a **rate constant**. The magnitude of the rate constant for a particular reaction indicates how difficult it is for the reactants to overcome the energy barrier of the reaction—that is, how hard it is to reach the transition state (Section 5.11).

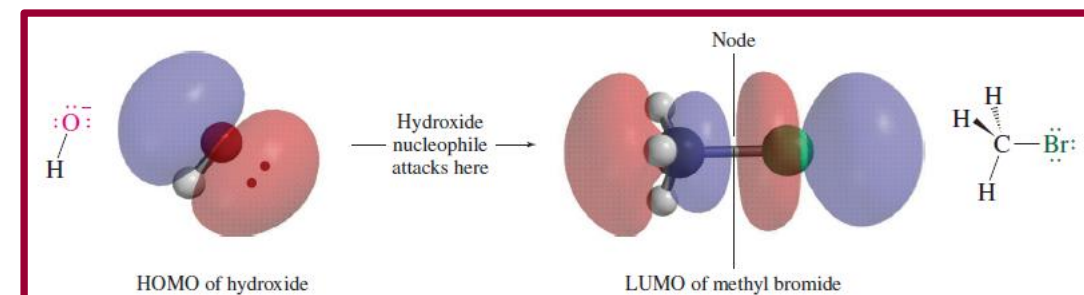
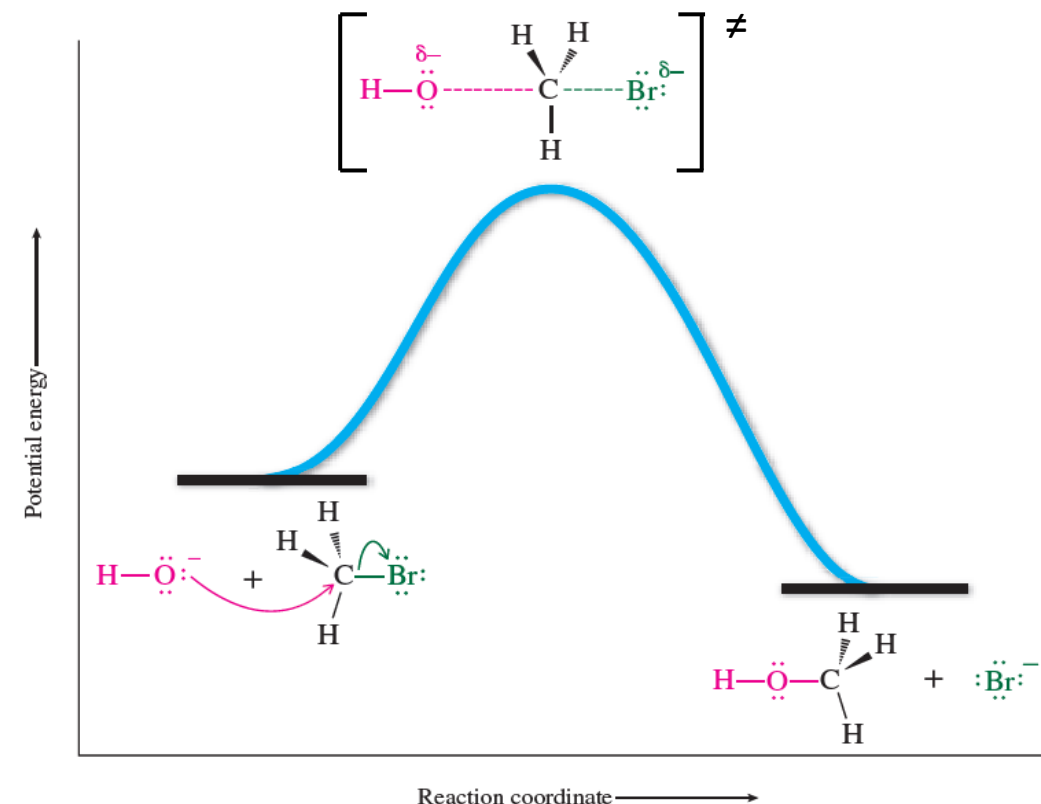
*the lower the energy barrier, the larger the rate constant*

Όσο μεγαλύτερο το ενεργειακό κόστος για την επίτευξη του μεταβατικού σταδίου, τόσο βραδύτερη καθίσταται η αντίδραση

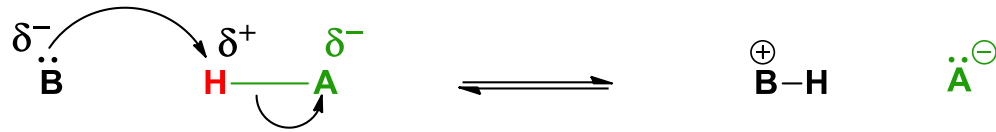
Rate Determining Step (RDS)

Το καθορίζον την ταχύτητα βήμα =

Το βήμα του μηχανισμού με το μεγαλύτερο ενεργειακό κόστος



# Παράγοντες που επηρεάζουν την αντίδραση S<sub>N</sub>2 – Η Αποχωρούσα ομάδα



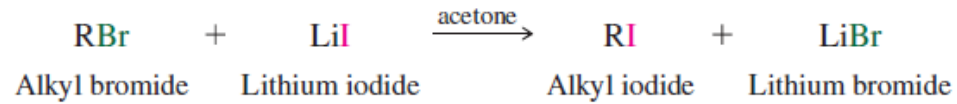
Οι συζυγείς βάσεις ισχυρών οξέων ( $pK_a < 1$ )  
συνιστούν καλές αποχωρούσες ομάδες



				relative rates of reaction	pK <sub>a</sub> values of HX	
HO <sup>-</sup>	+	RCH <sub>2</sub> I	→	RCH <sub>2</sub> OH + I <sup>-</sup>	30,000	-10
HO <sup>-</sup>	+	RCH <sub>2</sub> Br	→	RCH <sub>2</sub> OH + Br <sup>-</sup>	10,000	-9
HO <sup>-</sup>	+	RCH <sub>2</sub> Cl	→	RCH <sub>2</sub> OH + Cl <sup>-</sup>	200	-7
HO <sup>-</sup>	+	RCH <sub>2</sub> F	→	RCH <sub>2</sub> OH + F <sup>-</sup>	1	3.2

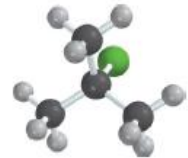
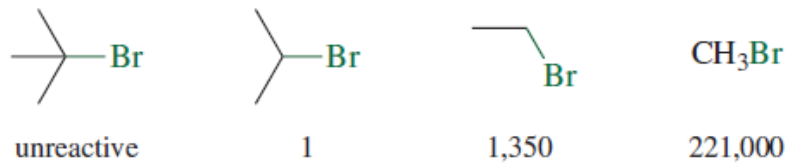
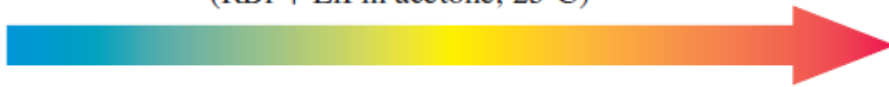
Acid	$pK_a$	Conjugate base	
Strongest acid		Most stable base	
$I-H$	-11	$I^-$	Best leaving group
$Br-H$	-9	$Br^-$	
$Cl-H$	-7	$Cl^-$	Good leaving groups
$H_3C-C_6H_4-SO_3H$	-3	$H_3C-C_6H_4-SO_3^-$	
$H_2O^+$	-2	$H_2O$	
$F-H$	3	$F^-$	
$H_2O$	15.7	$HO^-$	
$EtOH$	16	$EtO^-$	Bad leaving groups
$tBuOH$	18	$tBuO^-$	
$NH_3$	38	$NH_2^-$	Worst leaving group
Weakest acid		Least stable base	

# Παράγοντες που επηρεάζουν την αντίδραση $S_N2$ – Προσβασιμότητα του ηλεκτρονιόφιλου C (Στερικός συνωστισμός γύρω από το ηλεκτρονιόφιλο κέντρο)



the rates of nucleophilic substitution of a series of alkyl bromides differ by a factor of over  $10^6$ .

Increasing relative reactivity toward  $S_N2$  substitution  
(RBr + LiI in acetone, 25°C)



$(\text{CH}_3)_3\text{CBr}$



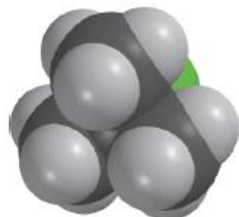
$(\text{CH}_3)_2\text{CHBr}$



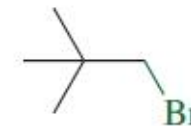
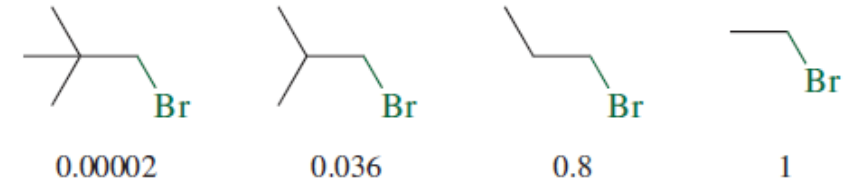
$\text{CH}_3\text{CH}_2\text{Br}$



$\text{CH}_3\text{Br}$



Increasing relative reactivity toward  $S_N2$  substitution  
(RBr + LiI in acetone, 25°C)

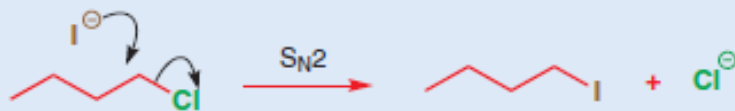


Neopentyl bromide  
(1-Bromo-2,2-dimethylpropane)



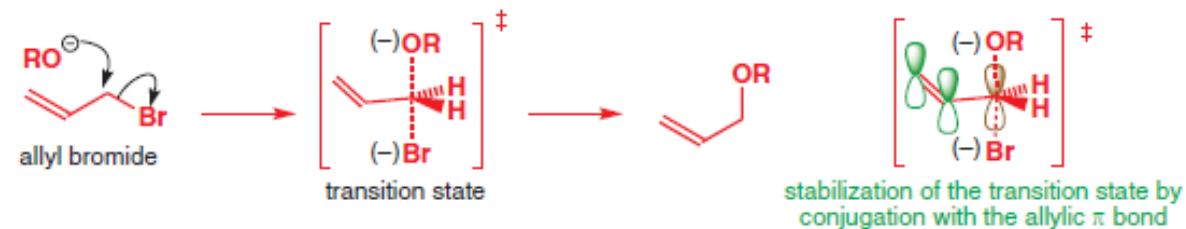
# Παράγοντες που επηρεάζουν την αντίδραση $S_N2$ – Δραστικότητα ηλεκτρονιόφιλου

Some actual data may help at this point. The rates of reaction of the following alkyl chlorides with KI in acetone at 50 °C broadly illustrate the patterns of  $S_N2$  reactivity we have just analysed. These are relative rates with respect to *n*-BuCl as a 'typical primary halide'. You should not take too much notice of precise figures but rather observe the trends and notice that the variations are quite large—the full range from 0.02 to 100,000 is eight powers of ten.

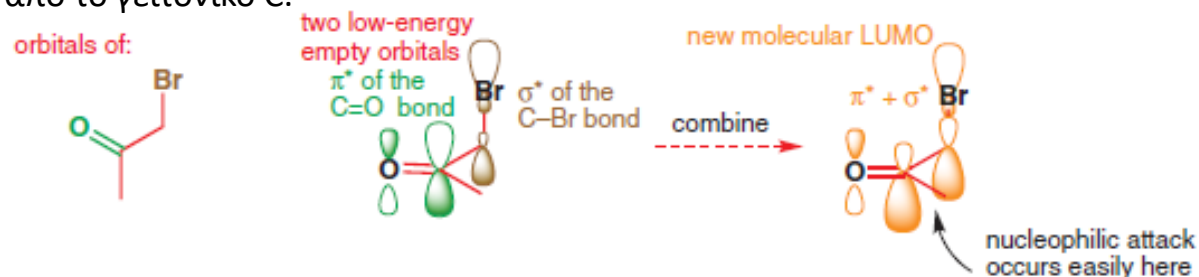


Relative rates of substitution reactions of alkyl chlorides with the iodide ion

Alkyl chloride	Relative rate	Comments
<p>Αλλυλικός C</p>	79	allyl chloride accelerated by $\pi$ conjugation in transition state
<p>Βενζυλικός C</p>	200	benzyl chloride a bit more reactive than allyl: benzene ring slightly better at $\pi$ conjugation than isolated double bond
	100,000	conjugation with carbonyl group much more effective than with simple alkene or benzene ring; these $\alpha$ -halo carbonyl compounds are the most reactive of all

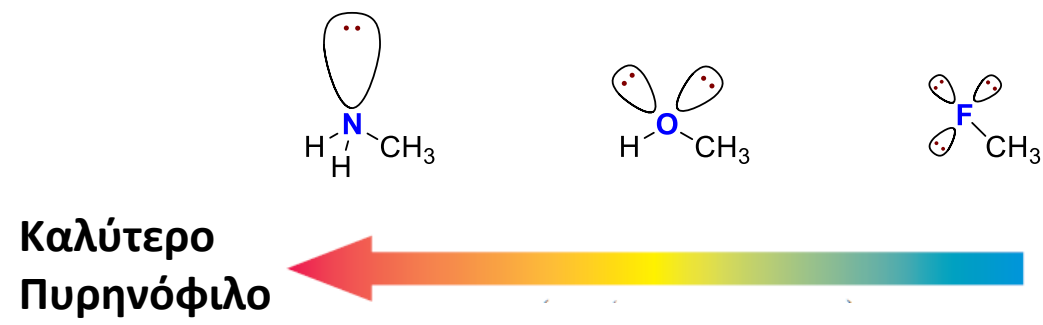


Κατά την προσβολή ενός ( $\delta^-$ ) πυρηνόφιλου σε έναν ηλεκτρονιόφιλο C (στη LUMO/ $\sigma^*$  του δεσμού C-X), αυξάνεται η ηλεκτρονιακή πυκνότητα σε αυτόν. Ένα  $\pi$  σύστημα συνδεδεμένο με τον ηλεκτρονιόφιλο C βοηθά να διοχετευτεί η αυξανόμενη ηλεκτρονιακή πυκνότητα στις στιβάδες του  $\pi$  συστήματος (στην  $\pi^*$  συγκεκριμένα) και να σταθεροποιηθεί το μεταβατικό στάδιο της  $S_N2$ . Το φαινόμενο είναι ακόμα πιο έντονο όταν το εν λόγω  $\pi$  σύστημα είναι επιπλέον και ηλεκτραρνητικό (όπως το C=O) δηλαδή με ακόμα μεγαλύτερη διάθεση (LUMO/ $\pi^*$  μικρότερης ενέργειας) να απορροφήσει  $e^-$  πυκνότητα από το γειτονικό C.



Αυτό το φαινόμενο είναι επιπρόσθετο του επαγωγικού που εξασκεί ο  $\delta^+$  άνθρακας του καρβονυλίου στον γειτονικό C-X. Για παράδειγμα, αν αντί για C=O υπήρχε CF<sub>3</sub> συνδεδεμένο στο C-X, η αντίδραση δεν θα ήταν εξίσου γρήγορη διότι το CF<sub>3</sub> αν και εξασκεί  $-I$ , δε διαθέτει  $\pi$  σύστημα που να βοηθά περισσότερο με τον παραπάνω τρόπο.

# Παράγοντες που επηρεάζουν την αντίδραση S<sub>N</sub>2 – Ποιότητα πυρηνόφιλου αντιδραστήριου



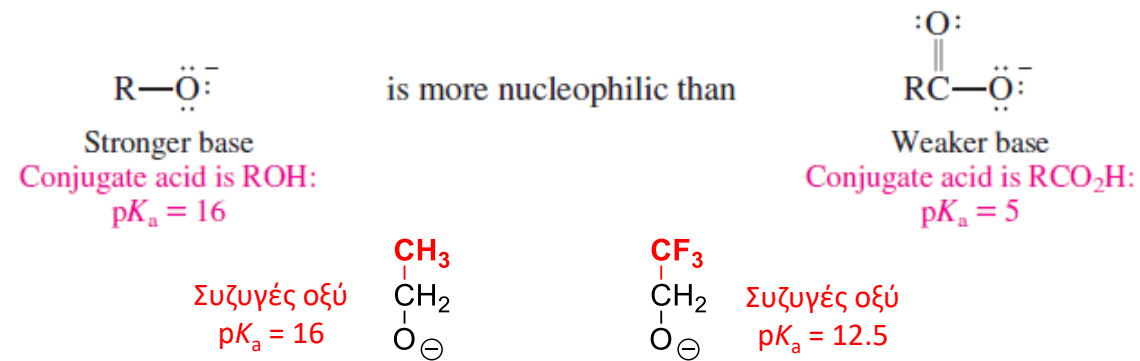
**Διαθεσιμότητα ζεύγους ηλεκτρονίων**  
(Αυξάνει την πυρηνοφιλία και τη βασικότητα)

Συγκρίνοντας  
άτομα της  
ίδιας περιόδου  
στον Π. Π.

R-NH <sup>⊖</sup>		R-O <sup>⊖</sup>		F <sup>⊖</sup>
stronger base, better nucleophile		weaker base, poorer nucleophile		
HO <sup>⊖</sup>	>	H <sub>2</sub> O		
CH <sub>3</sub> O <sup>⊖</sup>	>	CH <sub>3</sub> OH		
<sup>⊖</sup> NH <sub>2</sub>	>	NH <sub>3</sub>		
CH <sub>3</sub> CH <sub>2</sub> NH <sup>⊖</sup>	>	CH <sub>3</sub> CH <sub>2</sub> NH <sub>2</sub>		

**Φορτίο**  
(Αυξάνει την πυρηνοφιλία και τη βασικότητα)

Συγκρίνοντας  
ομόλογες  
ομάδες του  
ίδιου ατόμου



**Ενίσχυση e<sup>-</sup> πυκνότητας (+I /+M)**  
(Αυξάνει την πυρηνοφιλία και τη βασικότητα)

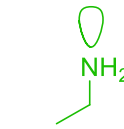
# Παράγοντες που επηρεάζουν την αντίδραση $S_N2$ – Στερικός συνωστισμός στο πυρηνόφιλο

Nucleophilicity is much more affected by steric hindrance than is basicity (affinity for the small proton). For example, the *t*-butoxide ion is one of the most basic alkoxides, but is a very poor nucleophile due to its steric bulk.

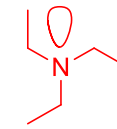
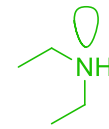
Basicity:	$\text{CH}_3\text{CH}_2\text{O}^- < (\text{CH}_3)_3\text{CO}^-$
Nucleophilicity:	$\text{CH}_3\text{CH}_2\text{O}^- \gg (\text{CH}_3)_3\text{CO}^-$
Steric bulk:	small $\rightarrow$ large

Στερική απαίτηση (όγκος):  
Μειώνει την πυρρηνοφιλία  
(παρεμποδίζεται η προσέγγιση με τον  $\delta^+ \text{C}$ )

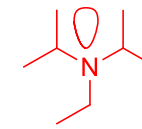
Συγκρίνοντας  
ομόλογες ομάδες  
του ίδιου ατόμου



Καλά πυρηνόφιλα

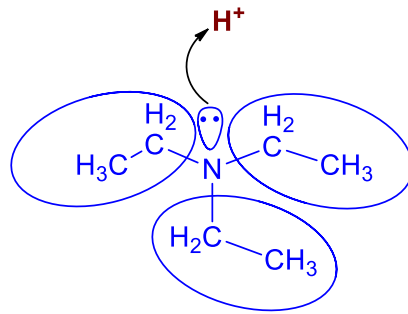
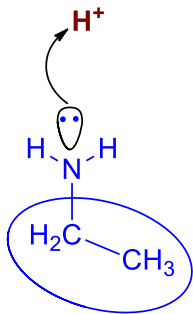


Χρησιμοποιούνται ως βάσεις,  
όχι ως πυρηνόφιλα



Οι επιπλέον  
αλκυλομάδες ενισχύουν  
την πυρρηνοφιλία μέσω +I  
αλλά από κάποιο σημείο  
και έπειτα λειτουργούν  
υπονομευτικά λόγω του  
στερικού συνωστισμού  
που εισάγουν

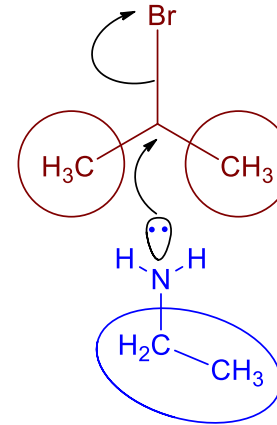
## Βασικότητα



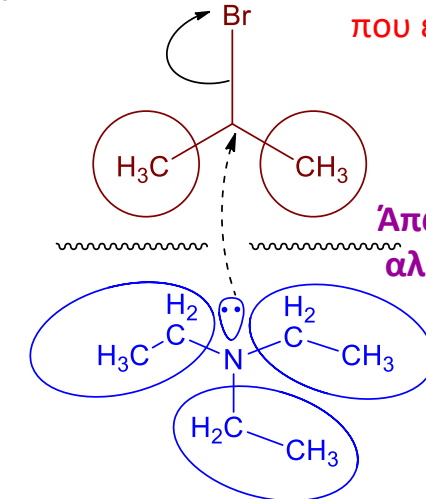
Το πρωτόνιο είναι αμελητέου όγκου και απαρεμπόδιστο.

Οι επιπλέον αλκυλομάδες ενισχύουν τη βασικότητα του N μέσω +I και δεν παρεμποδίζουν τη σύλληψη του εξαιρετικά μικρού πρωτονίου

## Πυρρηνοφιλία



Ευνοείται η προσέγγιση  
του πυρηνόφιλου



Δυσχεραίνεται η προσέγγιση  
του πυρηνόφιλου

Απωση μεταξύ  
αλκυλομάδων



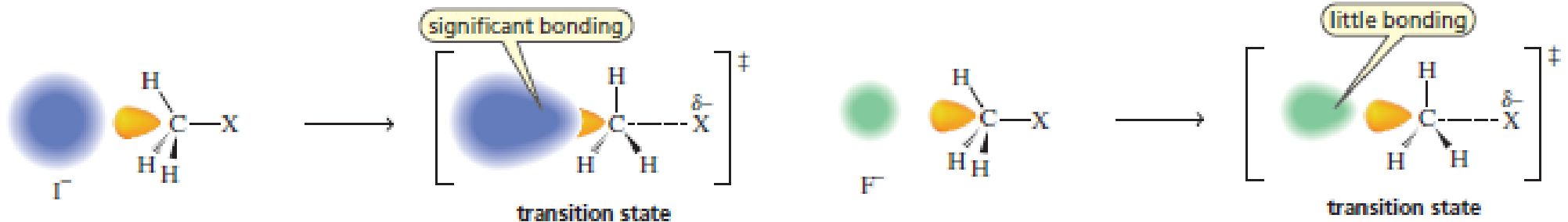
# Παράγοντες που επηρεάζουν την αντίδραση $S_{N2}$ – Πολωσιμότητα στοιβάδων πυρηνόφιλου

The larger ions have more diffuse electrons (higher polarizability) and are less strongly solvated by hydrogen bonding. They also have HOMOs of higher energy which can overlap more effectively at greater distances with the LUMO of the electrophilic carbon leading to stronger orbital interactions in the transition structures.

Nucleophilicity:	$I^- > Br^- > Cl^- > F^-$	$RS^- > RO^-$	$RSH > ROH$	$R_3P > R_3N$
Basicity:	$F^- > Cl^- > Br^- > I^-$	$RO^- > RS^-$		

Πολωσιμότητα στοιβάδων:  
Αυξάνει την πυρηνοφιλία  
(Αντιστρόφως για τη βασικότητα)

Συγκρίνοντας  
άτομα της ίδιας  
ομάδας στον Π. Π.



Τα ηλεκτρόνια σθένους του ανιόντος ιωδίου βρίσκονται σε πολύ μεγαλύτερη στιβάδα και μακρύτερα από τον πυρήνα συνεπώς συγκρατούνται χαλαρά από αυτόν. Αυτό καθιστά μια τέτοια στιβάδα πολώσιμη δηλαδή εύπλαστη/ελαστική με τα ηλεκτρόνια να μετατοπίζονται ευκολότερα προς  $\delta^+$  περιοχές. Έτσι, όταν μία πολώσιμη στιβάδα προσεγγίζει έναν ηλεκτρονιόφιλο άνθρακα, τα ηλεκτρόνια έλκονται και διαχέονται εύκολα προς αυτόν, αλληλεπιδρώντας με (γεμίζοντας την)  $\sigma^*$  (LUMO) του δεσμού C-X με αποτέλεσμα τη σταδιακή αποβολή του  $X^-$ . Τα αντίστοιχα ηλεκτρόνια σθένους του ανιόντος φθορίου βρίσκονται σε πολύ μικρότερες στιβάδες και πολύ κοντά στον πυρήνα συνεπώς έλκονται ισχυρά και δεν διαχέονται εύκολα προς άλλες  $\delta^+$  περιοχές (άλλους πυρήνες).

## Πυρρηνοφιλία vs Βασικότητα - Σκληρά / μαλακά

Για κάθε  $+/\delta^+$  ή  $-/\delta^-$  σκεφτείτε το λόγο  $Q/S$  όπου  $Q$  το φορτίο και  $S$  η επιφάνεια στην οποία βρίσκεται κατανεμημένο

Ένα  $+/\delta^+$  ή  $-/\delta^-$  που είναι εντοπισμένο σε πολύ μικρό χώρο (μεγάλο  $Q/S$ ) λέμε ότι είναι σκληρό.

Αντίθετα, ένα  $+/\delta^+$  ή  $-/\delta^-$  που είναι διεσπαρμένο σε μεγάλη επιφάνεια (μικρό  $Q/S$ ) λέμε ότι είναι μαλακό.

Για παράδειγμα ένα ανιόν ιωδίου  $I^-$  ή το  $\delta^-$  ενός ζεύγους  $e^-$  φωσφόρου σε μία φωσφίνη  $R_3P$ , είναι μαλακά διότι τα εν λόγω  $-/\delta^-$  είναι κατανεμημένα ομοιόμορφα σε μεγάλες στοιβάδες (μεγάλη επιφάνεια = μικρό πηλίκο  $Q/S$ ). Αντίθετα ένα ανιόν φθορίου  $F^-$  ή το  $\delta^-$  ενός ζεύγους  $e^-$  οξυγόνου σε μία αλκοόλη  $ROH$  είναι σκληρά διότι τα εν λόγω  $-/\delta^-$  είναι συγκεντρωμένα σε πολύ μικρό χώρο (μικρή επιφάνεια = μεγάλο πηλίκο  $Q/S$ ).

Αντίστοιχα, το  $\delta^+$  άτομο υδρογόνου στο  $H-Cl$  είναι σκληρό (το  $\delta^+$  εντοπισμένο σε απειροελάχιστο χώρο = μεγάλο πηλίκο  $Q/S$ ) ενώ το  $\delta^+$  ενός ατόμου άνθρακα όπως στο  $CH_3-Cl$  είναι μαλακό διότι είναι κατανεμημένο σε μεγαλύτερο άτομο/επιφάνεια

Γενικά ισχύει ότι τα σκληρά  $-/\delta^-$  αντιδρούν με τα σκληρά  $+/\delta^+$  και τα μαλακά  $-/\delta^-$  αντιδρούν με τα μαλακά  $+/\delta^+$

Για παράδειγμα, αν στο σκληρό ανιόν υδροξειδίου παρουσιάζονταν ένα  $H-Cl$  (σκληρό  $\delta^+$ ) και ένα  $CH_3-Cl$  (μαλακό  $\delta^+$ ), το υδροξείδιο θα αντιδρούσε ταχύτερα με το  $H-Cl$  ενώ το πολύ μεγαλύτερο/μαλακότερο/πολώσιμο  $I^-$  θα επέλεγε το  $CH_3-Cl$ .

Τα σκληρά  $-/\delta^-$  συμπεριφέρονται περισσότερο ως βάσεις (αντίδραση με τα σκληρά  $H +/\delta^+$ ) ενώ τα μαλακά  $-/\delta^-$  συμπεριφέρονται περισσότερο ως πυρηνόφιλα (αντιδρούν κυρίως με τα μαλακότερα  $+/\delta^+$  μεγαλύτερων ατόμων όπως ο  $C$ ).

## Παράγοντες που επηρεάζουν την αντίδραση $S_N2$ – Επίδραση του Διαλύτη

### (a) Protic solvents (polar to weakly polar)


$\text{H}_2\text{O}$ (80)	$\text{CH}_3\text{OH}$ (32)	$\text{C}_2\text{H}_5\text{OH}$ (25)	$\text{HCO}_2\text{H}$ (58)	$\text{CH}_3\text{CO}_2\text{H}$ (6.2)	$\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NHCH}_3$ (182)
water	methanol	ethanol	methanoic acid (formic acid)	ethanoic acid (acetic acid)	<i>N</i> -methyl formamide (NMF)

### (b) Polar aprotic solvents

$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$ (21)	$\text{CH}_3\text{CN}$ (36)	$\text{H}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2$ (37)	$\text{CH}_3-\overset{\text{O}}{\parallel}{\text{S}}-\text{CH}_3$ (47)
propanone (acetone)	ethanenitrile (acetonitrile)	<i>N,N</i> -dimethyl formamide (DMF)	diimethyl sulfoxide (DMSO)

Εξαιρετικοί  
διαλύτες για  
αντιδράσεις  $S_N2$

### (c) Aprotic solvents (nonpolar to weakly polar)

$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$ (1.9)	$\text{C}_6\text{H}_6$ (2.4)	$\text{CHCl}_3$ (4.9)	$(\text{C}_2\text{H}_5)_2\text{O}$ (4.4)	 (7.5)
hexane	benzene	trichloromethane (chloroform)	diethyl ether	tetrahydrofuran (THF)

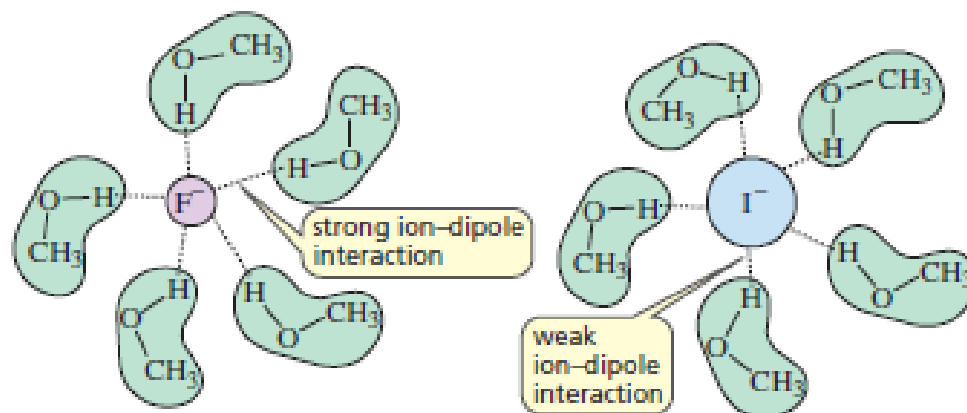
Στις παρενθέσεις αναγράφεται η διηλεκτρική σταθερά ( $\epsilon$ ) του κάθε διαλύτη (μέτρο πολικότητας)

## Παράγοντες που επηρεάζουν την αντίδραση $S_N2$ – Επίδραση του Διαλύτη

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**.

Σκληρά  $-/\delta^-$  ( $RO^-$ ,  $F^-$ ,  $Cl^-$ )  
συνάπτουν  
ισχυρούς δεσμούς υδρογόνου  
με τα σκληρά  $H^{\delta+}$  ενός  
πρωτικού διαλύτη και έτσι  
«παγιδεύονται» εμφανίζοντας  
ελαττωμένη δραστηριότητα ως  
πυρηνόφιλα σε αυτόν.

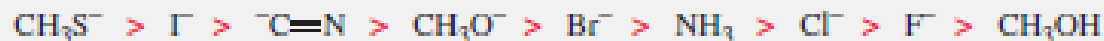


Μαλακά  $-/\delta^-$  ( $RS^-$ ,  $I^-$ ) δεν  
συνάπτουν ισχυρούς δεσμούς  
υδρογόνου με τα σκληρά  $H^{\delta+}$  ενός  
πρωτικού διαλύτη. Αποτέλεσμα  
είναι να μην «αγκιστρώνονται»  
από το διαλύτη και να εμφανίζουν  
αυξημένη δραστηριότητα ως  
πυρηνόφιλα σε αυτόν

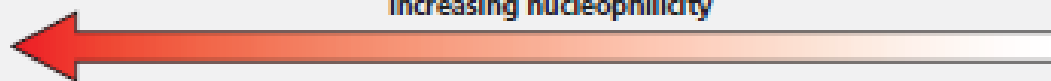
Because the solvent shields the nucleophile, at least one of the ion-dipole interactions must be broken before the nucleophile can participate in an  $S_N2$  reaction. Weak bases interact weakly with protic solvents, whereas strong bases interact strongly because they are better at sharing their electrons. It is easier, therefore, to break the ion-dipole interactions between an iodide ion (a weak base) and the solvent than between a fluoride ion (a stronger base) and the solvent. In a protic solvent, therefore, an iodide ion, even though it is a weaker base, is a better nucleophile than a fluoride ion (Table 9.2).

# Παράγοντες που επηρεάζουν την αντίδραση $S_{N2}$ – Επίδραση του Διαλύτη

**Table 9.2** Relative Nucleophilicity toward  $\text{CH}_3\text{I}$  in Methanol

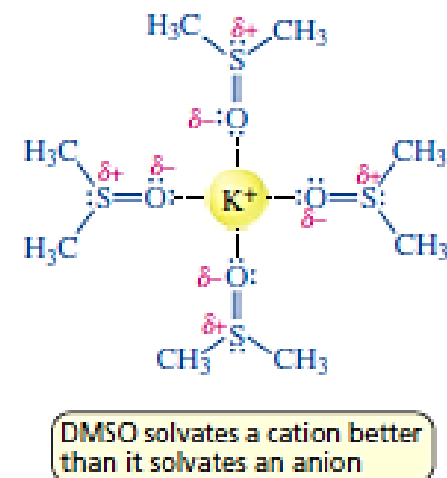
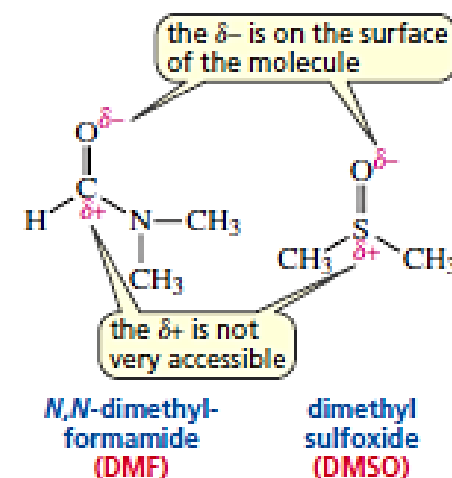


increasing nucleophilicity

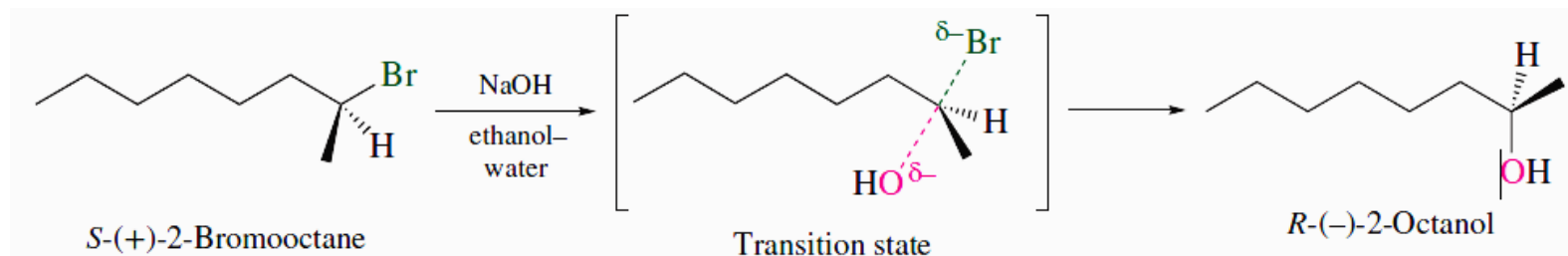


An **aprotic polar solvent** does not have any hydrogens with partial positive charges to form ion-dipole interactions. The molecules of an aprotic polar solvent (such as DMF or DMSO) have a partial negative charge on their surface that can solvate cations, but the partial positive charge is on the *inside* of the molecule and, therefore, less accessible to solvate anions. Thus, fluoride ion is a good nucleophile in DMSO and a poor nucleophile in water.

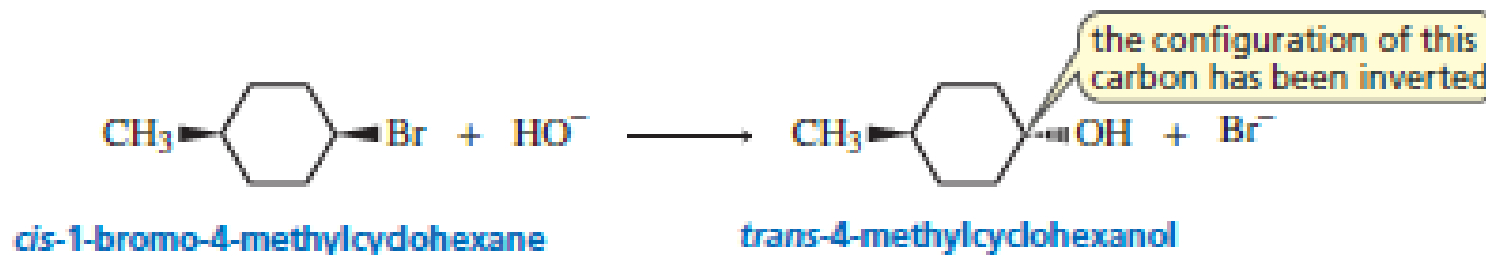
The anion in such solvents is sometimes described as 'naked' and often very reactive as a nucleophile (and base); consequently, polar aprotic solvents are generally excellent for reactions of nucleophiles such as  $S_{N2}$  reactions.



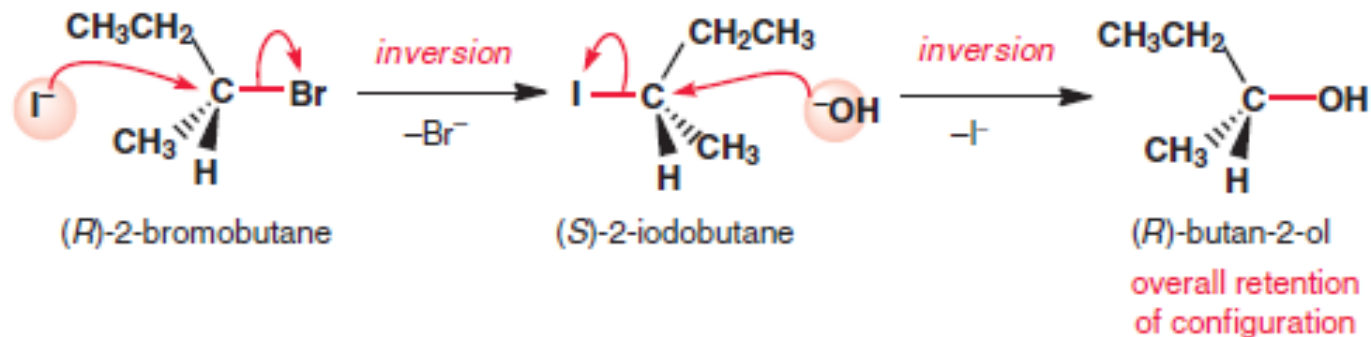
## Στεreoχημεία αντιδρώντων/προϊόντων στην αντίδραση $S_N2$



Στην  $S_N2$  λόγω της γεωμετρικής προϋπόθεσης για την επίτευξη του μεταβατικού σταδίου, στο προϊόν παρατηρείται αντιστροφή της στεreoχημείας του άνθρακα που υπέστη αντικατάσταση.

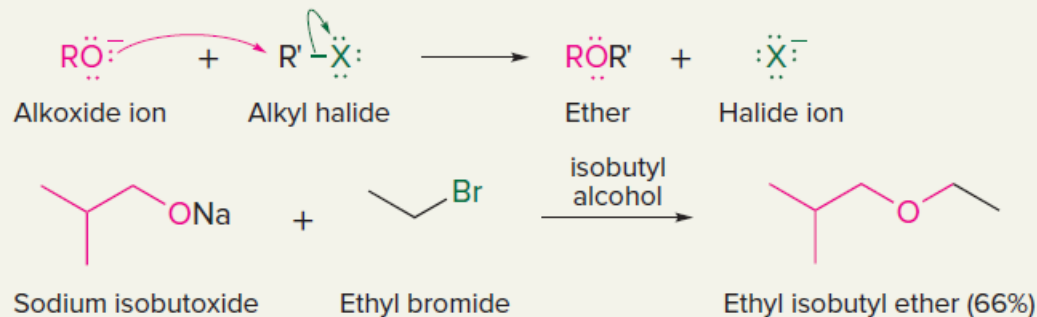


Αυτό συμβαίνει σε κάθε  $S_N2$  συνεπώς αν πραγματοποιηθούν δύο διαδοχικές αντιδράσεις  $S_N2$  σε ένα υπόστρωμα θα έχουμε συνολικά διατήρηση της αρχικής στεreoχημείας

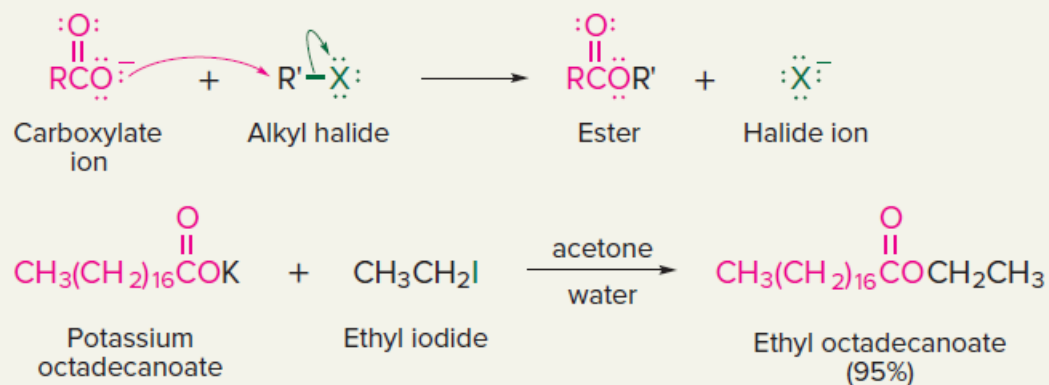


## Παραδείγματα αντιδράσεων S<sub>N</sub>2

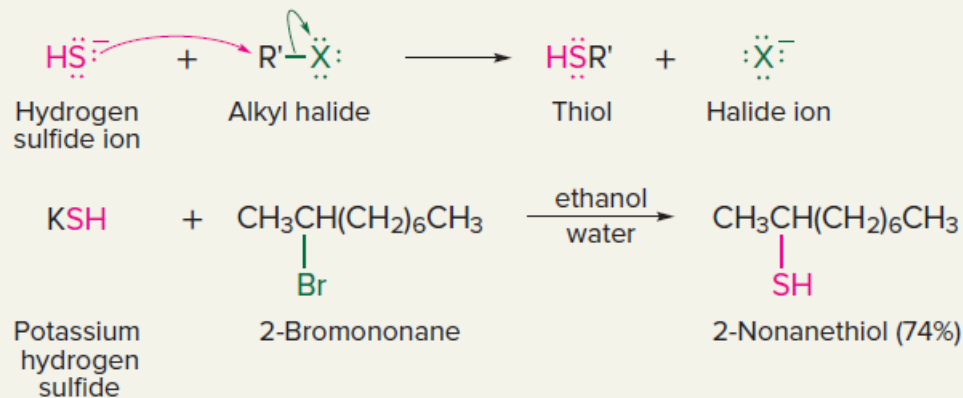
**Alkoxide ion:** The oxygen atom of a metal alkoxide is nucleophilic and replaces the halogen of an alkyl halide. The product is an *ether*.



**Carboxylate ion:** An ester is formed when the negatively charged oxygen of a carboxylate replaces the halogen of an alkyl halide.



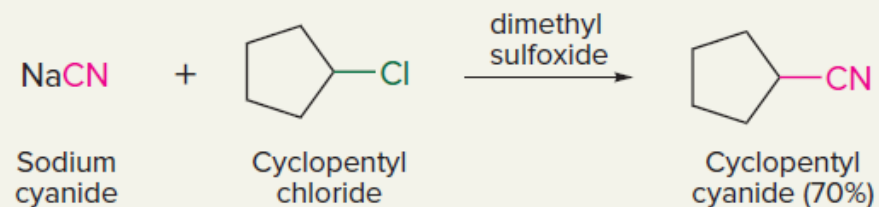
**Hydrogen sulfide ion:** Using hydrogen sulfide as a nucleophile permits the conversion of alkyl halides to *thiols*.



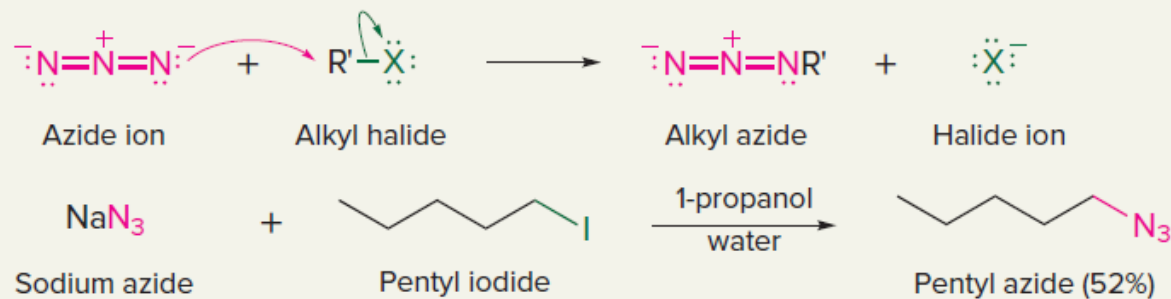


## Παραδείγματα αντιδράσεων S<sub>N</sub>2

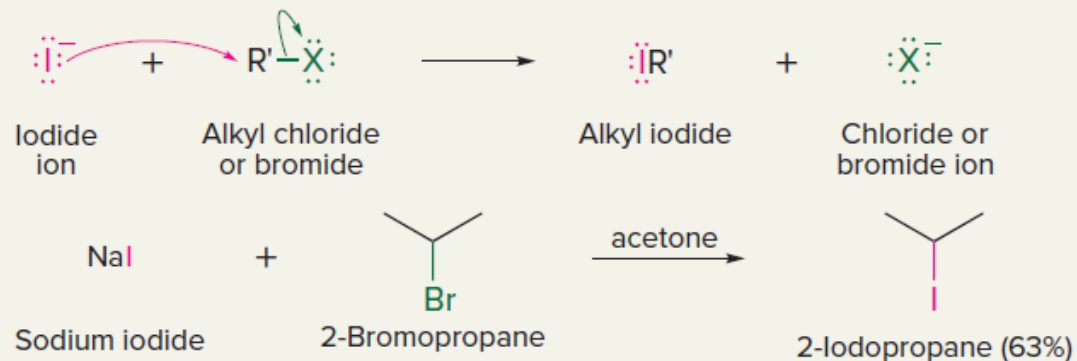
**Cyanide ion:** The negatively charged carbon of cyanide is the site of its nucleophilic character. Cyanide reacts with alkyl halides to extend a carbon chain by forming an *alkyl cyanide* or *nitrile*.



**Azide ion:** Sodium azide makes carbon–nitrogen bonds by converting an alkyl halide to an *alkyl azide*.

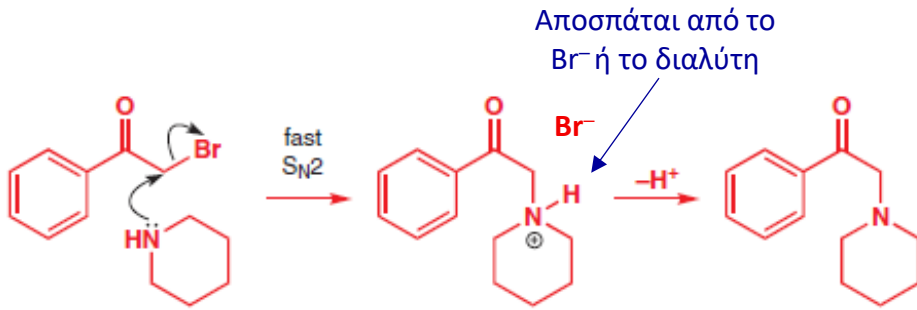


**Iodide ion:** Alkyl chlorides and bromides are converted to *alkyl iodides* by treatment with sodium iodide in acetone. NaI is soluble in acetone, but the NaCl or NaBr that is formed is not and crystallizes from the reaction mixture, making the reaction irreversible.

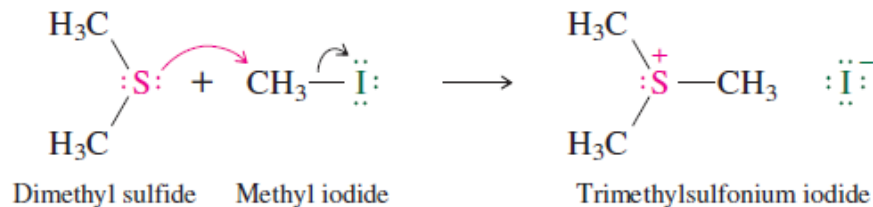


## Μη-φορτισμένα πυρηνόφιλα σε αντιδράσεις S<sub>N</sub>2

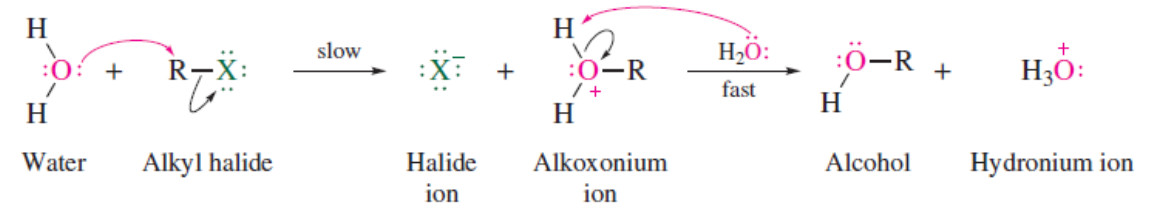
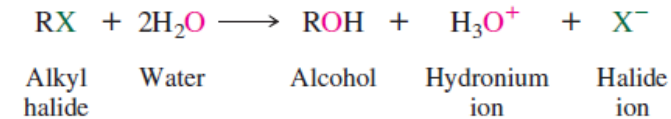
Οι αμίνες, οι φωσφίνες, οι θειόλες και τα σουλφίδια είναι πολύ καλά πυρηνόφιλα και αντιδρούν πολύ αποτελεσματικά στις S<sub>N</sub>2. Όταν ένα ουδέτερο πυρηνόφιλο προσφέρει ζεύγος e σε ένα ηλεκτρονιόφιλο αποβάλλοντας την αποχωρούσα ομάδα X<sup>-</sup>, φορτίζεται θετικά άρα το αρχικό προϊόν είναι ένα άλας. Εάν το πλέον θετικά φορτισμένο πυρηνόφιλο φέρει πρωτόνια τότε μπορεί να αποφορτιστεί αποβάλλοντας ένα πρωτόνιο H<sup>+</sup>



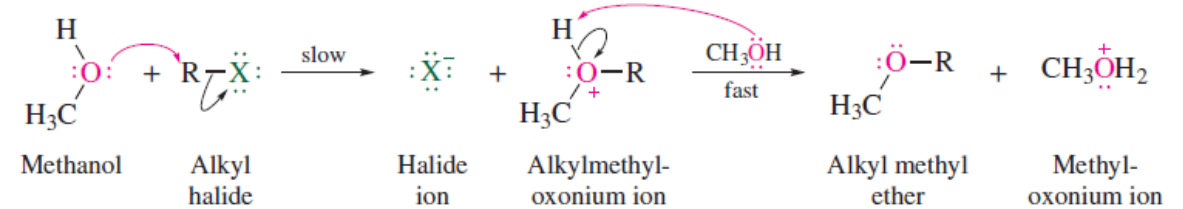
Εάν στο αρχικά σχηματιζόμενο άλας δεν υπάρχει η δυνατότητα αποβολής ενός όξινου πρωτονίου τότε το προϊόν της S<sub>N</sub>2 είναι το άλας.



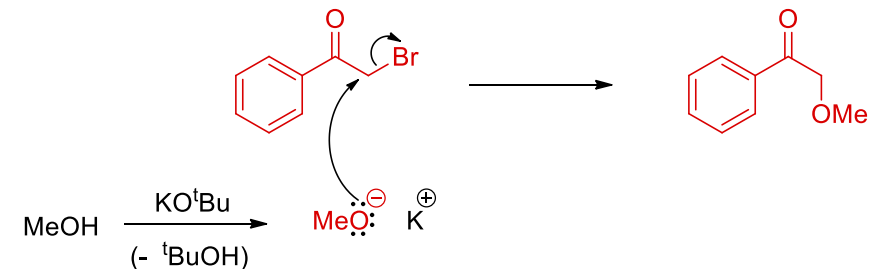
Other common examples of substitutions involving neutral nucleophiles include **solvolysis** reactions—substitutions where the nucleophile is the solvent in which the reaction is carried out. Solvolysis in water (*hydrolysis*) converts an alkyl halide to an alcohol.



Analogous reactions take place in other solvents that, like water, contain an —OH group. Solvolysis in methanol (*methanolysis*) gives a methyl ether.

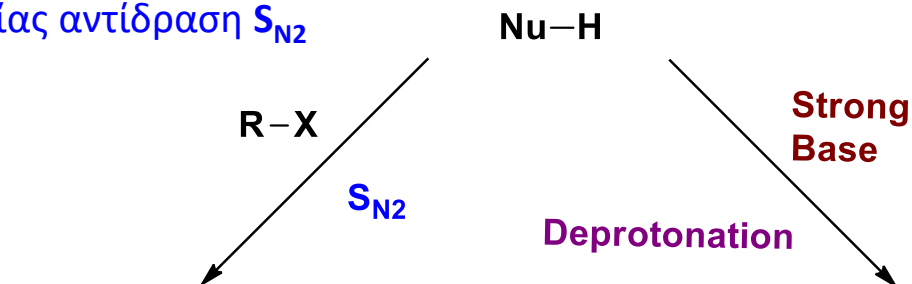


Επειδή τα H<sub>2</sub>O, ROH, ArOH, R-CO<sub>2</sub>H δεν είναι καλά πυρηνόφιλα στην ουδέτερή τους μορφή και οι S<sub>N</sub>2 αντιδράσεις τους είναι αργές, χρησιμοποιούμε κυρίως τα ανιόντα τους.

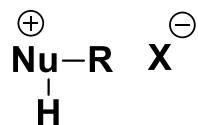


Παρατηρείστε ότι τα καλά πυρηνόφιλα αντιδρούν απευθείας και αργότερα αποπρωτονιώνεται το προϊόν της  $S_N2$  ενώ τα υποδεέστερα πυρηνόφιλα πρέπει πρώτα να αποπρωτονιοθούν προκειμένου να αντιδράσει το αποτελεσματικότερο ανιόν τους

Καλό πυρηνόφιλο π.χ  $RNH_2 \rightarrow$  απευθείας αντίδραση  $S_N2$



Εδώ χρησιμοποιείται μία βάση για να αποπρωτονιώσει το  $Nu-H$  (π.χ.  $H_2O$ ,  $ROH$ ,  $ArOH$ ,  $R-CO_2H$ ) προκειμένου να σχηματιστεί το καλύτερο πυρηνόφιλο  $Nu^-$ . Η βάση πρέπει να έχει εφάμιλλη ή μεγαλύτερη  $pK_a$ , ( $pK_{BH^+}$ ) από την  $pK_a$ , του  $NuH$ .

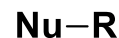


**Deprotonation**

**Mild Base**

$S_N2$

$R-X$



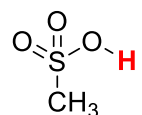
Εδώ χρησιμοποιείται μία ήπια βάση για να αποπρωτονιώσει το όξινο άλας. Αποπρωτονίωση του  $Nu-H$  θα απαιτούσε πολύ ισχυρότερη βάση.

Αντίδραση  $S_N2$  με το ανιόν  $Nu^-$ , όχι με το  $NuH$

# Μετατροπή του υδροξυλίου (OH) των αλκοολών σε αποχωρούσα ομάδα

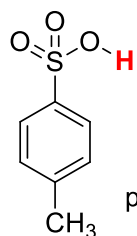
Οι αλκοόλες είναι ευρέως διαθέσιμες και σχετικά φθηνές για αυτό και αποτελούν χρήσιμες πρώτες ύλες /δομικά υλικά στην οργανική σύνθεση. Ωστόσο δεν αποτελούν υποστρώματα για την  $S_N2$  διότι το ανιόν υδροξειδίου ( $OH^-$ ) δεν είναι καλή αποχωρούσα ομάδα. Για να σπάσει ο δεσμός C-O, θα πρέπει το O να μπορεί να σταθεροποιεί επαρκώς το αρνητικό φορτίο που θα αποκτήσει κατά την αποβολή του/εκτόπισή του από ένα πυρηνόφιλο που προσβάλει τον C. Για αυτό, **στο άτομο οξυγόνου** μίας αλκοόλης προσαρτούμε μία ηλεκτραρνητική ομάδα που να έλκει  $e^-$  και να σταθεροποιεί αποτελεσματικότερα το αρνητικό φορτίο σε **αυτό**. Έτσι το **άτομο οξυγόνου** της αλκοόλης ενσωματώνεται σε μία νέα ομάδα που μπορεί να αποκοπεί/αποχωρήσει από τον C. Τέτοιες ομάδες είναι οι σουλφονυλομάδες

Methanesulfonic acid  
**MsOH**



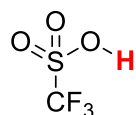
pKa -2.6

*p*-Toluenesulfonic acid  
**TsOH**



pKa -2.8

Trifluoromethanesulfonic acid  
**TfOH**



pKa -6.0

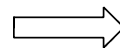
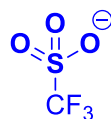
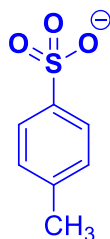
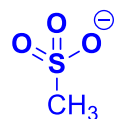
**Strong acids**



Conjugate bases

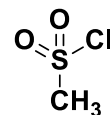


are excellent leaving groups

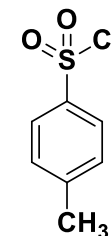


Conversion of alcohols (R-OH) to alkyl sulfonate esters with:

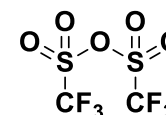
Methanesulfonyl chloride  
**MsCl**



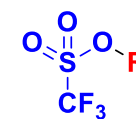
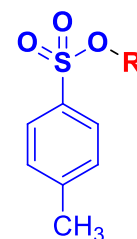
*p*-Toluenesulfonyl chloride  
**TsCl**



Trifluoromethanesulfonic anhydride  
**Tf2O**

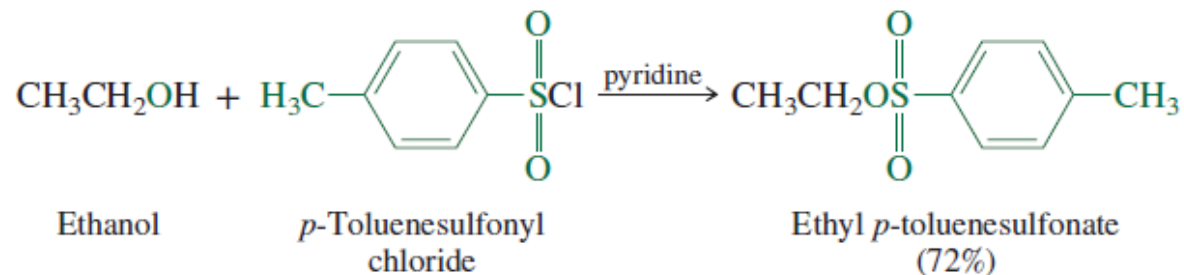


alkyl sulfonate esters are excellent substrates for  $S_N2$  reactions

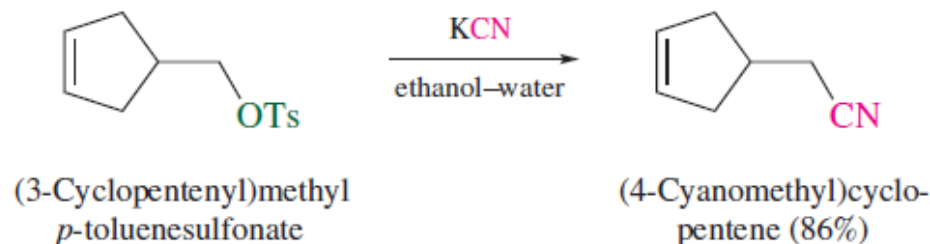


## Σύνθεση αλκυλο σουλφονικών εστέρων - υποστρώματα για S<sub>N</sub>2 από αλκοόλες

Alkyl sulfonates are derivatives of sulfonic acids prepared by treating an alcohol with the appropriate sulfonyl chloride, usually in the presence of pyridine.



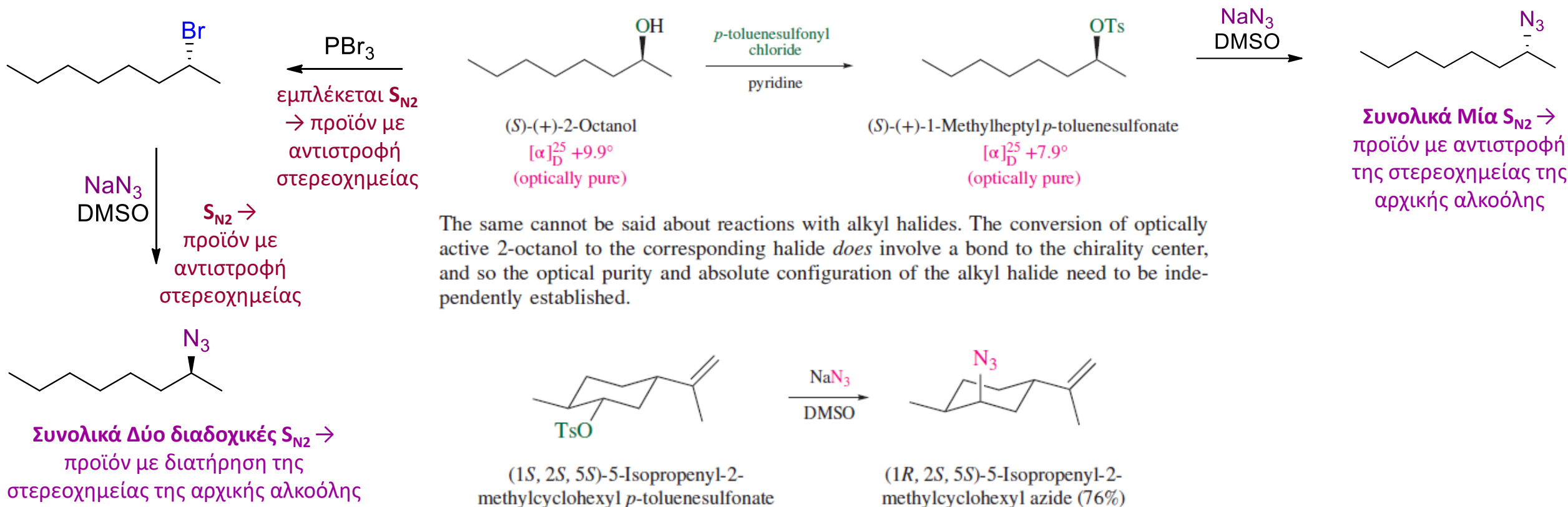
Alkyl sulfonates resemble alkyl halides in their ability to undergo nucleophilic substitution. Those used most frequently are the *p*-toluenesulfonates, commonly known as *tosylates* and abbreviated as ROTs.



As shown in Table 6.6, alkyl tosylates undergo nucleophilic substitution at rates that are even faster than those of the corresponding iodides. Iodide is the weakest base and the best leaving group among the halide anions. Similarly, sulfonate ions rank among the least basic of the oxygen-containing leaving groups. The weaker the base, the better the leaving group. Trifluoromethanesulfonate (*triflate*, CF<sub>3</sub>SO<sub>2</sub>O<sup>-</sup>) is a much weaker base than *p*-toluenesulfonate and is the best leaving group in the table.

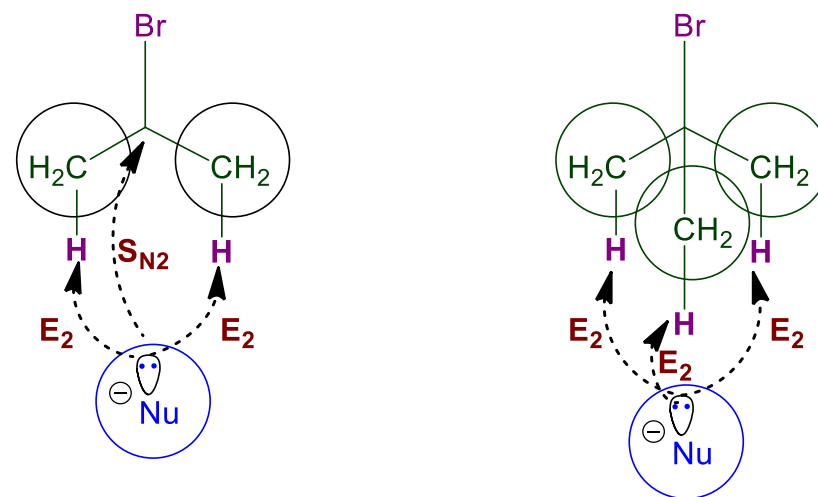
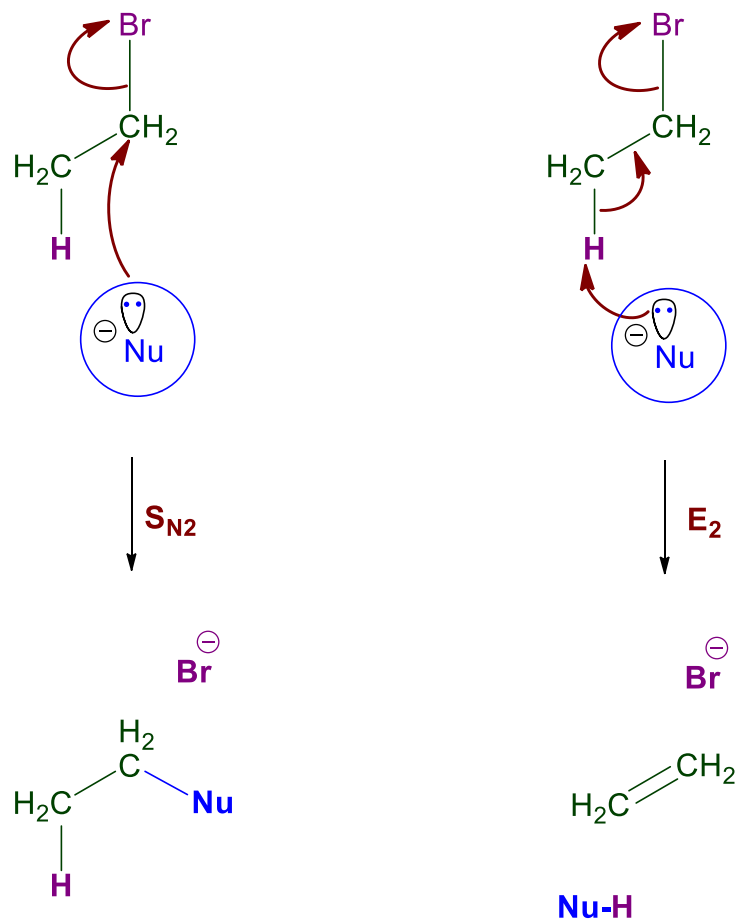
## Υποστρώματα για $S_N2$ από χειρόμορφες αλκοόλες

An advantage that sulfonates have over alkyl halides is that their preparation from alcohols does not involve any of the bonds to carbon. The alcohol oxygen becomes the oxygen that connects the alkyl group to the sulfonyl group. Thus, the stereochemical configuration of a sulfonate is the same as that of the alcohol from which it was prepared. If we wish to study the stereochemistry of nucleophilic substitution in an optically active substrate, for example, we know that a tosylate will have the same configuration and the same optical purity as the alcohol from which it was prepared.



# $S_N2$ vs $E_2$

Δύο πιθανά σενάρια για την αποβολή του  $Br^-$



Όταν η αποχωρούσα ομάδα είναι σε πρωτοταγή άνθρακα ευνοείται περισσότερο η  $S_N2$  γιατί ο άνθρακας είναι προσβάσιμος στο πυρηνόφιλο

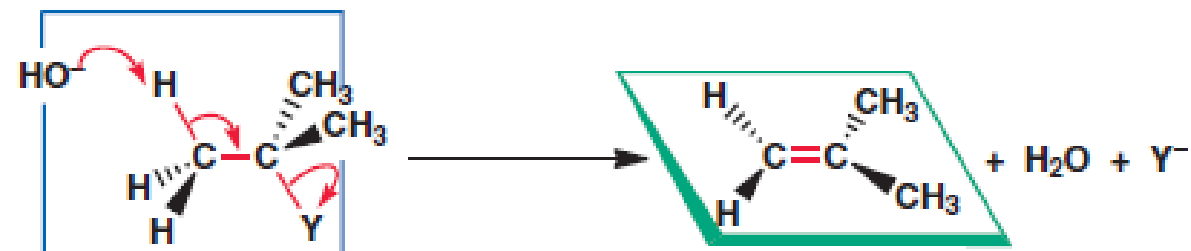
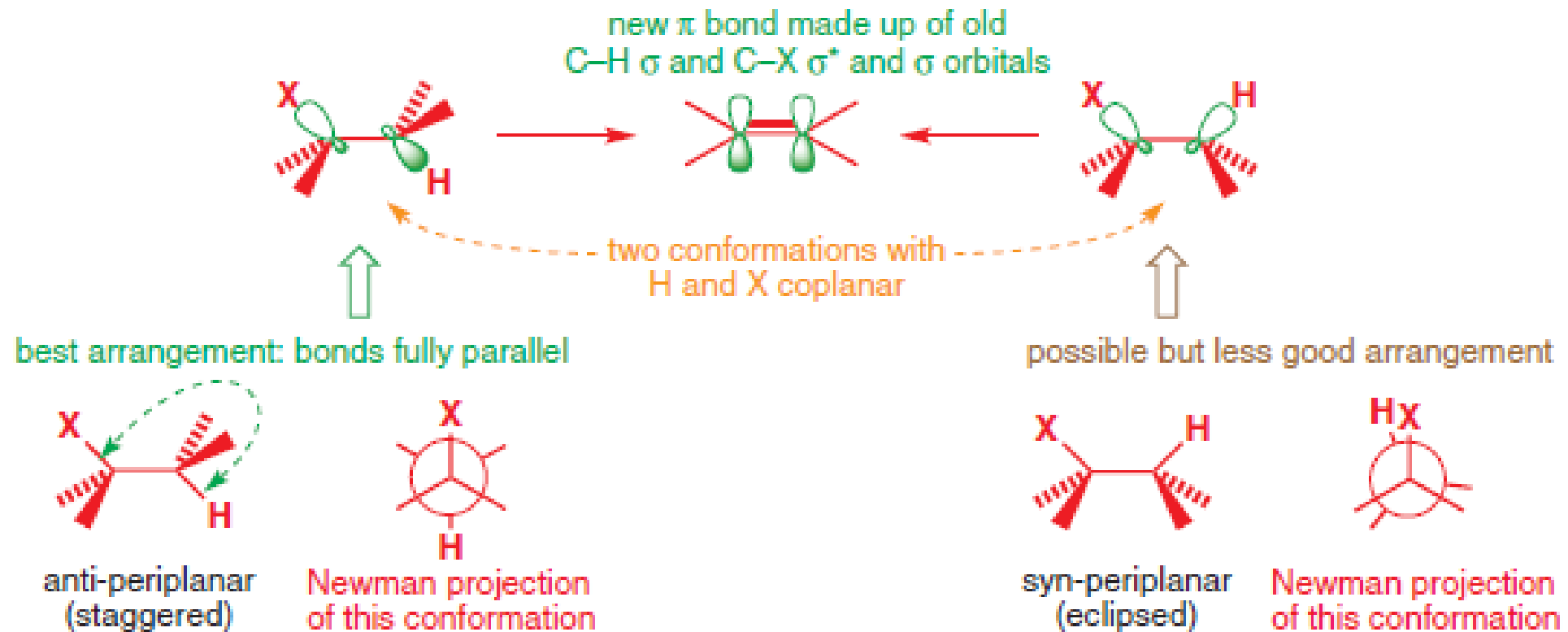
Όταν η αποχωρούσα ομάδα είναι σε δευτεροταγή άνθρακα αρχίζει να ευνοείται και η  $E_2$  γιατί ο άνθρακας γίνεται λιγότερο προσβάσιμος στο πυρηνόφιλο

Όταν η αποχωρούσα ομάδα είναι σε τριτοταγή άνθρακα, λόγω μηδαμινής προσβασιμότητας του πυρηνόφιλου σε αυτόν, είναι αδύνατο να συμβεί  $S_N2$  και παρατηρείται αποκλειστικά  $E2$ .

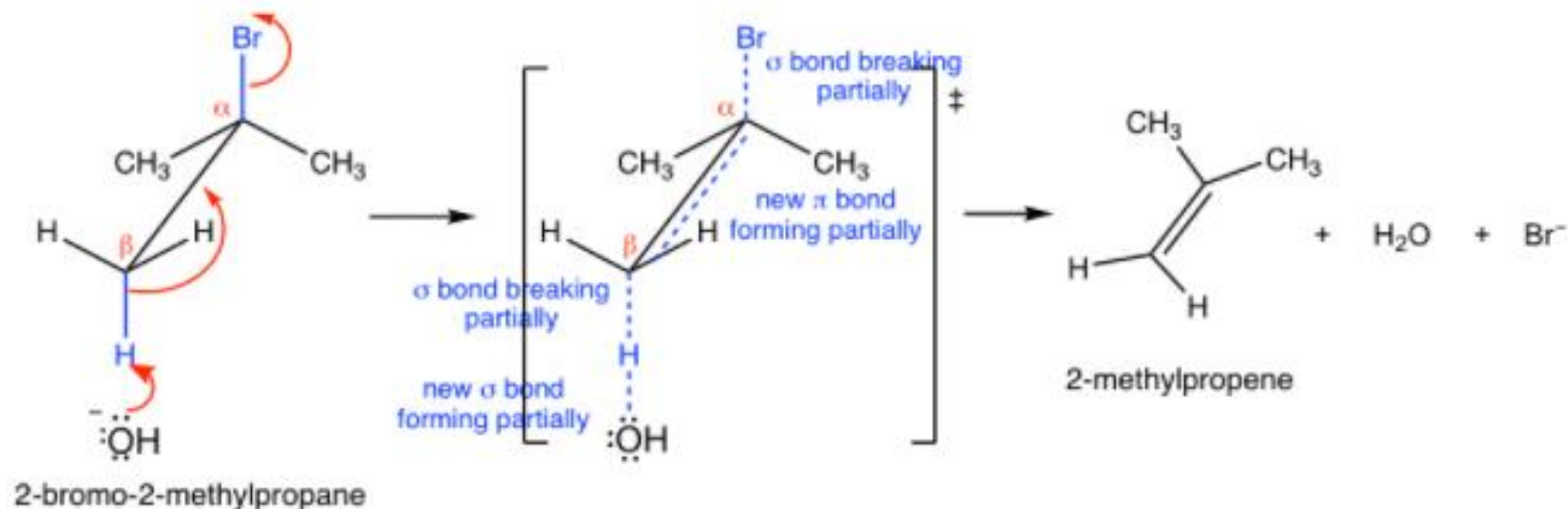
Γενικά, όπου είναι πιθανή τόσο η  $S_N2$  όσο και η  $E_2$  σκληρότερα (βασικότερα) ή/και ογκωδέστερα πυρηνόφιλα δίνουν αυξημένα ποσοστά  $E_2$  (ίσως και αποκλειστικά) ενώ μικρότερα και μαλακότερα δίνουν περισσότερο  $S_N2$  (ίσως και αποκλειστικά).



## Γεωμετρική προϋπόθεση για syn και anti αποσπάσεις



## Η αντίδραση E<sub>2</sub> – Μηχανισμός



Ο σχηματισμός και διάσπαση όλων των εμπλεκόμενων δεσμών γίνεται ταυτόχρονα. Δε σχηματίζεται διακριτό 1<sup>ο</sup> στον β-άνθρακα στην E<sub>2</sub> !

Base, OH<sup>-</sup>, uses its electron pair to attack a β-hydrogen on β-carbon, and starts to form a bond; at the same time, the β C-H sigma bond begins to move in to become the π bond of a double bond, and meanwhile Br begins to depart by taking the bonding electrons with it. A transition state is formed in the reaction process with partially breaking and partially forming bonds. At the completion of the reaction, the C=C double bond and H<sub>2</sub>O molecule are fully formed, with Br<sup>-</sup> leaves completely.

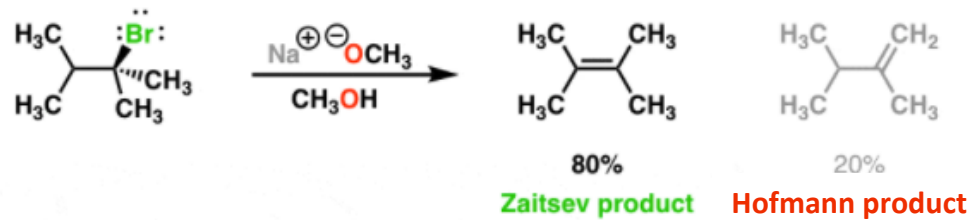
Since both the substrate (halide) and the base are involved in the single-step mechanism, E<sub>2</sub> is the second order reaction.

$$\text{Reaction Rate} = k \times [(\text{CH}_3)_3\text{Br}] \times [\text{OH}^-]$$

**second-order** reaction

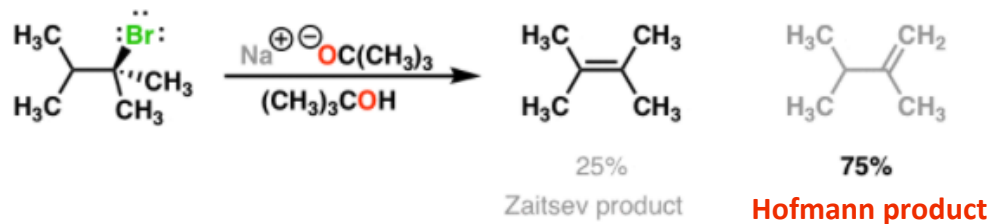
# Η αντίδραση E<sub>2</sub> – Τοποεκλεκτικότητα

Most elimination reactions follow **Zaitsev's rule** : you should expect that the “more substituted” alkene will be formed if at all possible. Like in the elimination reaction below, for instance, we get 80% of the tetrasubstituted alkene [“Zaitsev” – more substituted because there are 4 carbons attached to the alkene] and 20% of the disubstituted Hofmann product (= less substituted alkene)



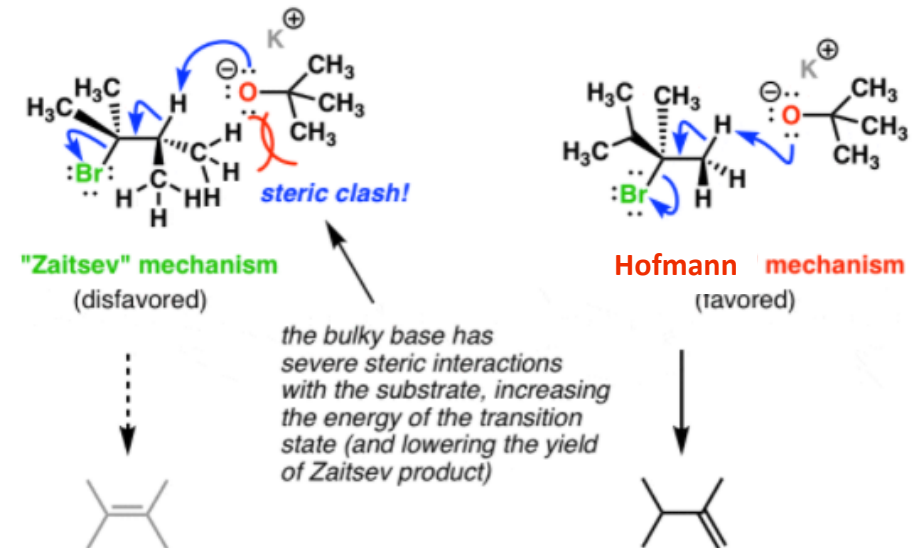
For instance, instead of using sodium methoxide, (NaOCH<sub>3</sub>) if you use the base NaOC(CH<sub>3</sub>)<sub>3</sub> [or KOC(CH<sub>3</sub>)<sub>3</sub>, changing sodium for potassium doesn't really matter here] you end up with an interesting reversal of products!

Changing the base can change the product distribution



in this instance – **potassium t-butoxide** – is an extremely **bulky** base, and the proton we remove to form the Zaitsev product is on a tertiary carbon. As the oxygen from the base draws nearer to this proton, a **steric clash** occurs. In essence the electron clouds around the methyl groups are interacting with each other, and the repulsion between these clouds will raise the energy of the transition state [remember – opposite charges attract, like charges repel]. This will slow down the reaction.

Why the reversal?

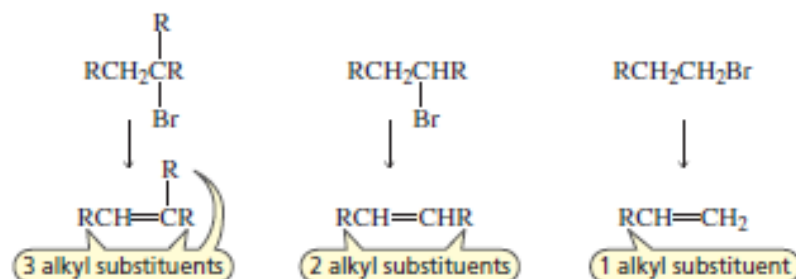


## Relative Reactivities in an E2 Reaction

Because elimination from a tertiary alkyl halide typically leads to a more substituted alkene than does elimination from a secondary alkyl halide, and because elimination from a secondary alkyl halide generally leads to a more substituted alkene than does elimination from a primary alkyl halide, the relative reactivities of alkyl halides in an E2 reaction are:

relative reactivities of alkyl halides in an E2 reaction

tertiary alkyl halide > secondary alkyl halide > primary alkyl halide



Επιρροή αποχωρούσας ομάδας

Table 9.5 Products Obtained From the E2 Reaction of  $\text{CH}_3\text{O}^-$  and 2-Halohexanes

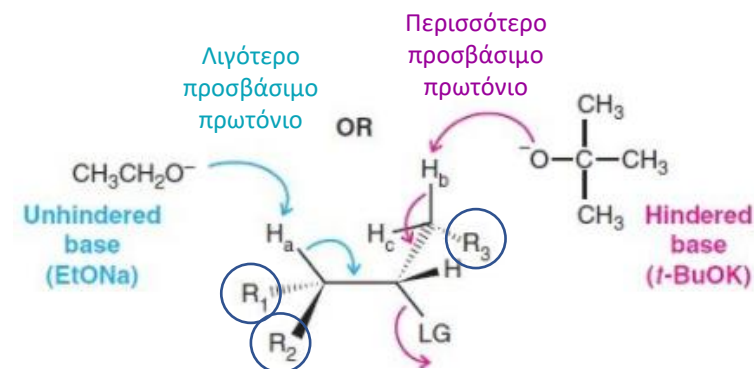
$\text{CH}_3\text{CH}(\text{X})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 + \text{CH}_3\text{O}^- \longrightarrow \text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_3 + \text{CH}_2=\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ <p>(mixture of E and Z)</p>				
Leaving group	Conjugate acid	$\text{p}K_a$	More stable product	Less stable product
X = I	HI	-10	81%	19%
X = Br	HBr	-9	72%	28%
X = Cl	HCl	-7	67%	33%
X = F	HF	3.2	30%	70%

Επιρροή στερικής απαίτησης της βάσης

Table 9.4 Effect of the Steric Properties of the Base on the Distribution of Products in an E2 Reaction

$\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3 + \text{RO}^- \longrightarrow \text{CH}_3\text{C}(\text{CH}_3)=\text{CHCH}_3 + \text{CH}_3\text{CH}(\text{CH}_3)\text{CH}=\text{CH}_2$		
Base	More stable alkene	Less stable alkene
$\text{CH}_3\text{CH}_2\text{O}^-$	79%	21%
$\text{CH}_3\text{CO}^-$	27%	73%
$\text{CH}_3\text{CO}^-$ $\text{CH}_2\text{CH}_3$	19%	81%
$\text{CH}_3\text{CH}_2\text{CO}^-$ $\text{CH}_2\text{CH}_3$	8%	92%

Όσο αυξάνεται η στερική απαίτηση της βάσης τόσο θα κατευθύνεται προς το πιο προσβάσιμο πρωτόνιο δίνοντας το Hofmann προϊόν

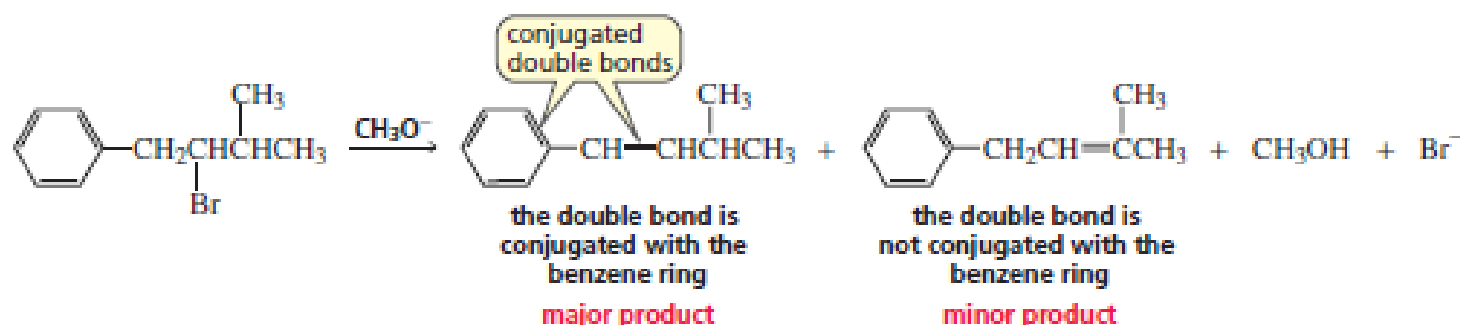
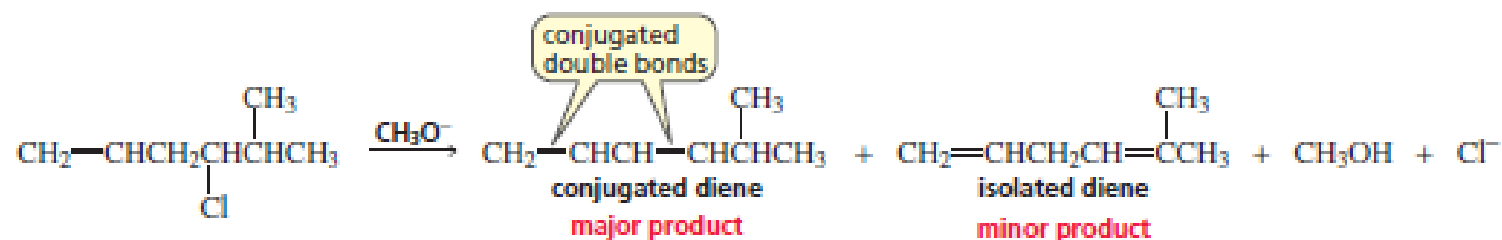


## Limitations of Zaitsev's Rule

You must be careful when using Zaitsev's rule. Keep in mind that the major product of an E2 reaction is generally the *more stable alkene*, and Zaitsev's rule is just a shortcut to determine which of the possible alkene products is the *more substituted alkene*. The more substituted alkene, however, is not always the more stable alkene, and in such cases, Zaitsev's rule cannot be used to predict the major product.

Zaitsev's rule leads to the more substituted alkene.

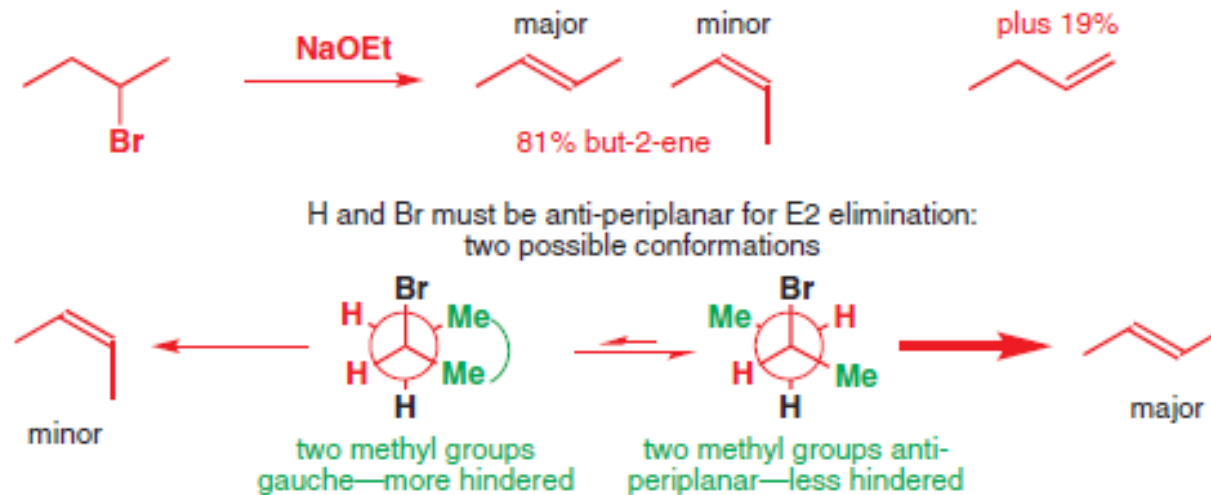
For example, in each of the following reactions, the major product is the alkene with conjugated double bonds because it is the more stable alkene, even though it is not the more substituted alkene.



**Bredt's rule:** Μία αντίδραση απόσπασης δεν μπορεί να δώσει διπλό δεσμό στον οποίο συμμετέχει άνθρακας γέφυρας (εκτός και αυτός περιέχεται σε δακτυλίου άνω του οκταμελούς).

## Η αντίδραση E<sub>2</sub> – Διαστερεοεκλεκτικότητα

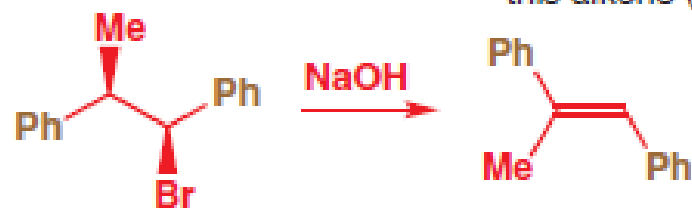
E2 eliminations therefore take place preferentially from the anti-periplanar conformation. We shall see shortly how we know this to be the case, but first we consider an E2 elimination that gives mainly one of two possible stereoisomers. 2-Bromobutane has two conformations with H and Br anti-periplanar, but the one that is less hindered leads to more of the product, and the *E* alkene predominates.



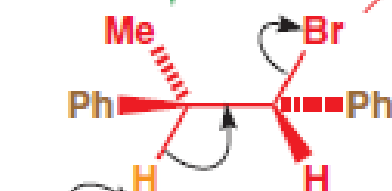
There is a choice of protons to be eliminated—the stereochemistry of the product results from which proton is anti-periplanar to the leaving group when the reaction takes place, and the reaction is stereoselective as a result.

## Η αντίδραση E<sub>2</sub> – Διαστερεοεκλεκτικότητα

this diastereoisomer -----> eliminates to give this alkene (E)



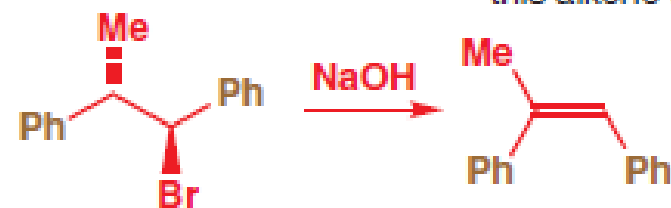
redraw



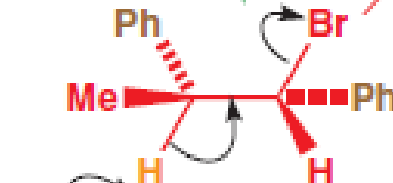
only this proton can be attacked by HO<sup>-</sup>

H and Br must be anti-periplanar

this diastereoisomer -----> eliminates to give this alkene (Z)



redraw



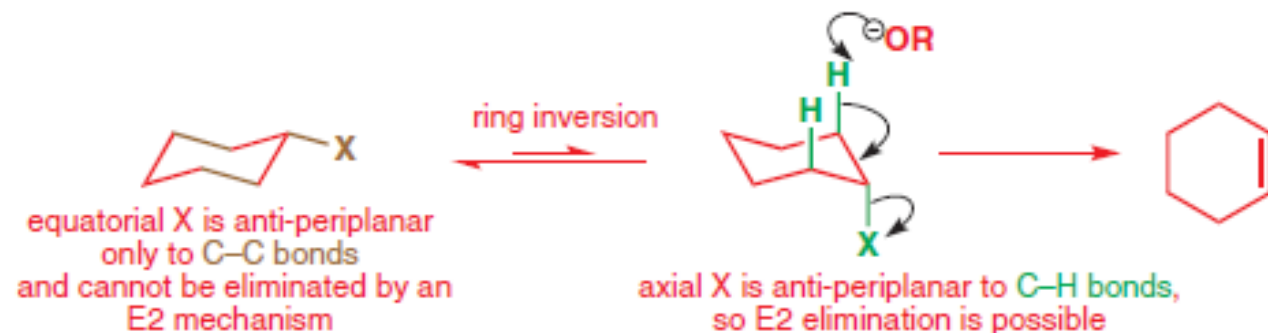
only this proton can be attacked by HO<sup>-</sup>

H and Br must be anti-periplanar

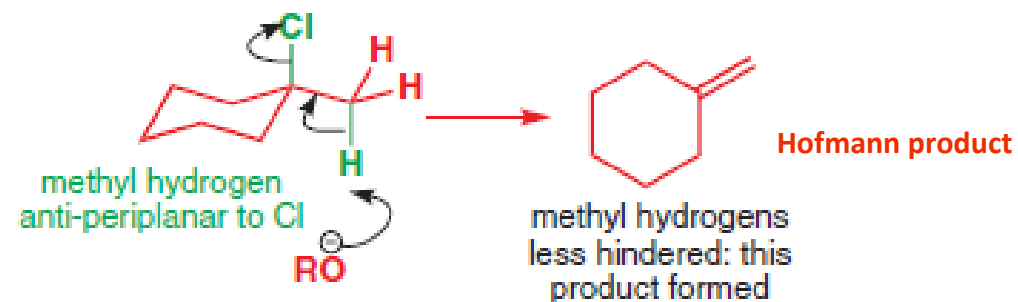
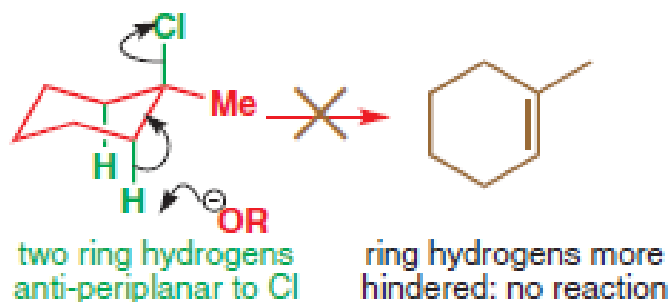
slower: gauche Ph-Ph interactions in reactive conformation



## Η αντίδραση E<sub>2</sub> σε κυκλικά συστήματα



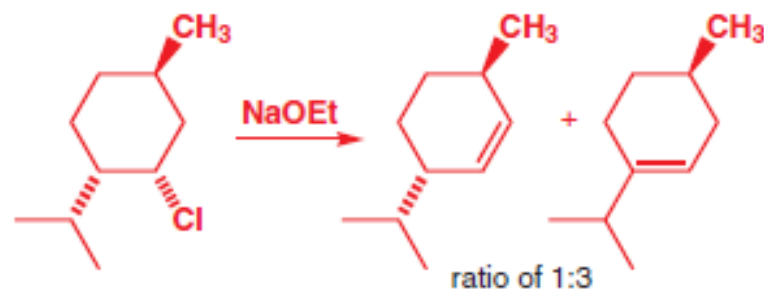
- For E2 elimination in cyclohexanes, both C-H and C-X must be axial.



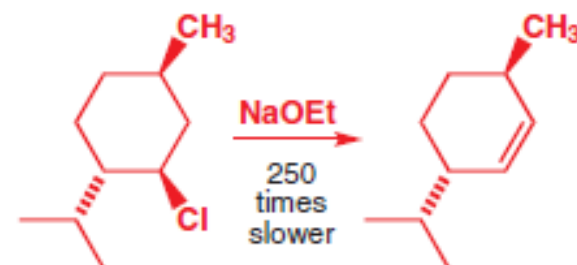
Τα β-πρωτόνια στο δακτύλιο είναι πολύ λιγότερο προσβάσιμα στη βάση.  
Παρατηρείται απόσπαση ενός από τα εξοκυκλικά β-πρωτόνια του μεθυλίου – περισσότερο προσβάσιμα

# Η αντίδραση E<sub>2</sub> σε κυκλικά συστήματα

elimination of diastereoisomer A

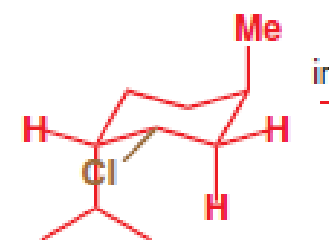


elimination of diastereoisomer B



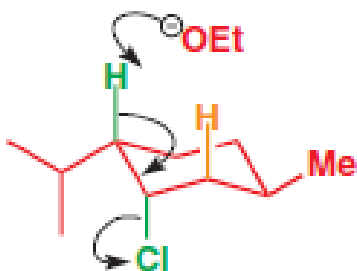
conformation of diastereoisomer A

No C-H bonds anti-periplanar to the C-Cl bond: no elimination



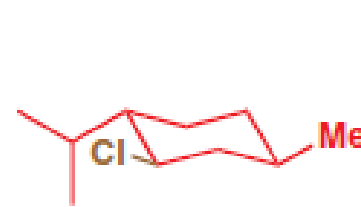
ring inversion

two anti-periplanar C-H bonds: either can eliminate to give different products



conformation of diastereoisomer B

No C-H bonds anti-periplanar to the C-Cl bond: no elimination



ring inversion

one anti-periplanar C-H bond: single alkene formed

