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Substituição Nucleofílica ao Carbono Saturado

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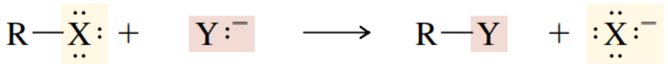

$$R{-}\ddot{\underset{\cdot\cdot}{X}}: + Y:^{-} \longrightarrow R{-}Y + :\ddot{\underset{\cdot\cdot}{X}}:^{-}$$

Alkyl halide

Lewis base

Product of nucleophilic substitution

Halide anion

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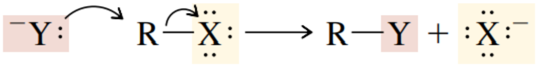
$\overset{\delta+}{R}{-}\overset{\delta-}{X}$ X = I, Br, Cl, F



$$^{-}Y{:} \quad R{-}\ddot{\underset{\cdot\cdot}{X}}{:} \longrightarrow R{-}Y + {:}\ddot{\underset{\cdot\cdot}{X}}{:}^{-}$$

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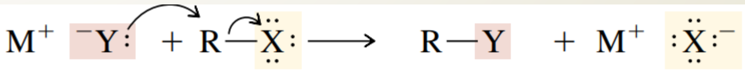
MOR	(a metal *alkoxide,* a source of the nucleophilic anion $R\ddot{\underset{\cdot\cdot}{O}}{:}^{-}$)
$MO\overset{\overset{O}{\|}}{C}R$	(a metal *carboxylate,* a source of the nucleophilic anion $R\overset{\overset{:O:}{\|}}{C}{-}\ddot{\underset{\cdot\cdot}{O}}{:}^{-}$)
MSH	(a metal *hydrogen sulfide,* a source of the nucleophilic anion $H\ddot{\underset{\cdot\cdot}{S}}{:}^{-}$)
MCN	(a metal *cyanide,* a source of the nucleophilic anion $^{-}{:}C{\equiv}N{:}$)
MN_3	(a metal *azide,* a source of the nucleophilic anion ${:}\overset{-}{\underset{\cdot\cdot}{N}}{=}\overset{+}{N}{=}\overset{-}{\underset{\cdot\cdot}{N}}{:}$)



$$M^{+}\ ^{-}Y{:} + R{-}\ddot{\underset{\cdot\cdot}{X}}{:} \longrightarrow R{-}Y + M^{+}\ {:}\ddot{\underset{\cdot\cdot}{X}}{:}^{-}$$

Nucleophilic reagent

Alkyl halide

Product of nucleophilic substitution

Metal halide

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Increasing rate of substitution by nucleophiles

$$\mathrm{RF} \ll \mathrm{RCl} < \mathrm{RBr} < \mathrm{RI}$$

Least reactive — Most reactive

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Mecanismo da reação

$$\underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Hydroxide ion}}{HO^-} \longrightarrow \underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Bromide ion}}{Br^-}$$

$$\text{Rate} = k[CH_3Br][HO^-]$$

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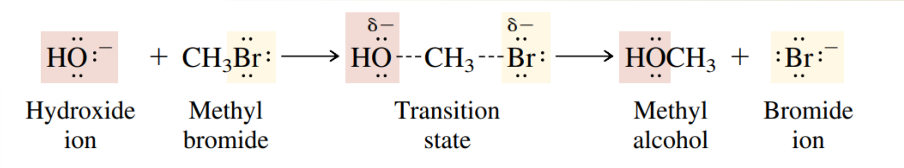

$$HO{:}^{-} + CH_3Br{:} \longrightarrow \overset{\delta-}{HO}\text{---}CH_3\text{---}\overset{\delta-}{Br{:}} \longrightarrow HOCH_3 + {:}Br{:}^{-}$$

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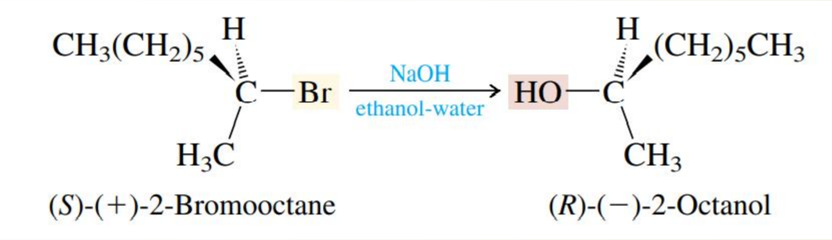
Estereoquímica da S_N



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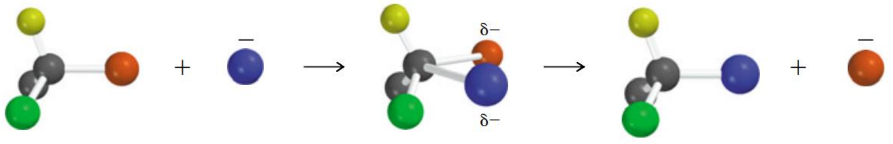
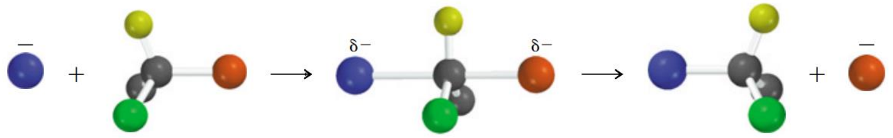
Inversão ou Retenção?



(*a*) Nucleophilic substitution with retention of configuration



(*b*) Nucleophilic substitution with inversion of configuration

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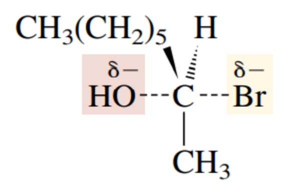
Estado de Transição



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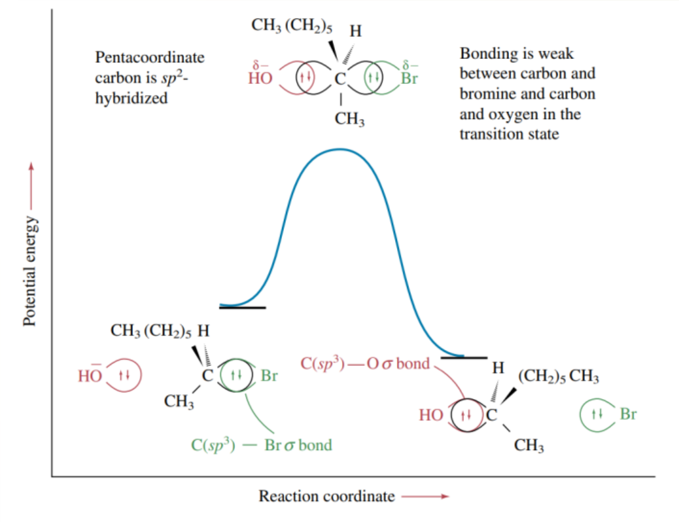
Como ocorre?



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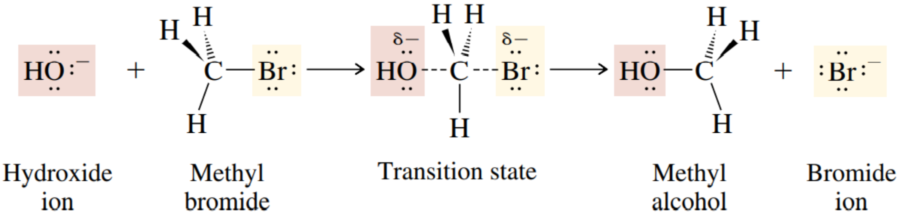

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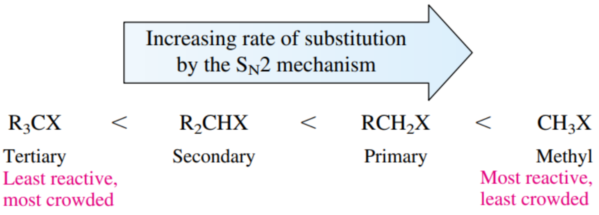
Estereoquímica da S_N2



Increasing rate of substitution by the S_N2 mechanism

R_3CX < R_2CHX < RCH_2X < CH_3X

Tertiary
Least reactive, most crowded

Secondary

Primary

Methyl
Most reactive, least crowded

Reactivity of Some Alkyl Bromides Toward Substitution by the S_N2 Mechanism*

Alkyl bromide	Structure	Class	Relative rate[†]
Methyl bromide	CH_3Br	Unsubstituted	221,000
Ethyl bromide	CH_3CH_2Br	Primary	1,350
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	1
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	Too small to measure

*Substitution of bromide by lithium iodide in acetone.

[†] Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for isopropyl bromide at 25°C.

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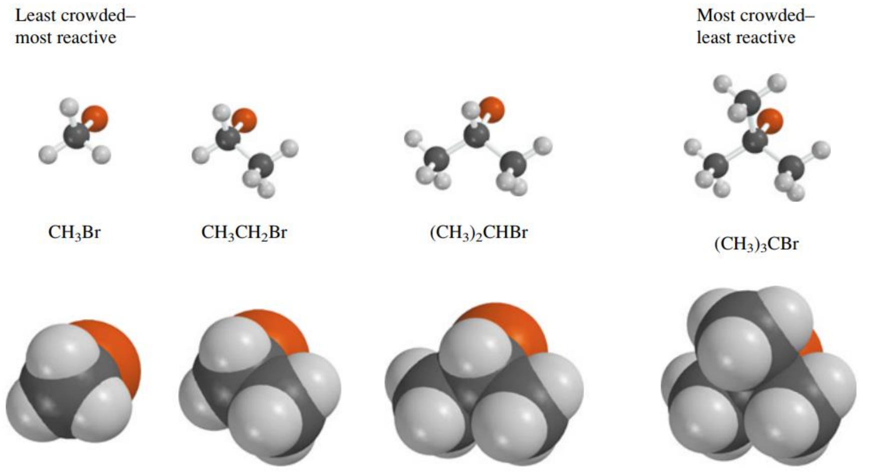
Impedimento Estereoquímico



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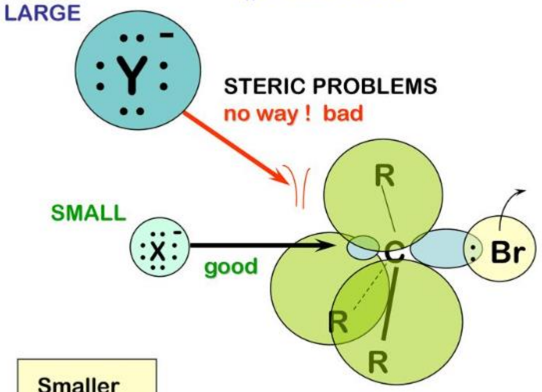
WHAT IS THE IDEAL NUCLEOPHILE ?

S_N2 REACTIONS



Smaller
is better !

For an S_N2 reaction the nucleophile must find the back lobe of the sp^3 hybrid orbital that the leaving group is bonded to.

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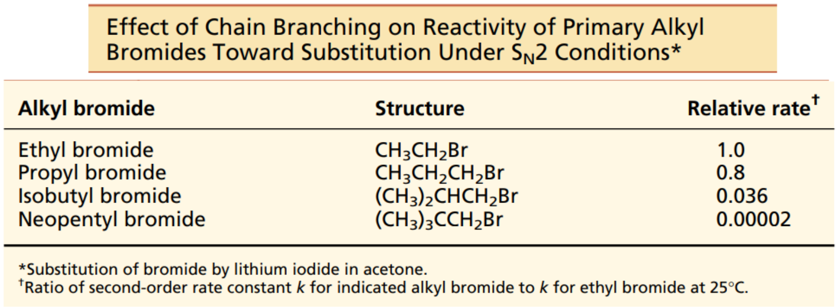


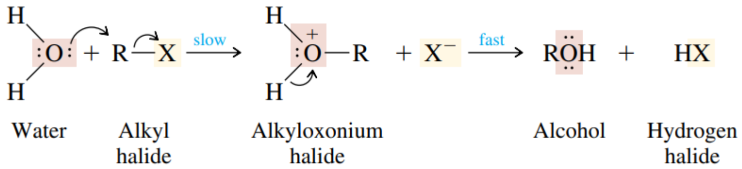
Effect of Chain Branching on Reactivity of Primary Alkyl Bromides Toward Substitution Under S_N2 Conditions*

Alkyl bromide	Structure	Relative rate[†]
Ethyl bromide	CH_3CH_2Br	1.0
Propyl bromide	$CH_3CH_2CH_2Br$	0.8
Isobutyl bromide	$(CH_3)_2CHCH_2Br$	0.036
Neopentyl bromide	$(CH_3)_3CCH_2Br$	0.00002

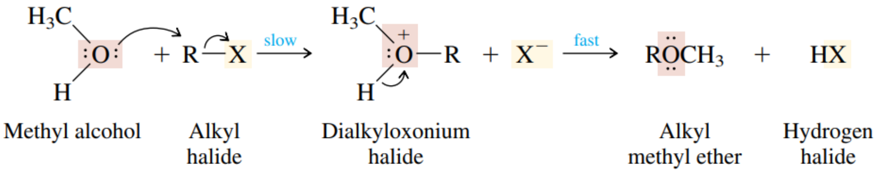
*Substitution of bromide by lithium iodide in acetone.

[†] Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for ethyl bromide at 25°C.

Nucleófilos e Nucleofilia



Solvolysis in *methyl alcohol* converts an alkyl halide to an *alkyl methyl ether.*



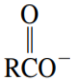
Nucleophilicity of Some Common Nucleophiles

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

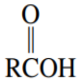
*Relative reactivity is *k*(nucleophile)/*k*(methanol) for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

RO^- is more nucleophilic than ROH

Alkoxide ion — Alcohol


$RC(=O)O^-$

is more nucleophilic than


$RC(=O)OH$

Carboxylate ion — Carboxylic acid

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Mais básico, mais Nu!

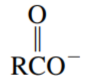
$$\mathbf{Nu}: + R\text{—}\mathbf{L} \longrightarrow R\text{—}\mathbf{Nu}^+ + :\mathbf{L}^-$$

$$\mathbf{Nu}:^- + R\text{—}\mathbf{L} \longrightarrow R\text{—}\mathbf{Nu} + :\mathbf{L}^-$$

$$\mathbf{Nu}: + R\text{—}\mathbf{L}^+ \longrightarrow R\text{—}\mathbf{Nu}^+ + :\mathbf{L}$$

$$\mathbf{Nu}:^- + R\text{—}\mathbf{L}^+ \longrightarrow R\text{—}\mathbf{Nu} + :\mathbf{L}$$

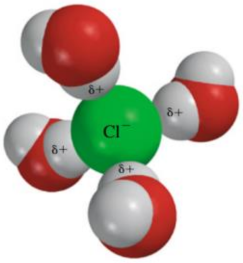
RO^- is more nucleophilic than



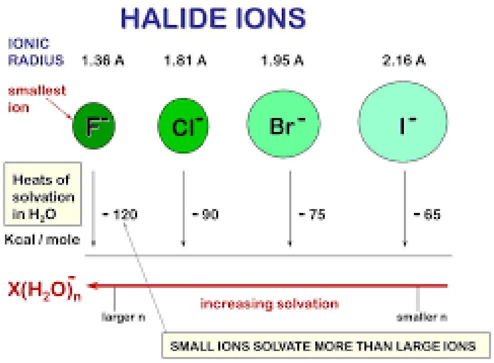
$R\overset{\overset{O}{\|}}{C}O^-$

Stronger base
Conjugate acid is ROH:
$K_a = 10^{-16}$ ($pK_a = 16$)

Weaker base
Conjugate acid is RCO_2H:
$K_a = 10^{-5}$ ($pK_a = 5$)



Solvatação



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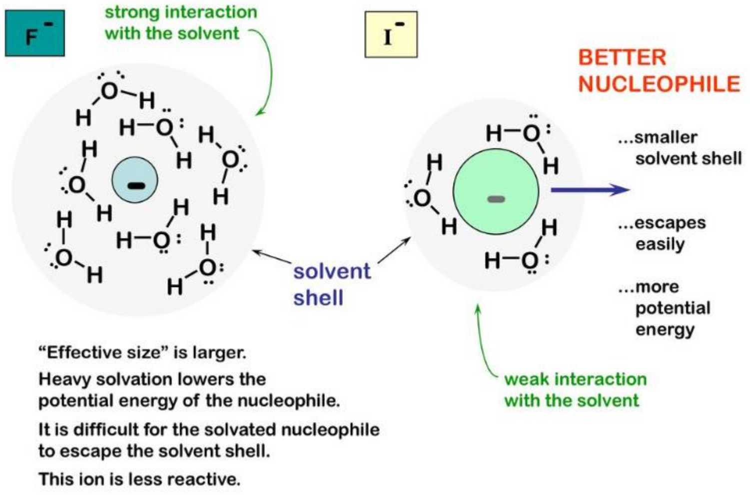
SMALL IONS SOLVATE MORE HEAVILY THAN LARGE ONES



"Effective size" is larger.

Heavy solvation lowers the potential energy of the nucleophile.

It is difficult for the solvated nucleophile to escape the solvent shell.

This ion is less reactive.

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O Mecanismo S_N1

$$\underset{\textit{tert}\text{-Butyl bromide}}{(CH_3)_3CBr} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\textit{tert}\text{-Butyl alcohol}}{(CH_3)_3COH} + \underset{\text{Hydrogen bromide}}{HBr}$$

$$\text{Rate} = k[(CH_3)_3CBr]$$

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O} \xrightarrow{\text{formic acid}} \underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX}$$

S_N1 reactivity: methyl < primary < secondary < tertiary
S_N2 reactivity: tertiary < secondary < primary < methyl

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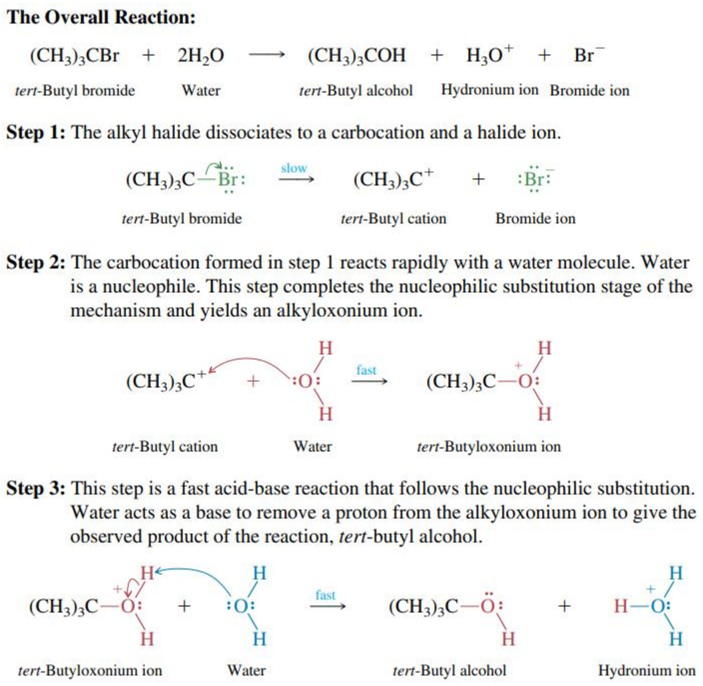

The Overall Reaction:

$(CH_3)_3CBr + 2H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Br^-$

tert-Butyl bromide, Water, *tert*-Butyl alcohol, Hydronium ion, Bromide ion

Step 1: The alkyl halide dissociates to a carbocation and a halide ion.

$(CH_3)_3C{-}\ddot{\underset{..}{Br}}: \xrightarrow{slow} (CH_3)_3C^+ + :\ddot{\underset{..}{Br}}:^-$

tert-Butyl bromide, *tert*-Butyl cation, Bromide ion

Step 2: The carbocation formed in step 1 reacts rapidly with a water molecule. Water is a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an alkyloxonium ion.

$(CH_3)_3C^+ + H_2O: \xrightarrow{fast} (CH_3)_3C{-}\overset{+}{O}H_2$

tert-Butyl cation, Water, *tert*-Butyloxonium ion

Step 3: This step is a fast acid-base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.

$(CH_3)_3C{-}\overset{+}{O}H_2 + H_2O: \xrightarrow{fast} (CH_3)_3C{-}\ddot{O}{-}H + H{-}\overset{+}{O}H_2$

tert-Butyloxonium ion, Water, *tert*-Butyl alcohol, Hydronium ion

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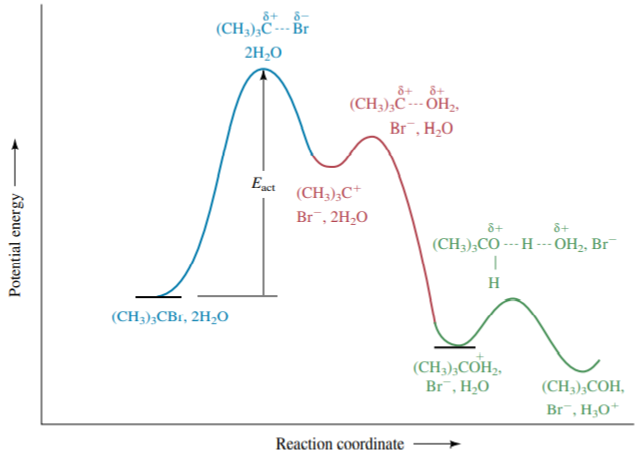
Diagrama de Energia da S_N1



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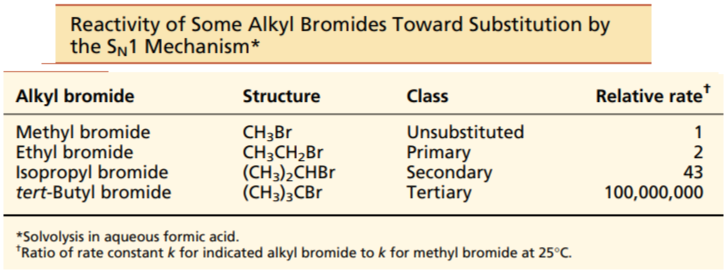

Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism*

Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	1
Ethyl bromide	CH_3CH_2Br	Primary	2
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	43
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	100,000,000

*Solvolysis in aqueous formic acid.
†Ratio of rate constant *k* for indicated alkyl bromide to *k* for methyl bromide at 25°C.

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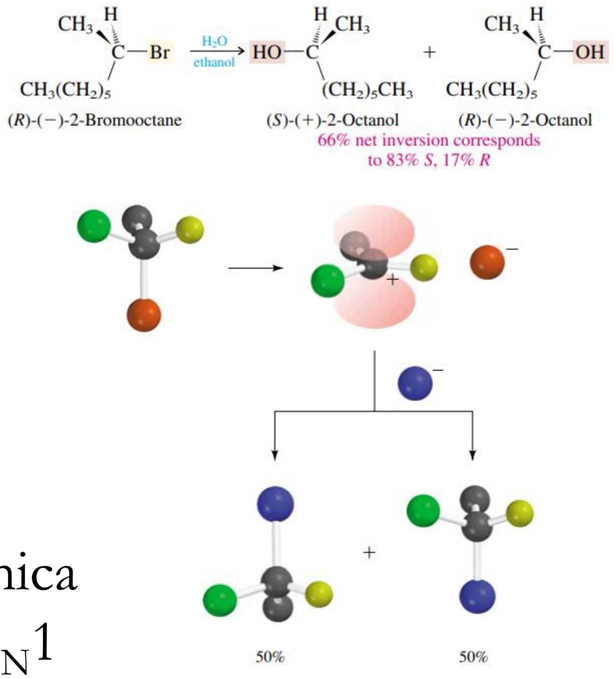
Estereoquímica da reação S_N1



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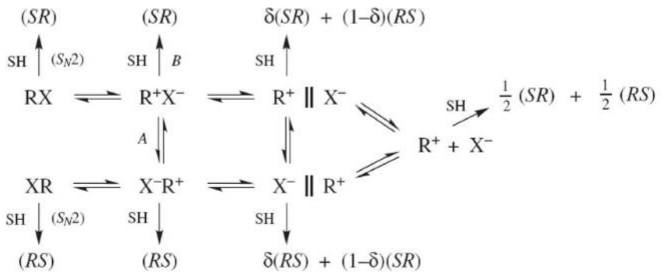
Par-iônico



The ion-pair concept thus predicts that SN1 reactions can display either complete racemization or partial inversion.

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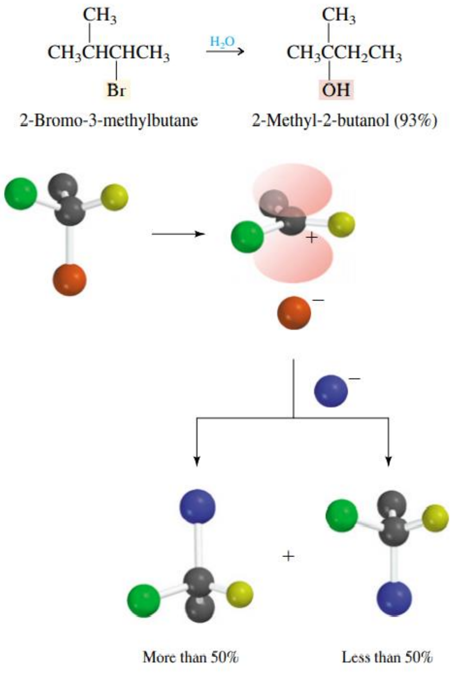
Rearranjo de carbocátion



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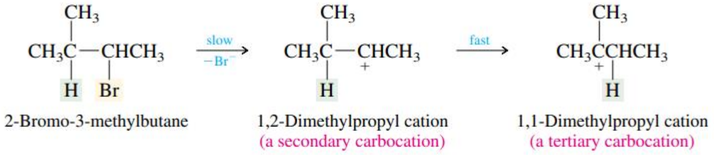
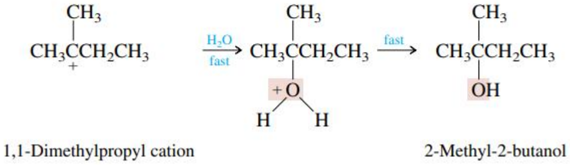
Provável mecanimo



The tertiary carbocation then reacts with water to yield the observed product.



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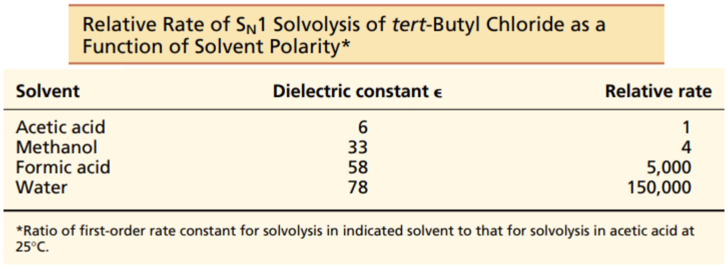
Efeito do Solvente



Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

*Ratio of first-order rate constant for solvolysis in indicated solvent to that for solvolysis in acetic acid at 25°C.

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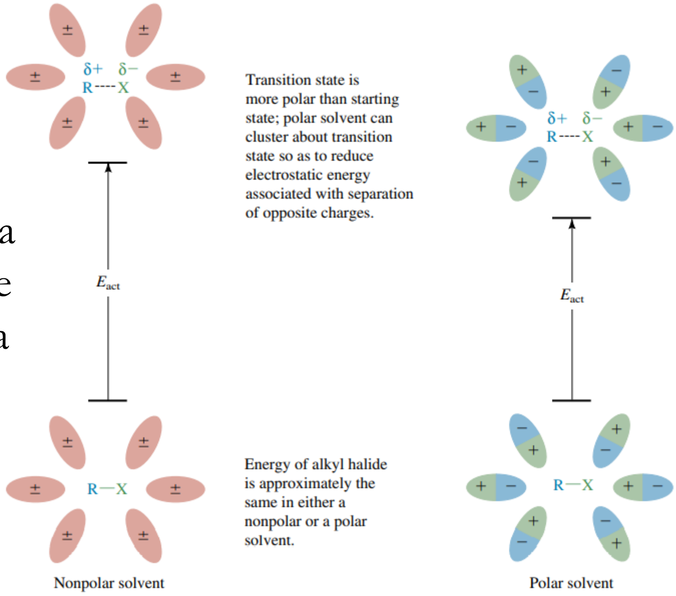
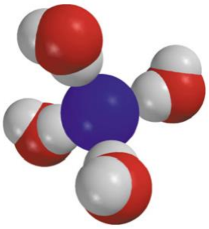
O solvente polar estabiliza o ET da S_N1 e aumenta a sua velocidade



Transition state is more polar than starting state; polar solvent can cluster about transition state so as to reduce electrostatic energy associated with separation of opposite charges.

Energy of alkyl halide is approximately the same in either a nonpolar or a polar solvent.



Efeito do solvente na reação S_N2

$$CH_3CH_2CH_2CH_2Br + N_3^- \longrightarrow CH_3CH_2CH_2CH_2N_3 + Br^-$$

1-Bromobutane Azide ion 1-Azidobutane Bromide ion

Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,N-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

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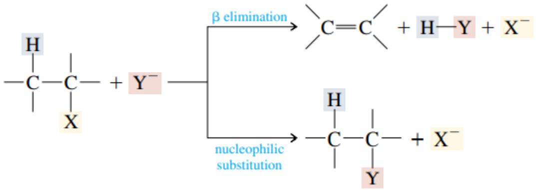
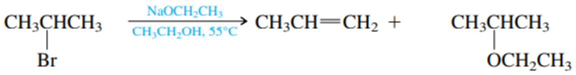
Substituição ou Eliminação?





$$CH_3\underset{Br}{CH}CH_3 \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + CH_3\underset{OCH_2CH_3}{CH}CH_3$$

Isopropyl bromide

Propene (87%)

Ethyl isopropyl ether (13%)

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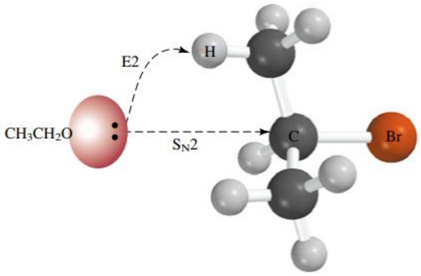

$$CH_3CH_2CH_2Br \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + CH_3CH_2CH_2OCH_2CH_3$$

Propyl bromide

Propene (9%)

Ethyl propyl ether (91%)

$$CH_3(CH_2)_{15}CH_2CH_2Br \xrightarrow[(CH_3)_3COH,\ 40°C]{KOC(CH_3)_3} CH_3(CH_2)_{15}CH{=}CH_2 + CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3$$

1-Bromooctadecane

1-Octadecene (87%)

tert-Butyl octadecyl ether (13%)

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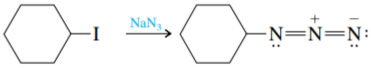
$$\underset{\displaystyle Cl}{CH_3CH}(CH_2)_5CH_3 \xrightarrow[DMSO]{KCN} \underset{\displaystyle CN}{CH_3CH}(CH_2)_5CH_3$$

2-Chlorooctane 2-Cyanooctane (70%)

Cyanide is a weaker base than hydroxide because its conjugate acid HCN (pK_a 9.1) is a stronger acid than water (pK_a 15.7).



Cyclohexyl iodide Cyclohexyl azide (75%)

The conjugate acid of azide ion is called *hydrazoic acid* (HN_3). It has a pK_a of 4.6, and so is similar to acetic acid in its acidity.

Hydrogen sulfide (pK_a 7.0) is a stronger acid than water (pK_a 15.7). Therefore HS^- is a much weaker base than HO^-.

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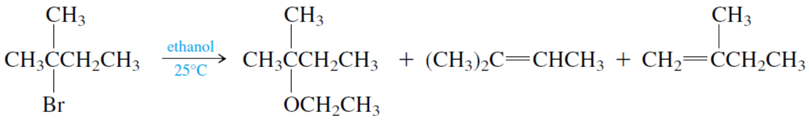

$$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle Br}{C}}CH_2CH_3 \xrightarrow[25°C]{ethanol} CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle OCH_2CH_3}{C}}CH_2CH_3 + (CH_3)_2C{=}CHCH_3 + CH_2{=}\overset{\displaystyle CH_3}{C}CH_2CH_3$$

2-Bromo-2-methylbutane

2-Ethoxy-2-methylbutane
(Major product in absence of sodium ethoxide)

2-Methyl-2-butene

2-Methyl-1-butene

(Alkene mixture is major product in presence of sodium ethoxide)

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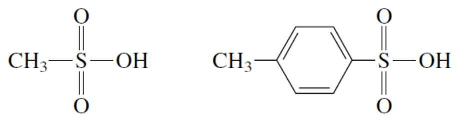
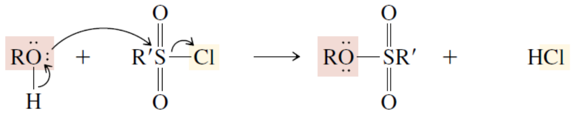
Sulfonatos


Methanesulfonic acid

p-Toluenesulfonic acid


Alcohol

Sulfonyl chloride

Sulfonate ester

Hydrogen chloride

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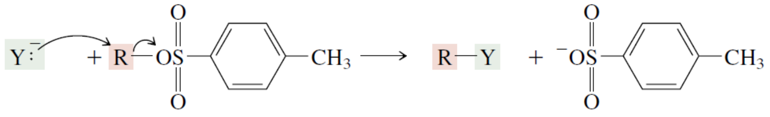
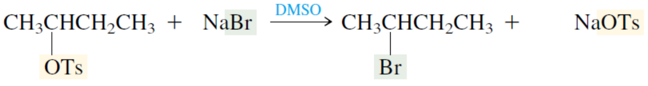

Nucleophile

p-Toluenesulfonate ester

Product of nucleophilic substitution

p-Toluenesulfonate anion



$$\underset{\text{OTs}}{CH_3CHCH_2CH_3} + NaBr \xrightarrow{\text{DMSO}} \underset{\text{Br}}{CH_3CHCH_2CH_3} + NaOTs$$

sec-Butyl *p*-toluenesulfonate

Sodium bromide

sec-Butyl bromide (82%)

Sodium *p*-toluenesulfonate

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Approximate Relative Leaving-Group Abilities*

Leaving group	Relative rate	Conjugate acid of leaving group	K_a of conjugate acid	pK_a
F^-	10^{-5}	HF	3.5×10^{-4}	3.5
Cl^-	10^0	HCl	10^7	−7
Br^-	10^1	HBr	10^9	−9
I^-	10^2	HI	10^{10}	−10
H_2O	10^1	H_3O^+	55	−1.7
TsO^-	10^5	TsOH	6×10^2	−2.8
$CF_3SO_2O^-$	10^8	CF_3SO_2OH	10^6	−6

*Values are approximate and vary according to substrate.

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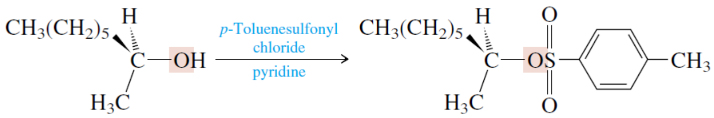

(S)-(+)-2-Octanol
$[\alpha]_D^{25}$ +9.9°
(optically pure)

(S)-(+)-1-Methylheptyl p-toluenesulfonate
$[\alpha]_D^{25}$ +7.9°
(optically pure)

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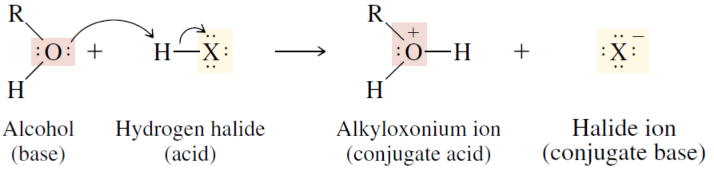
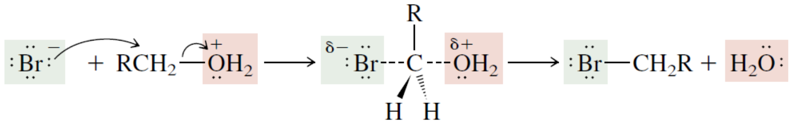
Reações de Álcoois com Haletos de Hidrogênio

$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX} \longrightarrow \underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O}$$


Alcohol (base)
Hydrogen halide (acid)
Alkyloxonium ion (conjugate acid)
Halide ion (conjugate base)


Bromide ion
Primary alkyl-oxonium ion
S_N2 transition state
Primary alkyl bromide
Water

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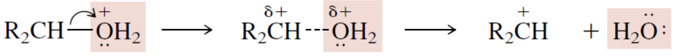
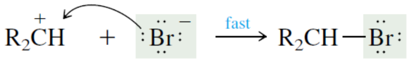

Secondary alkyloxonium ion
S_N1 transition state
Secondary carbocation
Water


Secondary carbocation
Bromide ion
Secondary alkyl bromide

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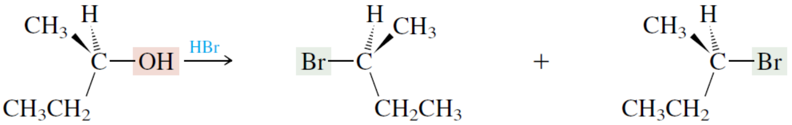
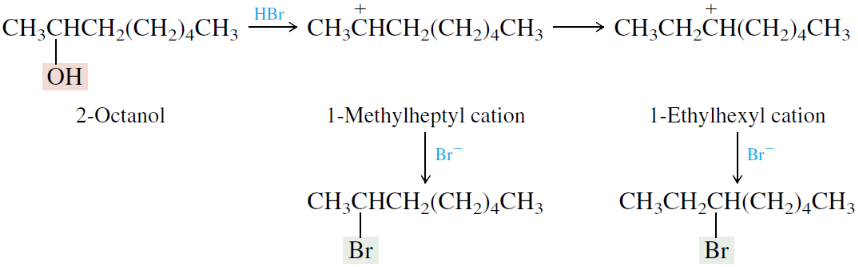


(*R*)-(−)-2-Butanol

(*S*)-(+)-2-Bromobutane (87%)

(*R*)-(−)-2-Bromobutane (13%)



2-Octanol

1-Methylheptyl cation

1-Ethylhexyl cation

2-Bromooctane (93%)

3-Bromooctane (7%)

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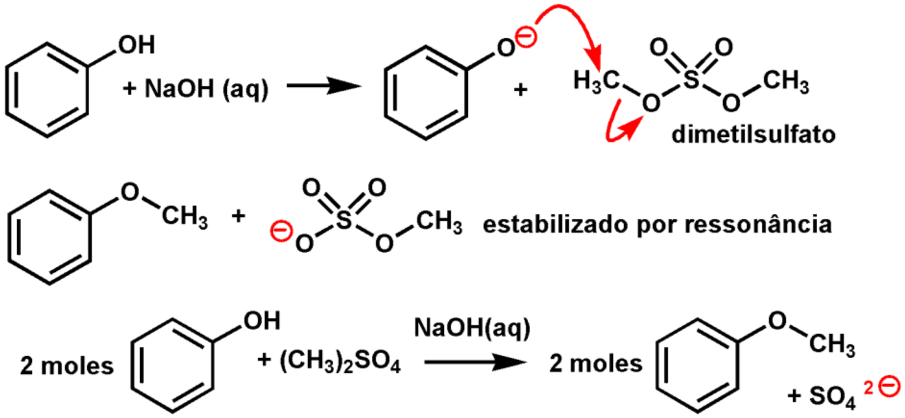
Exemplo: síntese de éteres
Síntese de Williamson



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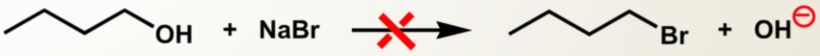
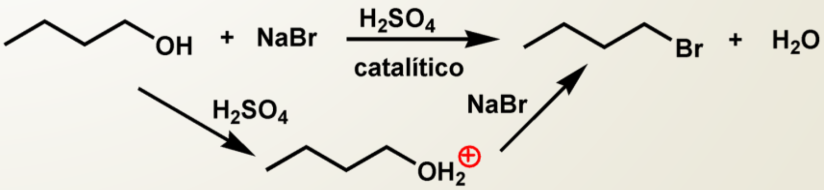
Exemplos: I-



mas...



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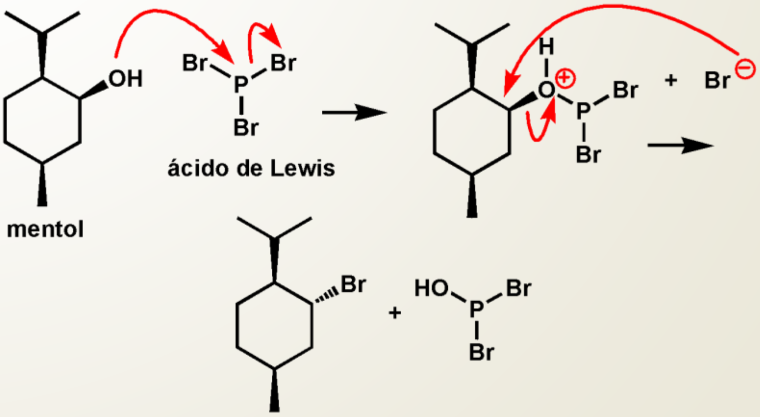
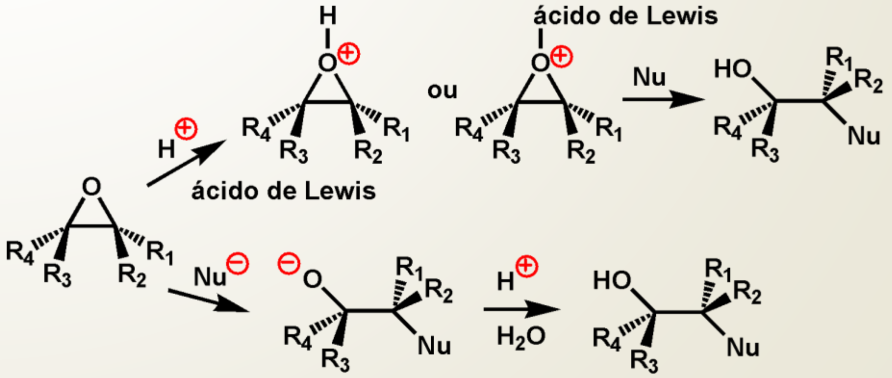
Importância do grupo abandonador

Exemplos PBr_3 ou PCl_3



Exemplos: epóxidos, classe especial de éteres, muito reativos, tanto com ácidos como com bases

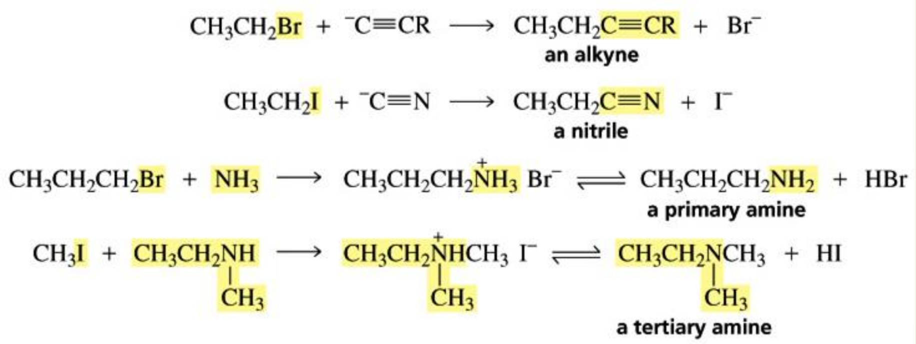


Reações em carbonos saturados sp^3

Substituição Nucleofílica S_N2

Reversibilidade

Algumas reações S_N2 são irreversíveis, mas outras são reversíveis



$$CH_3CH_2Br + {}^-C{\equiv}CR \longrightarrow CH_3CH_2C{\equiv}CR + Br^-$$

an alkyne

$$CH_3CH_2I + {}^-C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + I^-$$

a nitrile

$$CH_3CH_2CH_2Br + NH_3 \longrightarrow CH_3CH_2CH_2\overset{+}{N}H_3\ Br^- \rightleftharpoons CH_3CH_2CH_2NH_2 + HBr$$

a primary amine

$$CH_3I + CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{N}}H \longrightarrow CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{\overset{+}{N}}}HCH_3\ I^- \rightleftharpoons CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{N}}CH_3 + HI$$

a tertiary amine

Depende do nucleófilo, do grupo abandonador e do substrato

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Reação de S_N ou Ácido-Base?

O Reagente de Grignard