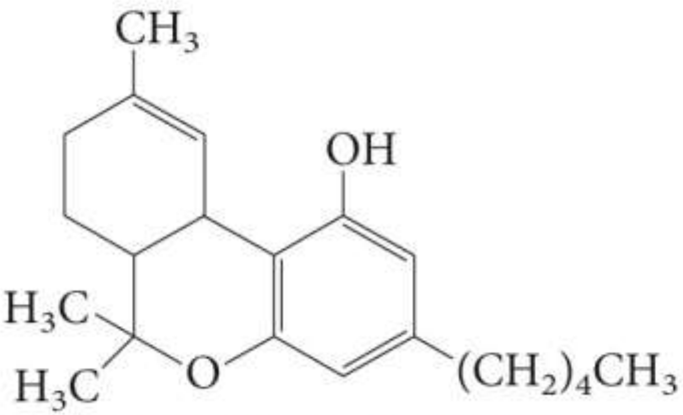
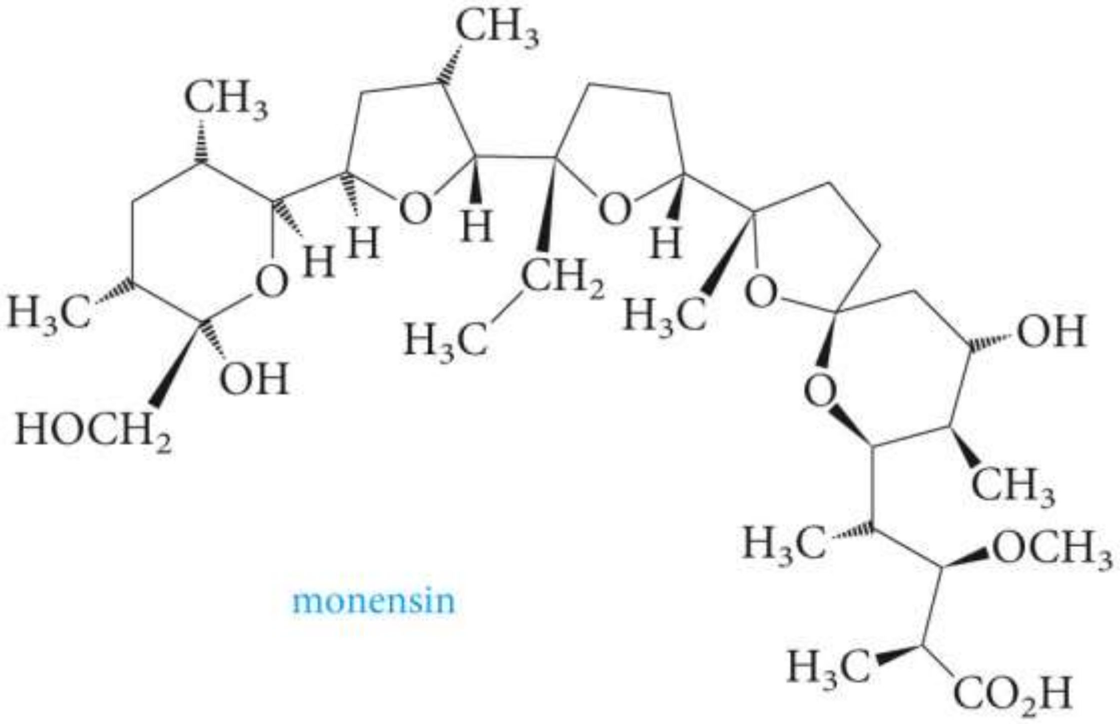
Chapter 8: Ethers and Epoxides

Diethyl ether in starting fluid

Examples of compounds with ether groups



tetrahydrocannabinol (THC)



monensin

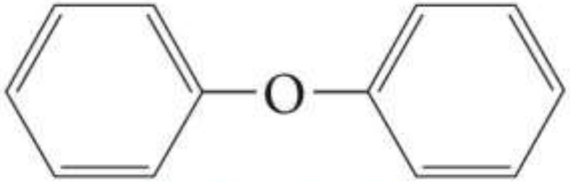
Nomenclature of Ethers

$CH_3CH_2{-}O{-}CH_3$

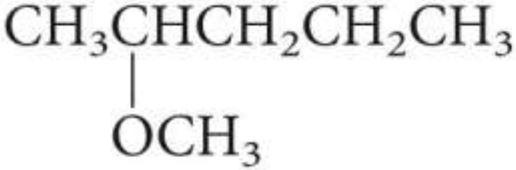
ethyl methyl ether

$CH_3CH_2{-}O{-}CH_2CH_3$

diethyl ether (the prefix *di-* is sometimes omitted)

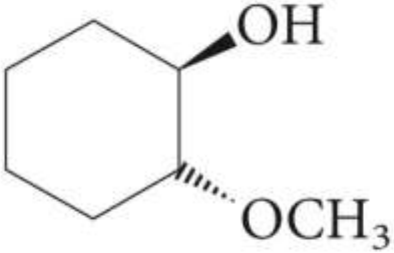


diphenyl ether

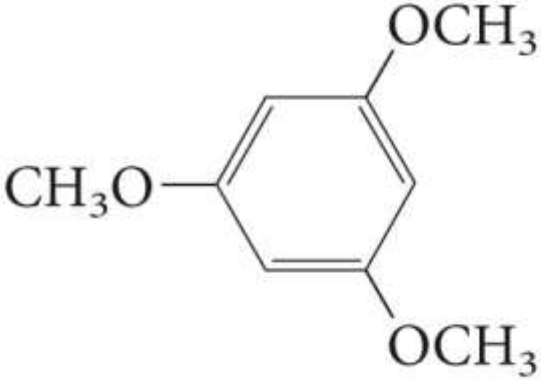


$$\underset{\displaystyle OCH_3}{CH_3\underset{|}{C}HCH_2CH_2CH_3}$$

2-methoxypentane

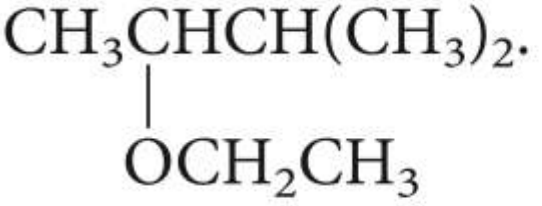


trans-2-methoxycyclohexanol

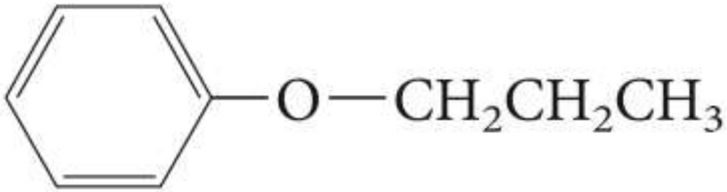


1,3,5-trimethoxybenzene

What are the correct names for the following ethers?



$CH_3\underset{\substack{|\\ OCH_2CH_3}}{CH}CH(CH_3)_2.$



Physical Properties of Ethers

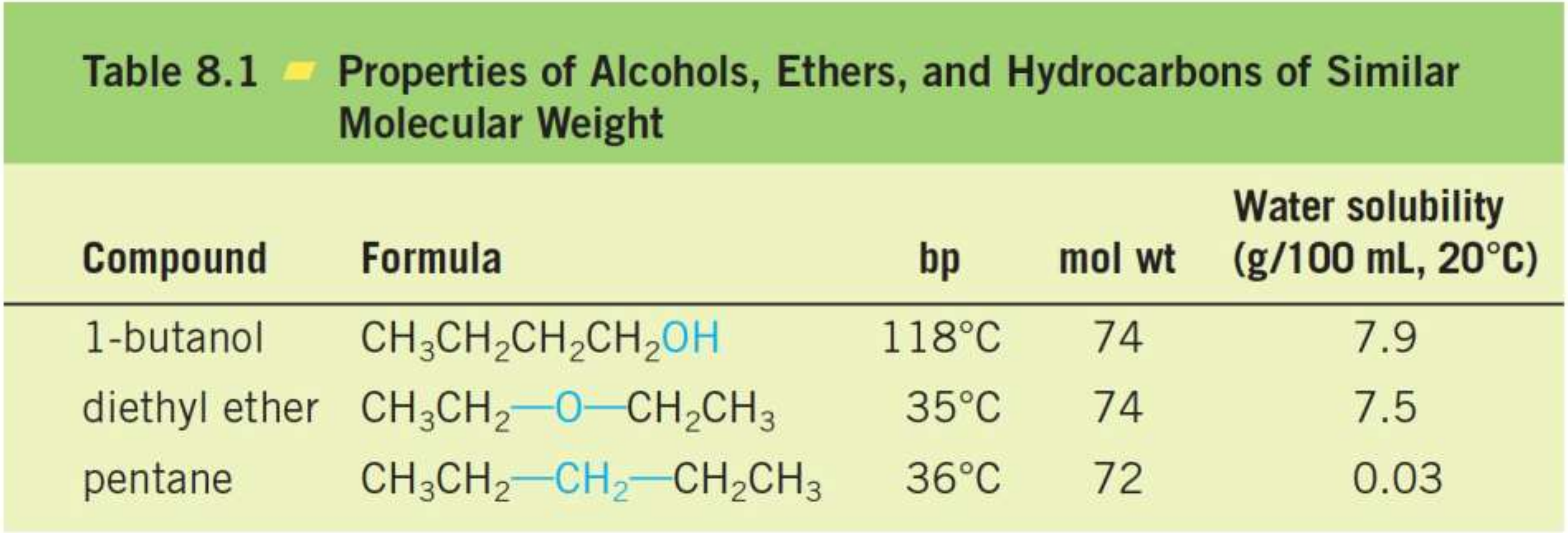
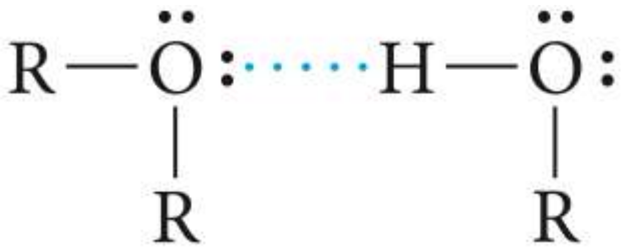


Table 8.1 **Properties of Alcohols, Ethers, and Hydrocarbons of Similar Molecular Weight**

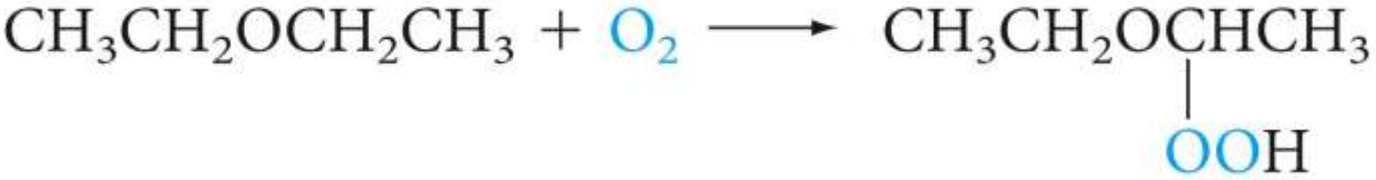
Compound	Formula	bp	mol wt	Water solubility (g/100 mL, 20°C)
1-butanol	$CH_3CH_2CH_2CH_2OH$	118°C	74	7.9
diethyl ether	$CH_3CH_2—O—CH_2CH_3$	35°C	74	7.5
pentane	$CH_3CH_2—CH_2—CH_2CH_3$	36°C	72	0.03



Although ethers cannot form hydrogen bonds with one another, they do form hydrogen bonds with alcohols. This explains why ethers and alcohols are mutually soluble.

Ethers as Solvents

Ethers are relatively inert compounds. They do no usually react with dilute acids or bases or common oxidizing and reducing agents.
They do not react with metallic sodium unlike alcohols.
Their inert nature and the fact that most organic compounds are ether-soluble makes them excellent solvents for organic reactions.



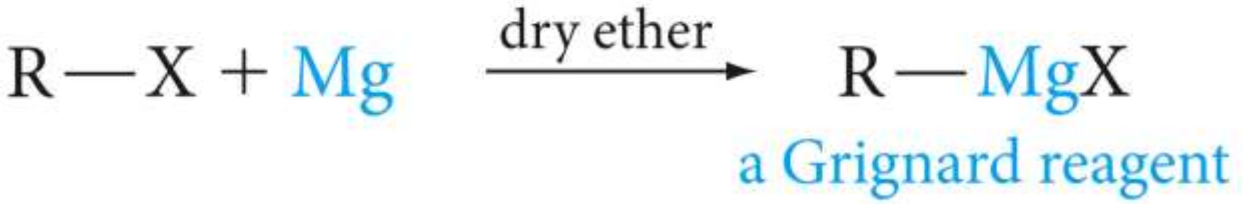
$$CH_3CH_2OCH_2CH_3 + O_2 \longrightarrow CH_3CH_2O\underset{\overset{|}{OOH}}{C}HCH_3$$

an ether hydroperoxide

When ethers are exposed to air for a long time, they form peroxides and may result to explosives. $FeSO_4$ is usually added to destroy the peroxides.

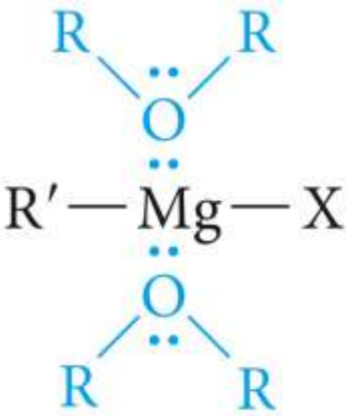
The Grignard Reagent : an Organometallic Compound

Pronounced greenyar(d)



$$R{-}X + Mg \xrightarrow{\text{dry ether}} R{-}MgX$$

a Grignard reagent

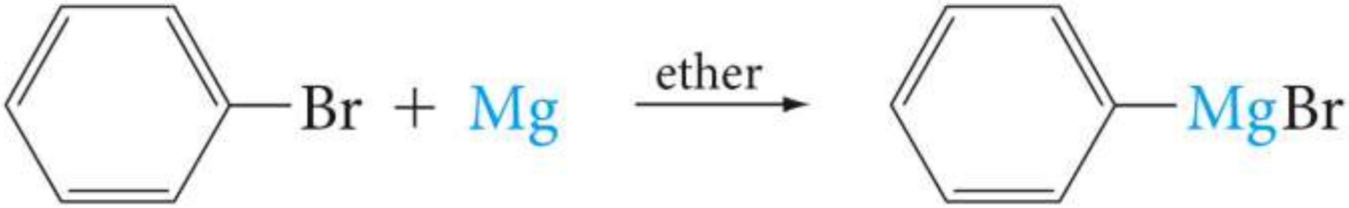


Acting as a Lewis base, ether stabilizes a Grignard reagent.

$$CH_3{-}I + Mg \xrightarrow{\text{ether}} CH_3MgI$$

methyl iodide

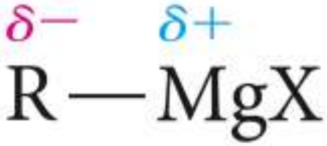
methylmagnesium iodide



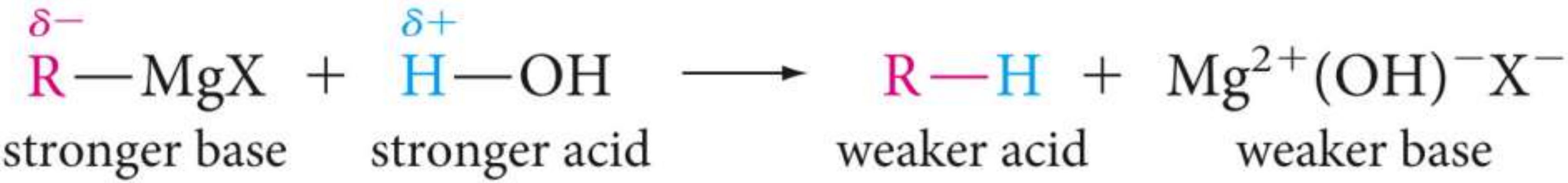
bromobenzene

phenylmagnesium bromide

A carbanion is an alkyl or aryl group with a negatively charged carbon atom.
Carbanions are strong bases

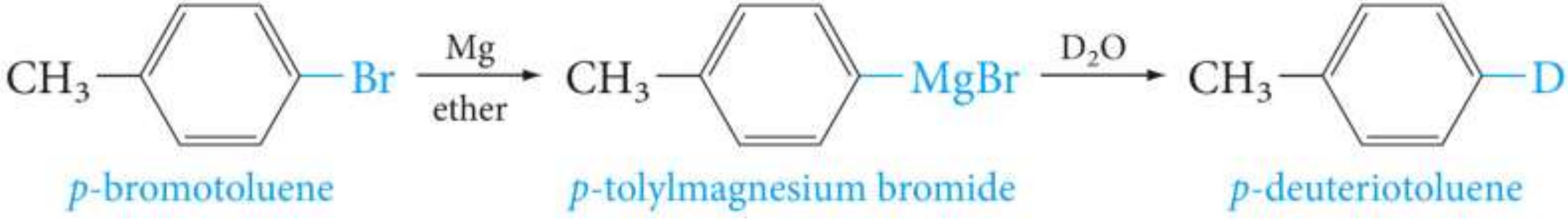


$$\overset{\delta-}{\mathrm{R}}-\overset{\delta+}{\mathrm{MgX}}$$



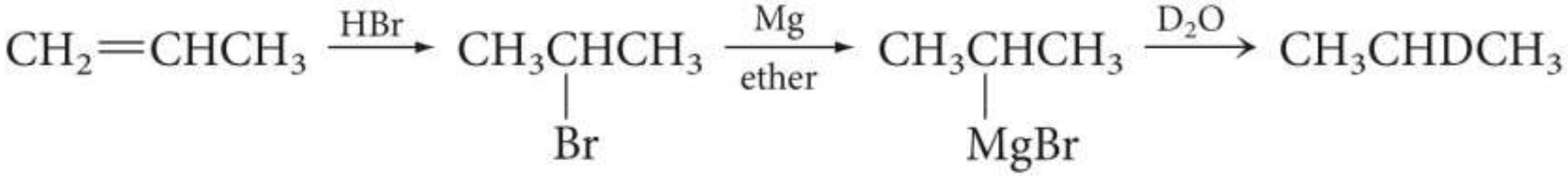
$$\underset{\text{stronger base}}{\overset{\delta-}{\mathrm{R}}-\mathrm{MgX}} + \underset{\text{stronger acid}}{\overset{\delta+}{\mathrm{H}}-\mathrm{OH}} \longrightarrow \underset{\text{weaker acid}}{\mathrm{R}-\mathrm{H}} + \underset{\text{weaker base}}{\mathrm{Mg}^{2+}(\mathrm{OH})^{-}\mathrm{X}^{-}}$$

Grignard reagent reaction with water



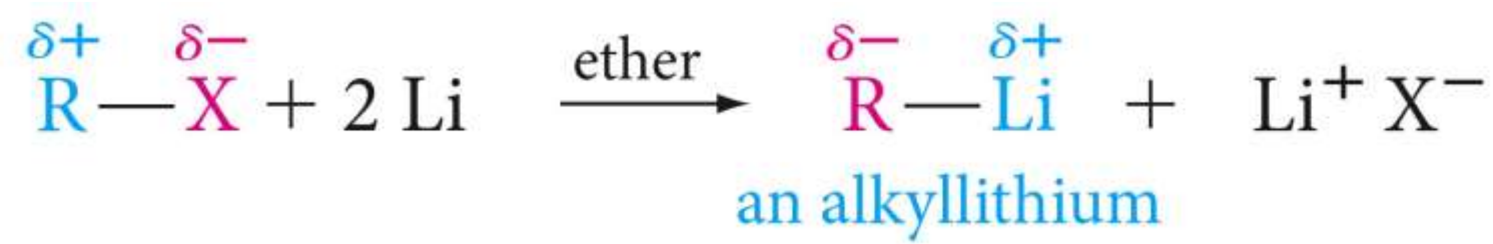
Reaction of Grignard reagent with water can be used to place deuterium isotopes by reacting them with heavy water (D_2O), where the deuterium substitutes the halogen

Question: Show how to prepare CH_3CHDCH_3 from $CH_2{=}CHCH_3$



$$CH_2{=}CHCH_3 \xrightarrow{HBr} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \xrightarrow[ether]{Mg} CH_3\underset{\displaystyle MgBr}{\underset{|}{C}}HCH_3 \xrightarrow{D_2O} CH_3CHDCH_3$$

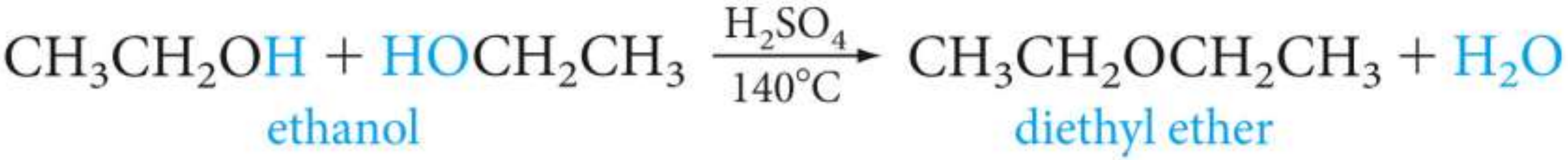
Organolithium compounds



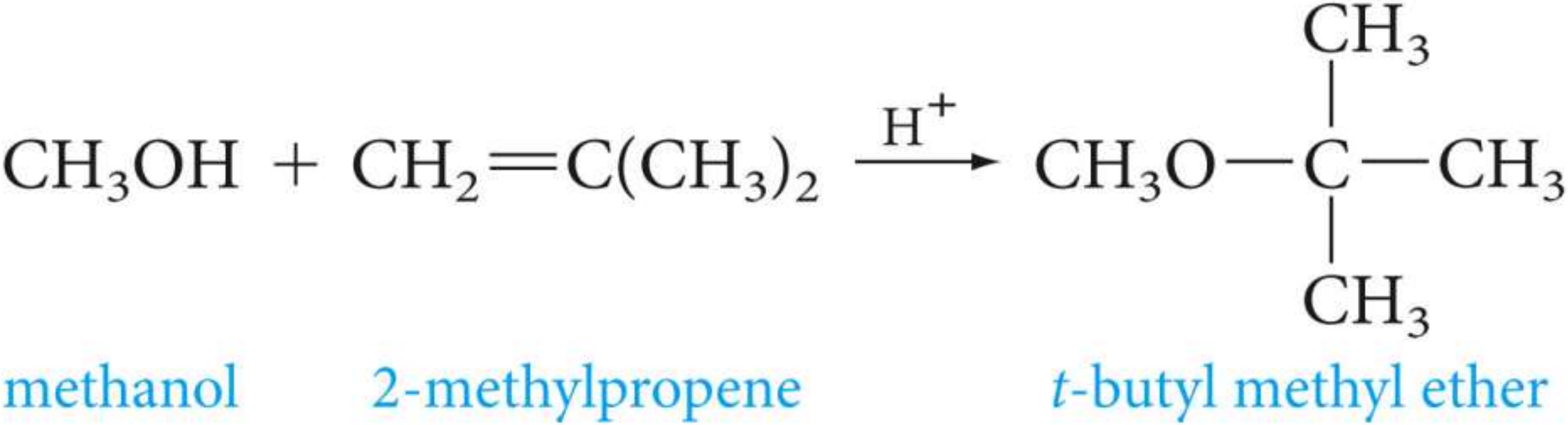
$$\overset{\delta+}{R}-\overset{\delta-}{X} + 2\,Li \xrightarrow{\text{ether}} \underbrace{\overset{\delta-}{R}-\overset{\delta+}{Li}}_{\text{an alkyllithium}} + Li^{+}X^{-}$$

These compounds contain carbon- metal (lithium) bond. They react in a similar manner to Grignard reagents, and are very useful in synthesis

Preparation of Ethers



$$\underbrace{CH_3CH_2OH + HOCH_2CH_3}_{\text{ethanol}} \xrightarrow[140°C]{H_2SO_4} \underbrace{CH_3CH_2OCH_2CH_3}_{\text{diethyl ether}} + H_2O$$



$$\mathrm{CH_3OH} + \mathrm{CH_2{=}C(CH_3)_2} \xrightarrow{\mathrm{H^+}} \mathrm{CH_3O{-}}\overset{\displaystyle \mathrm{CH_3}}{\underset{\displaystyle \mathrm{CH_3}}{\mathrm{C}}}\mathrm{{-}CH_3}$$

Williamson Synthesis

$$2\,ROH + 2\,Na \longrightarrow 2\,RO^{-}Na^{+} + H_2$$

$$RO^{-}Na^{+} + R'{-}X \longrightarrow ROR' + Na^{+}X^{-}$$

$CH_3OCH_2CH_2CH_3$ or $CH_3OCH_2CH_2CH_3$

from from

$CH_3O^-Na^+ + XCH_2CH_2CH_3$ $CH_3X + Na^+ \,^-OCH_2CH_2CH_3$

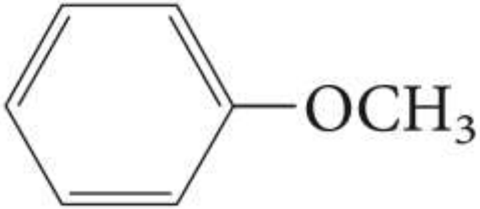
$$2\,CH_3OH + 2\,Na \longrightarrow 2\,CH_3O^-Na^+ + H_2$$

$$CH_3O^-Na^+ + CH_3CH_2CH_2X \longrightarrow CH_3OCH_2CH_2CH_3 + Na^+X^-$$

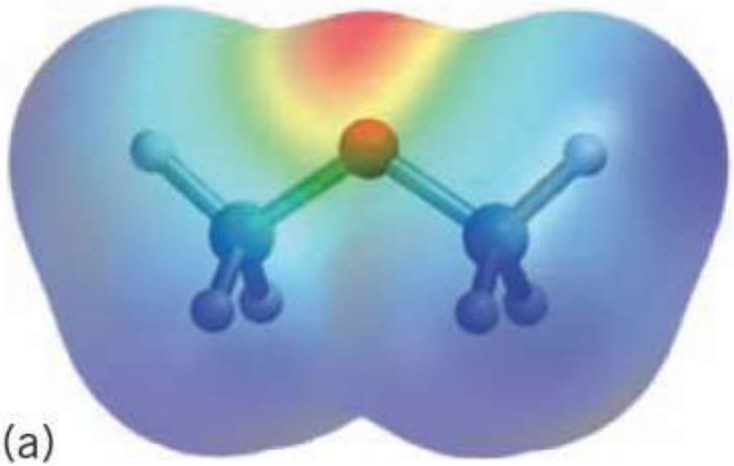
$$2\,CH_3CH_2CH_2OH + 2\,Na \longrightarrow 2CH_3CH_2CH_2O^-Na^+ + H_2$$

$$CH_3CH_2CH_2O^-Na^+ + CH_3X \longrightarrow CH_3CH_2CH_2OCH_3 + Na^+X^-$$

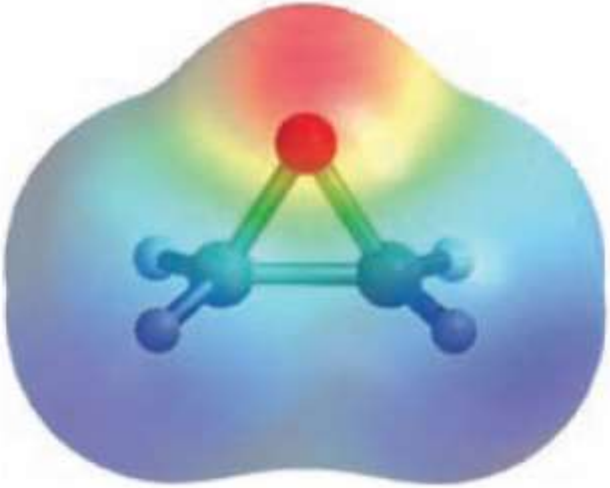
Show how this compound could be made



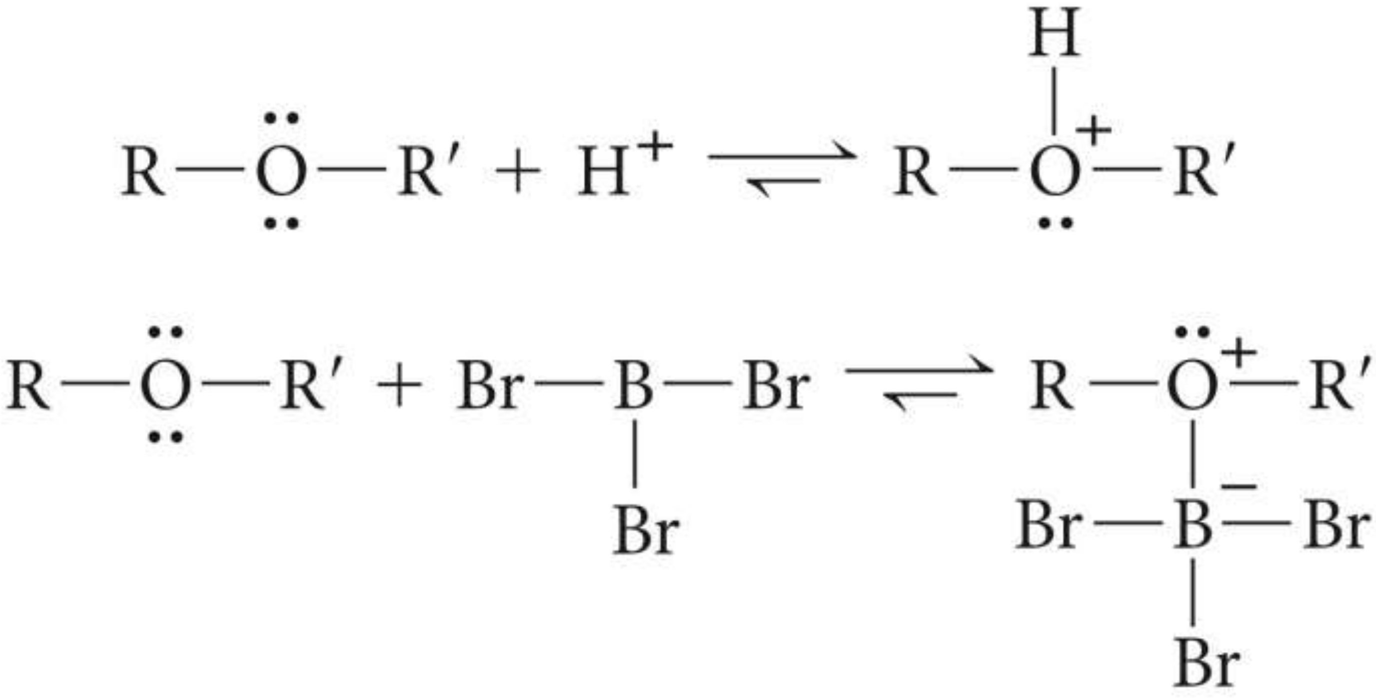
Cleavage of Ethers



(a)



(b)

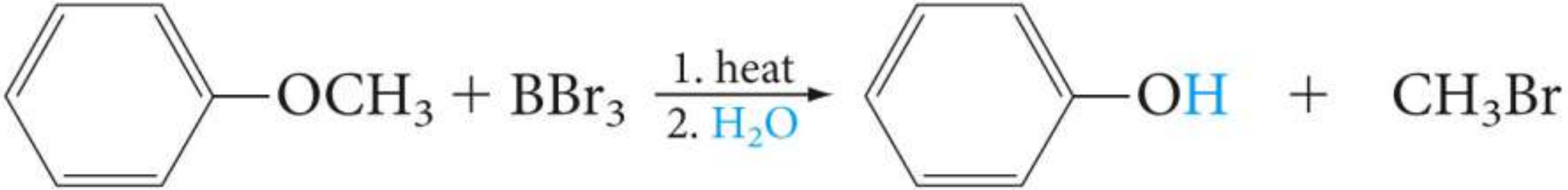


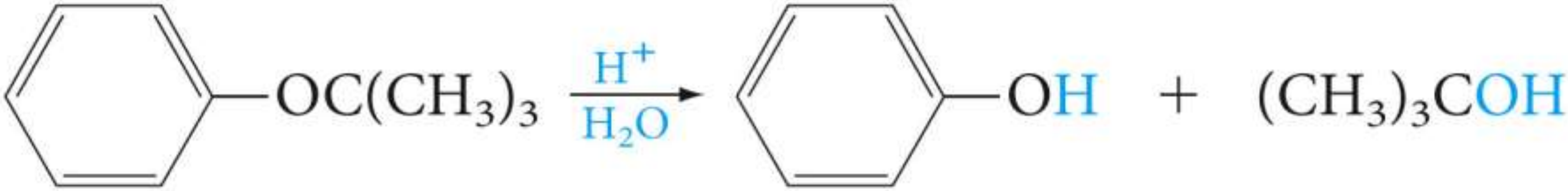
$$\mathrm{R-\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}-R'} + \mathrm{H^+} \rightleftharpoons \mathrm{R-\underset{\cdot\cdot}{\overset{\overset{\large H}{|}}{O^+}}-R'}$$

$$\mathrm{R-\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}-R'} + \mathrm{Br-\underset{\underset{\large Br}{|}}{B}-Br} \rightleftharpoons \mathrm{R-\underset{\underset{Br-\underset{\underset{\large Br}{|}}{B^-}-Br}{|}}{\overset{\cdot\cdot}{O^+}}-R'}$$

$$CH_3CH_2OCH(CH_3)_2 + HI \xrightarrow{\text{heat}} CH_3CH_2I + HOCH(CH_3)_2$$

ethyl isopropyl ether — ethyl iodide — isopropyl alcohol





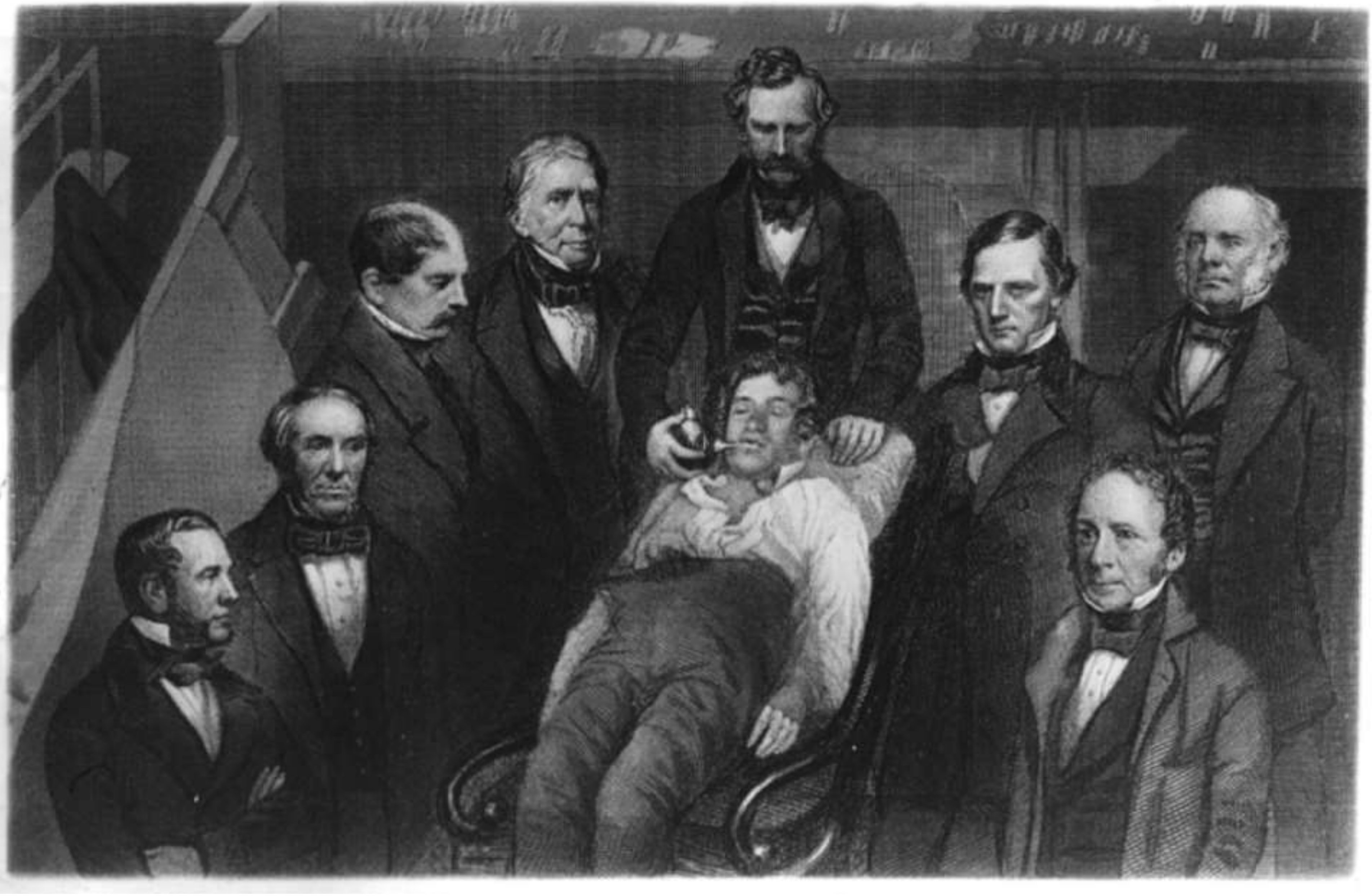
t-butyl phenyl ether

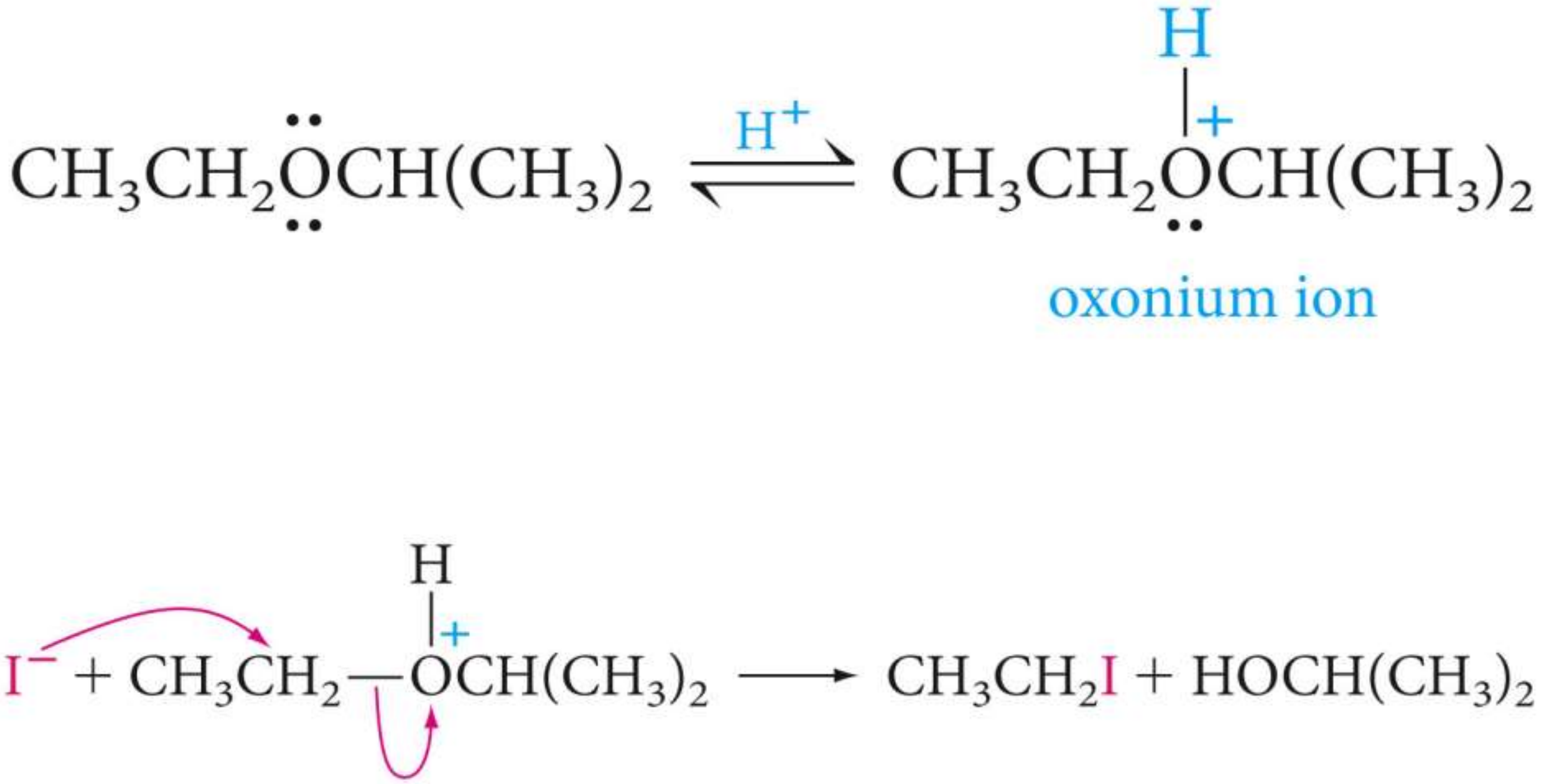
phenol

t-butyl alcohol

(and $(CH_3)_2C{=}CH_2$)

Ethers and Anesthesia



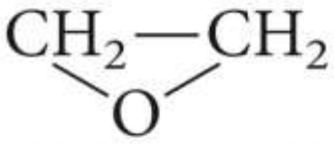


$$CH_3CH_2\underset{\cdot\cdot}{\ddot{O}}CH(CH_3)_2 \overset{H^+}{\rightleftharpoons} CH_3CH_2\underset{\cdot\cdot}{\overset{\overset{H}{|}}{O}}{}^{+}CH(CH_3)_2$$

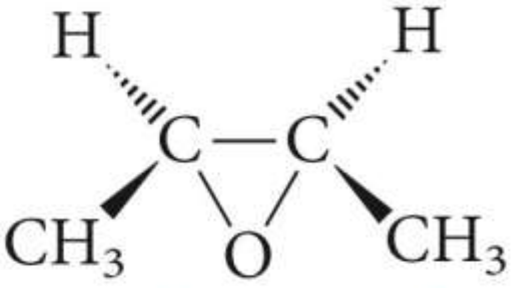
oxonium ion

$$I^- + CH_3CH_2{-}\overset{\overset{H}{|}}{O}{}^{+}CH(CH_3)_2 \longrightarrow CH_3CH_2I + HOCH(CH_3)_2$$

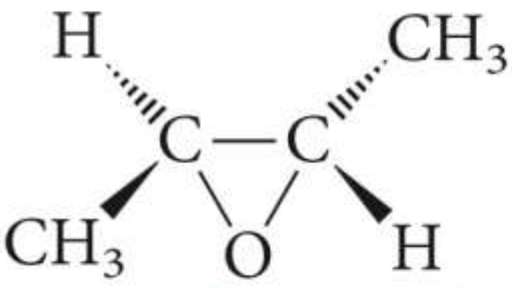
Epoxides (Oxiranes)



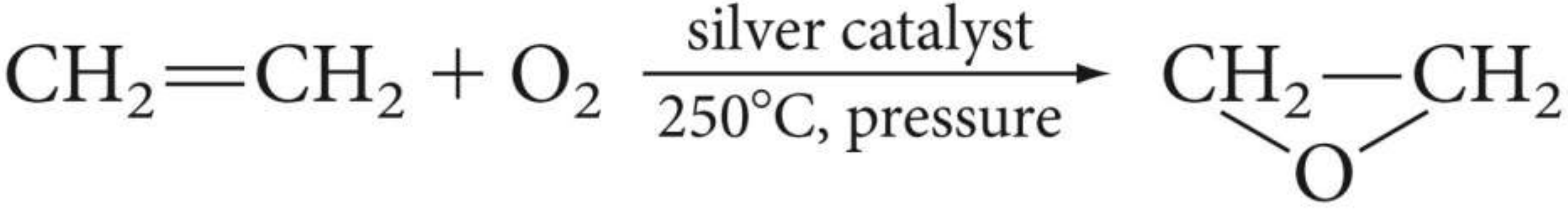
ethylene oxide
(oxirane)
bp 13.5°C



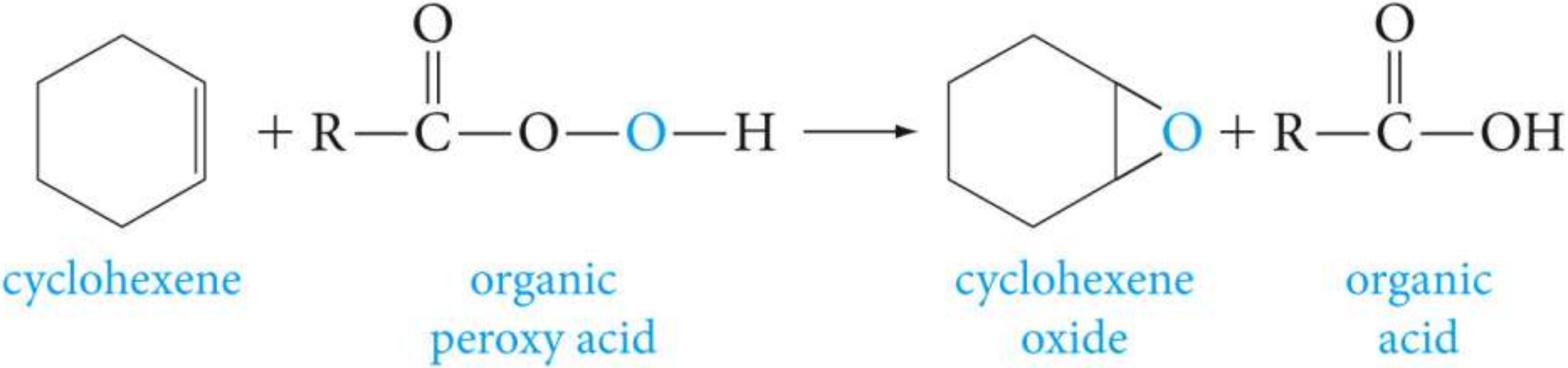
cis-2-butene oxide
(*cis*-2,3-dimethyloxirane)
bp 60°C

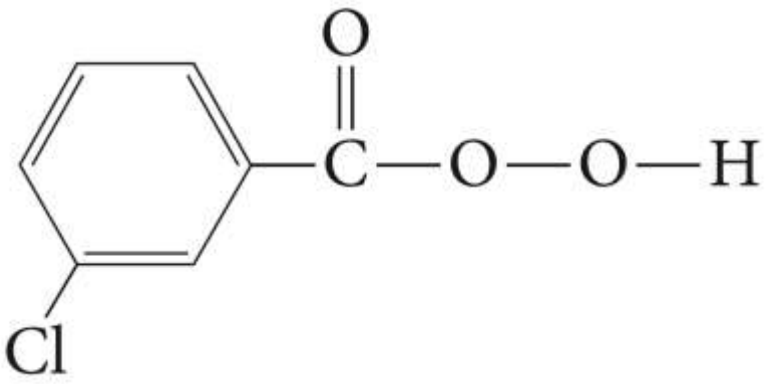


trans-2-butene oxide
(*trans*-2,3-dimethyloxirane)
bp 54°C

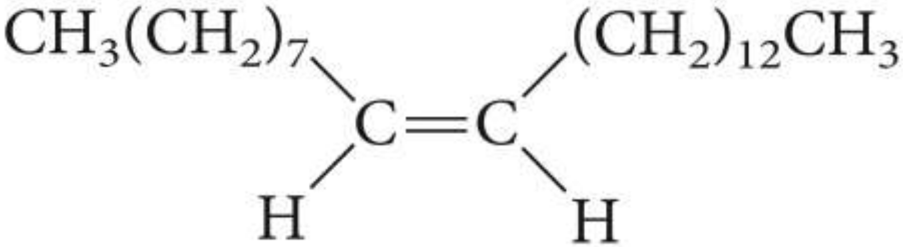


ethylene oxide

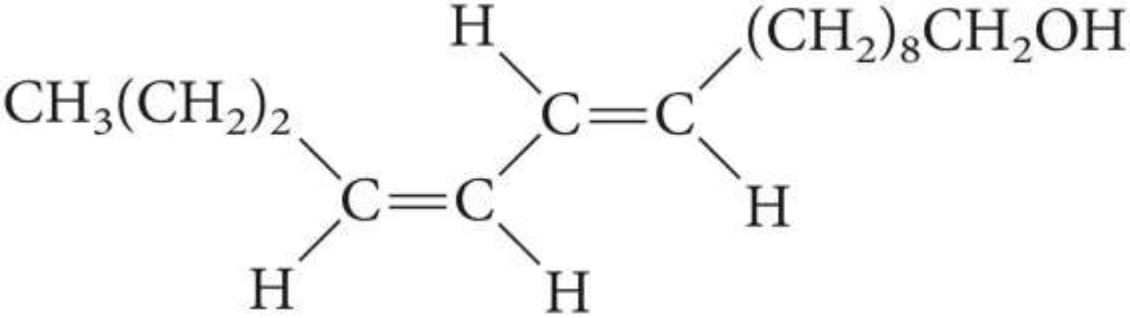

O
R—C—O—O—H
O
R—C—OH
cyclohexene
organic peroxy acid
cyclohexene oxide
organic acid



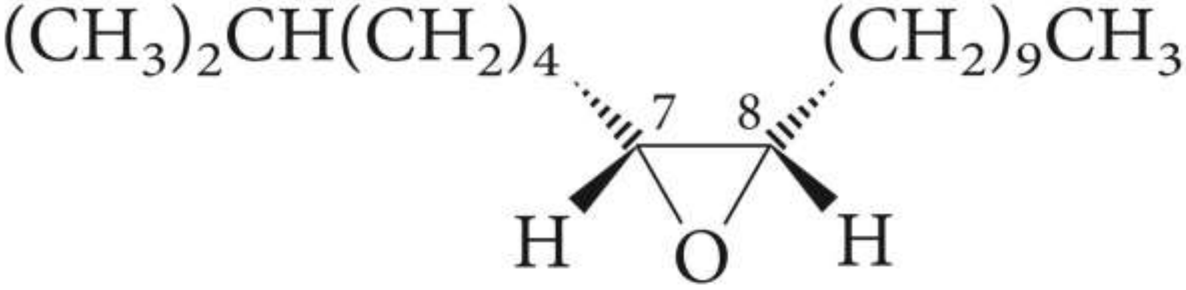
m-chloroperbenzoic acid (MCPBA) is an oxidizing agent frequently used in epoxidation reactions.



muscalure



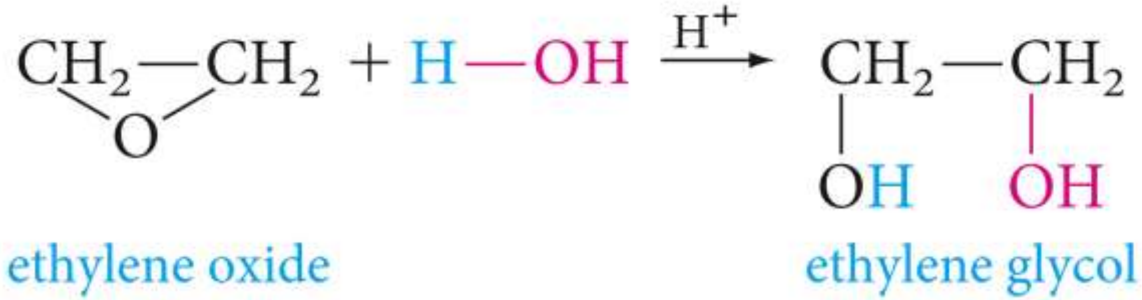
bombykol

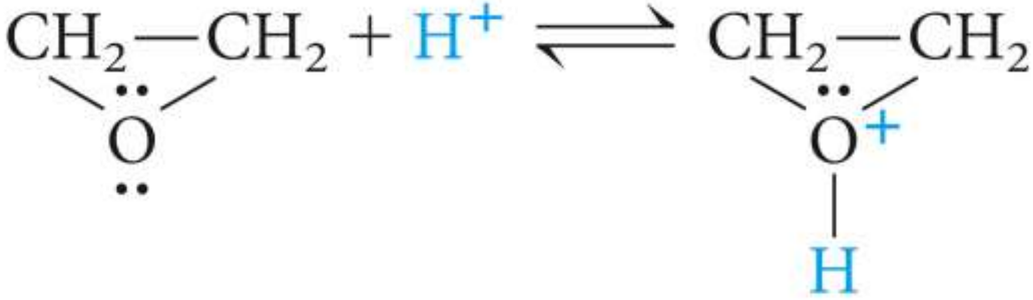


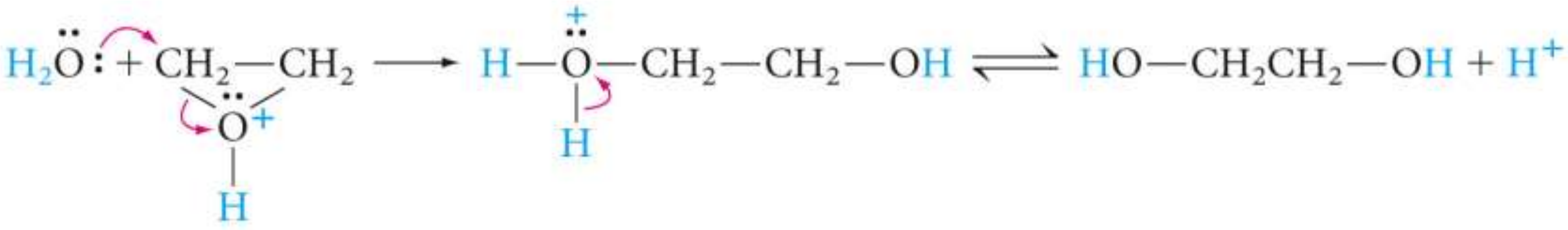
(7*R*,8*S*)-(+)-7,8-epoxy-2-methyloctadecane

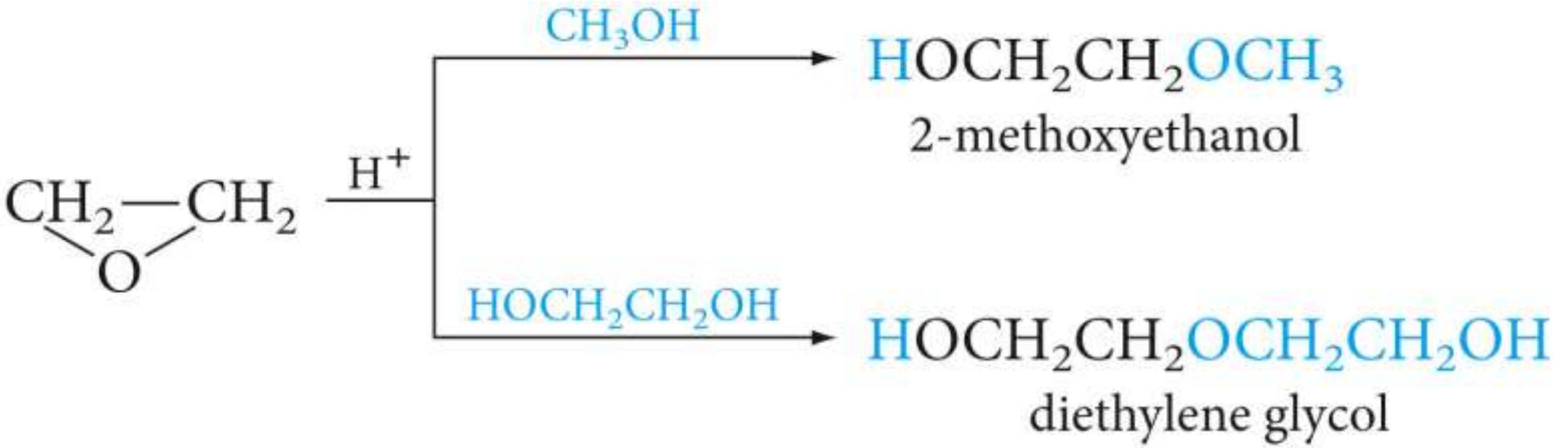
(disparlure)

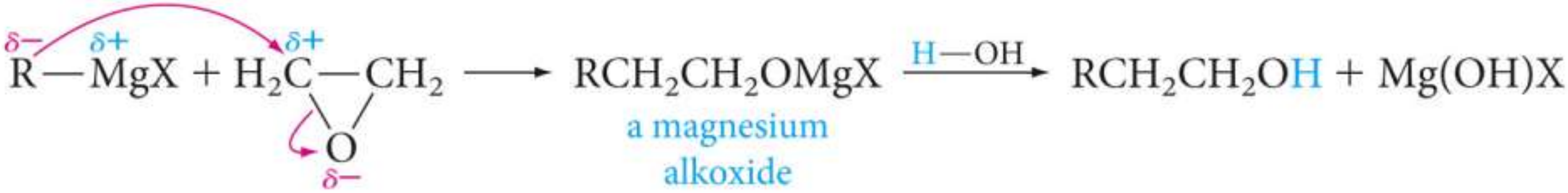
Reactions of Epoxides






H₂O: + CH₂—CH₂ (O⁺—H)
H—O⁺(H)—CH₂—CH₂—OH
HO—CH₂CH₂—OH + H⁺


CH₂—CH₂ (O)
H⁺
CH₃OH
HOCH₂CH₂OCH₃
2-methoxyethanol
HOCH₂CH₂OH
HOCH₂CH₂OCH₂CH₂OH
diethylene glycol

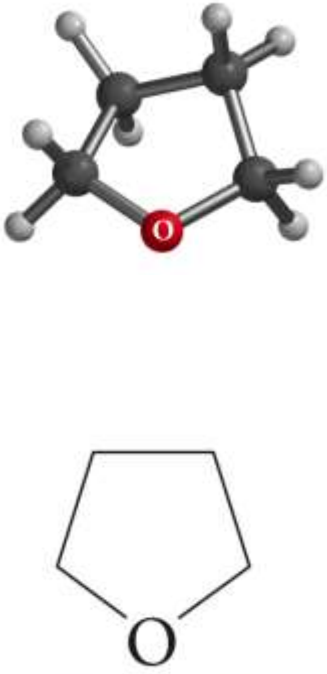


$$R-MgX + H_2C-CH_2 \longrightarrow RCH_2CH_2OMgX \xrightarrow{H-OH} RCH_2CH_2OH + Mg(OH)X$$

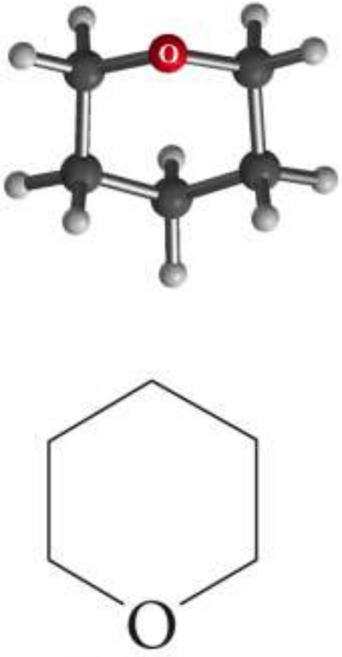
$$R-Li + H_2C-CH_2 \longrightarrow RCH_2CH_2OLi \xrightarrow{H-OH} RCH_2CH_2OH + LiOH$$

Grignard reagents and organolithium compounds are strong nucleophiles capable of opening the ethylene oxide (epoxide) ring. The initial product is a magnesium alkoxide of lithium alkoxide, but after hydrolysis, we obtain a primary alcohol with two carbon atoms than the organometallic reagent.

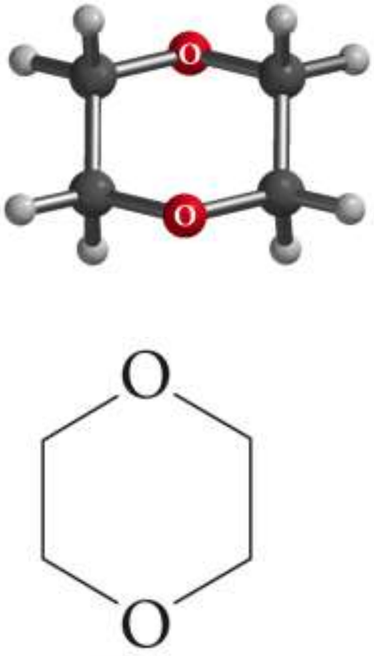
Cyclic Ethers



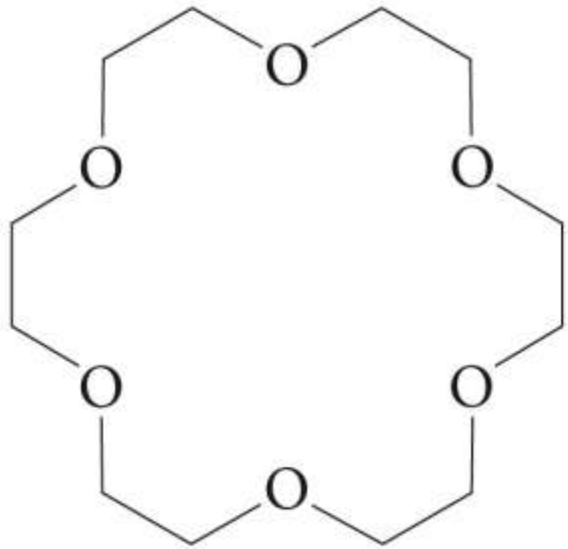
tetrahydrofuran
(oxolane)
bp 67°C



tetrahydropyran
(oxane)
bp 88°C

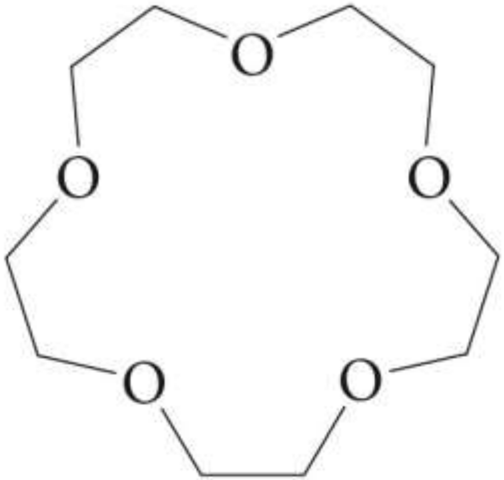


1,4-dioxane
bp 101°C



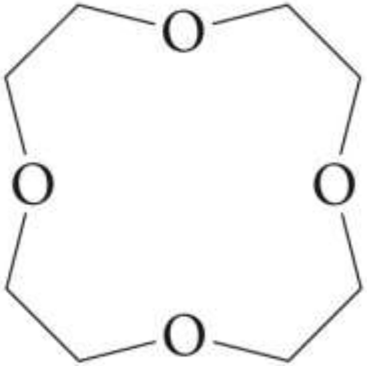
[18]crown-6

mp 39–40°C



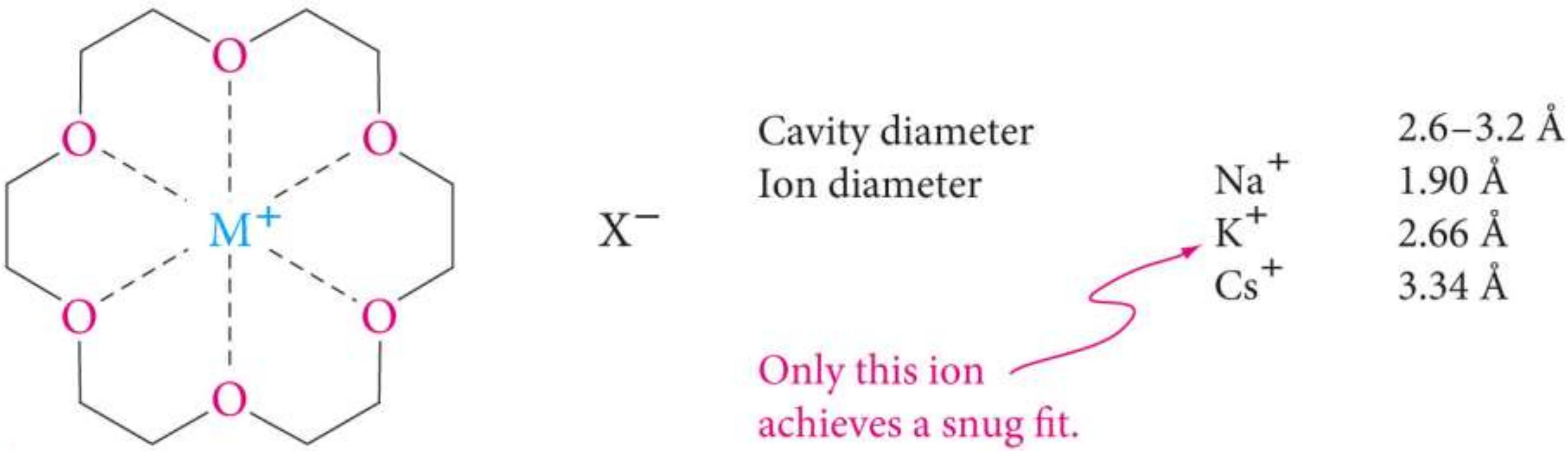
[15]crown-5

(liquid)



[12]crown-4

These compounds are called **Crown ethers** because their molecule have a crown-like shape. The bracket number represents the ring size and the terminal numbers gives the number of oxygens. The oxygens are usually separated by two carbons.

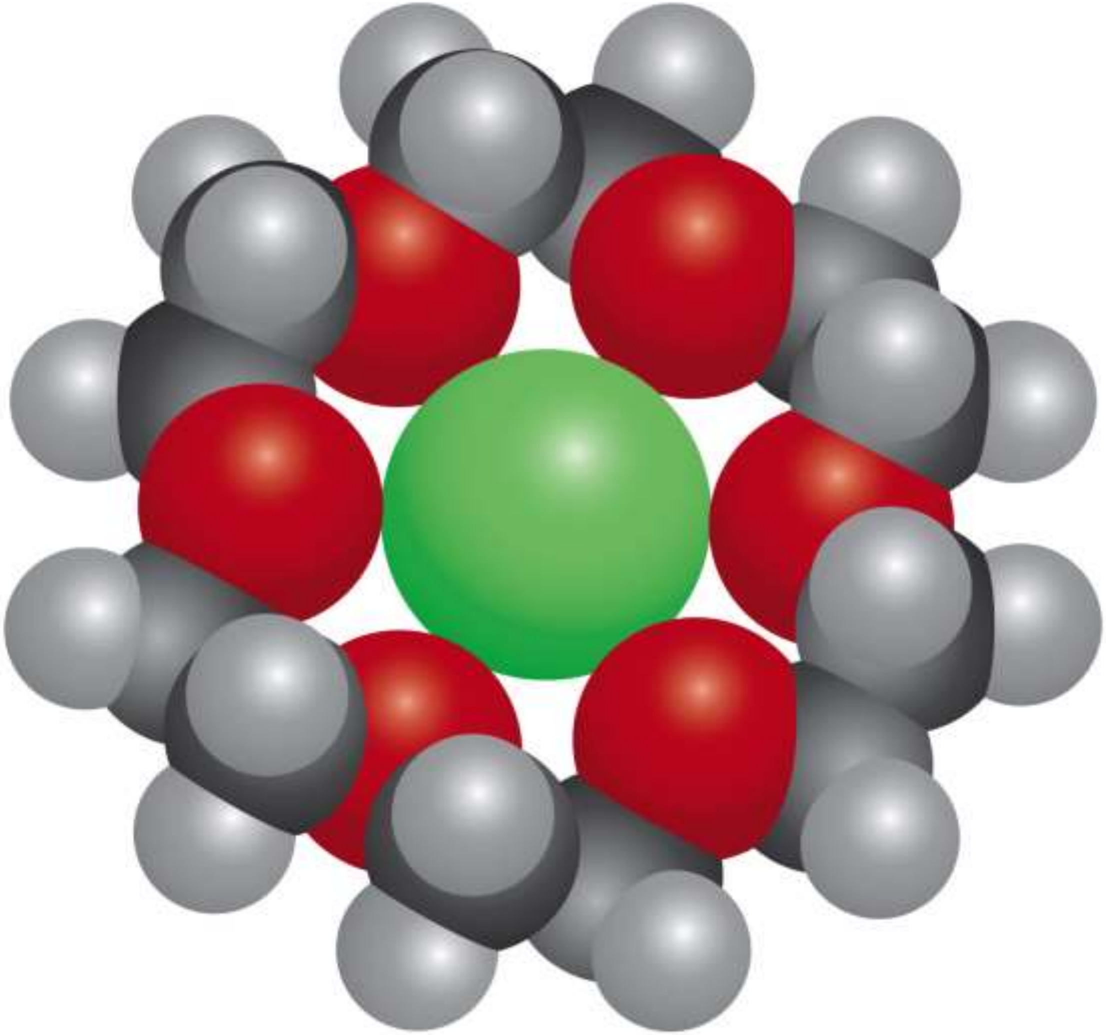


Cavity diameter		2.6–3.2 Å
Ion diameter	Na^+	1.90 Å
	K^+	2.66 Å
	Cs^+	3.34 Å

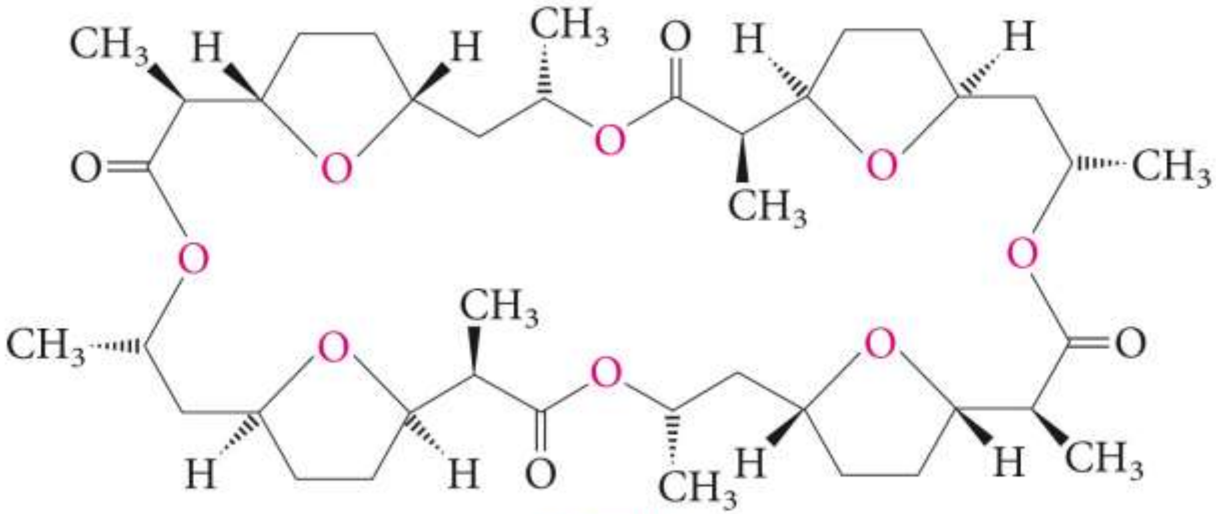
Only this ion achieves a snug fit.

M^+ complexed in [18]crown-6

Crown ethers have the unique property of forming complexes with positive ions (Na^+, K^+) the positive ions fit within the macrocyclic rings selectively depending on the sizes. For example [18]crown-6 binds K^+ more tightly than it does the smaller Na^+ (too loose a fit) or the larger Cs^+ (too large to fit in the hole). Similarly [15]crown-5 binds Na^+ , and [12]crown-4 binds Li^+. The crown ethers act as hosts for their anionic guests.



Model of [18]crown-6 complex with K^+



nonactin

The selective binding of metallic ions by macrocyclic compounds is important in nature. Several antibiotics, such as **nonactin**, have large rings that contain regularly spaced oxygen atoms. Nonactin (which contains four tetrahydrofuran rings joined by four ester links) selectively binds K^+ (in the presence of Na^+) in aqueous media. Thus allowing selective transport of K^+ (but not Na^+) through the cell membranes