Organic Chemistry III

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Organic Chemistry, *Structure and Function* **(7th edition)**

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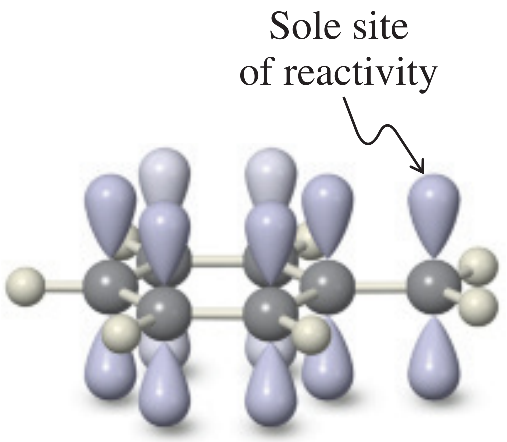
22. Chemistry of Benzene Substituents

Alkylbenzenes, Phenols, and Benzenamines

22-1 REACTIVITY AT THE PHENYLMETHYL (BENZYL) CARBON:

Methylbenzene is readily metabolized because its methyl C–H bonds are relatively weak with respect to homolytic and heterolytic cleavage.

When one of these methyl hydrogens has been removed, the resulting **phenylmethyl (benzyl)** group, $C_6H_5CH_2$, may be viewed as a benzene ring whose **π** system overlaps with an extra *p* orbital located on an attached alkyl carbon.

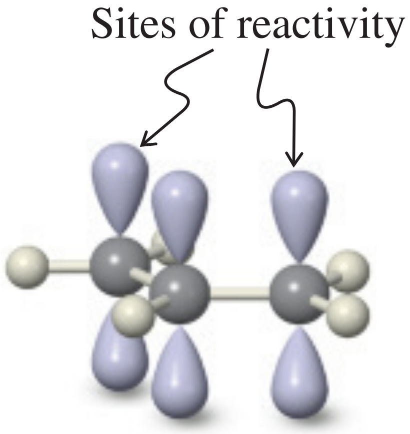


Phenylmethyl (benzyl) system

This interaction, generally called **benzylic resonance,** stabilizes adjacent radical, cationic, and anionic centers in much the same way that overlap of a **π** bond and a third *p* orbital stabilizes 2-propenyl (allyl) intermediates.

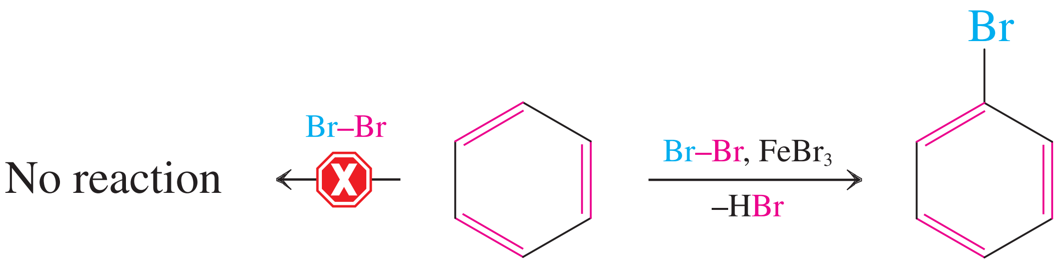
However, unlike allylic systems, which may undergo transformations at either terminus and give product mixtures (in the case of unsymmetrical substrates), benzylic reactivity is regioselective and occurs only at the benzylic carbon.

The reason for this selectivity lies in the disruption of aromaticity that goes with attack on the benzene ring.



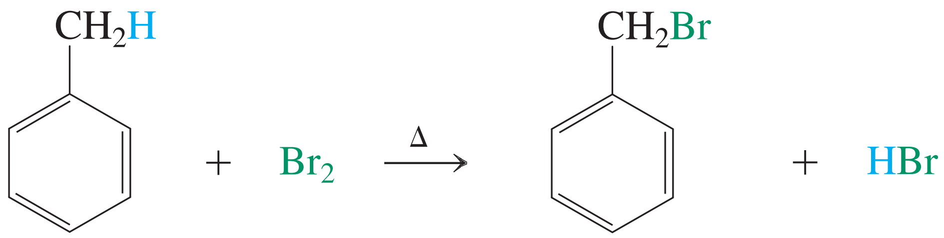
2-Propenyl (allyl) system

Benzene will not react with chlorine or bromine unless a Lewis acid is added. The acid catalyzes halogenation of the ring.

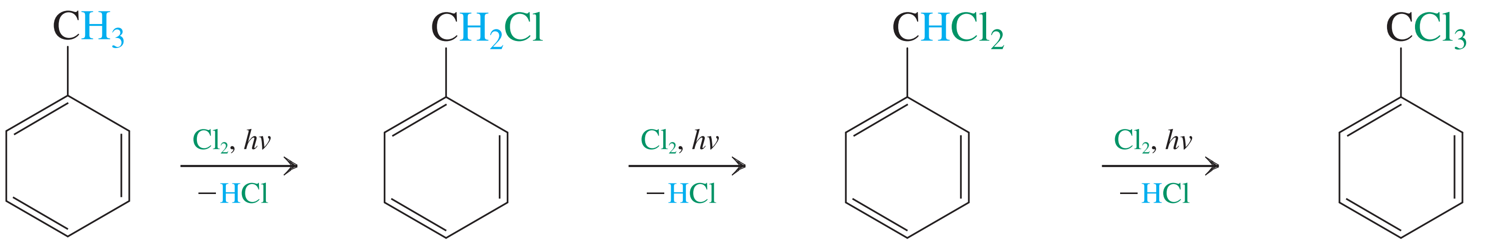


In contrast, heat or light allows attack by chlorine or bromine on methylbenzene (toluene) even in the absence of a catalyst.

The reaction takes place at the methyl group, *not* at the aromatic ring, and that excess halogen leads to multiple substitution.



(Bromomethyl)-benzene



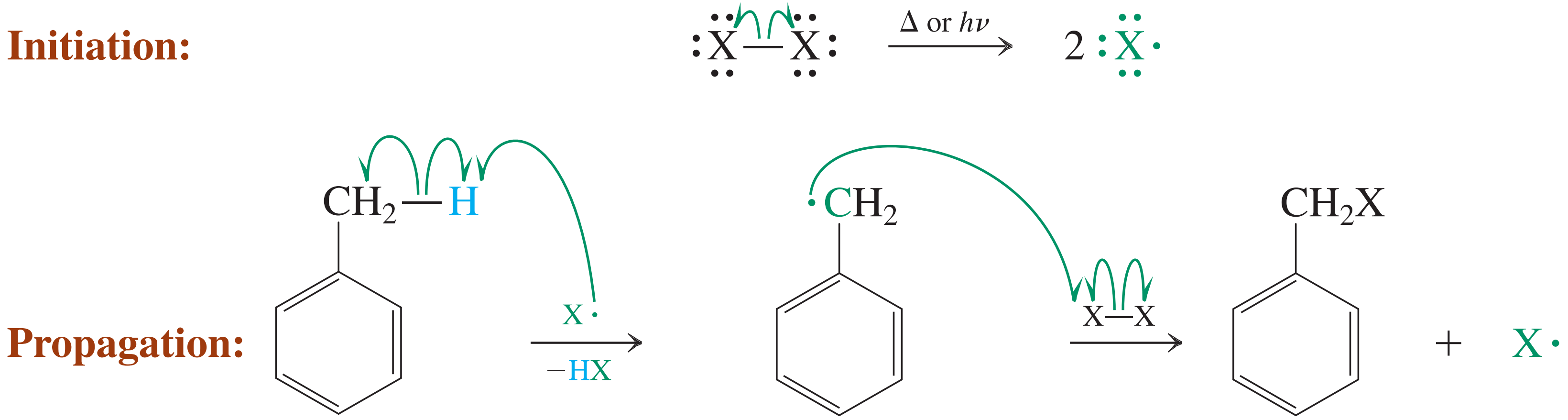
(Chloromethyl)-benzene **(Dichloromethyl)-benzene** **(Trichloromethyl)-benzene**

As in the halogenation of alkanes and the allylic halogenation of alkenes, the mechanism of benzylic halogenation proceeds through radical intermediates.

Heat or light induces dissociation of the halogen molecule into atoms. One of them abstracts a benzylic hydrogen, a reaction giving HX and a benzyl radical.

This intermediate reacts with another molecule of halogen to give the product, a (halomethyl)benzene, and another halogen atom, which propagates the chain process.

Mechanism of Benzylic Halogenation

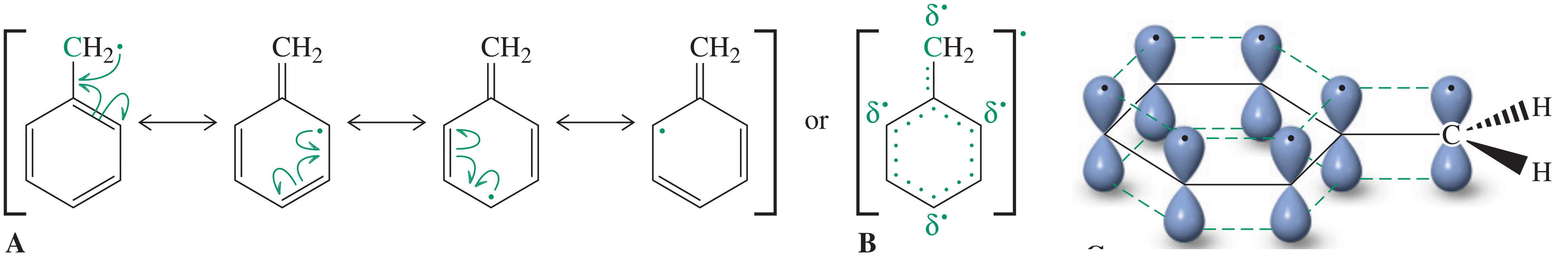


Phenylmethyl (benzyl) radical

What explains the ease of benzylic halogenation?

The answer lies in the stabilization of the benzyl radical by the phenomenon called benzylic resonance. As a consequence, the benzylic C–H bond is relatively weak (DH^{o} = 87 kcal mol^{-1}, 364 kJ mol^{-1}); its cleavage is relatively favorable and proceeds with a low activation energy.

Inspection of the resonance structures reveals why the halogen attacks only the *benzylic* position and not an aromatic carbon: Reaction at any but the benzylic carbon would destroy the aromatic character of the benzene ring.

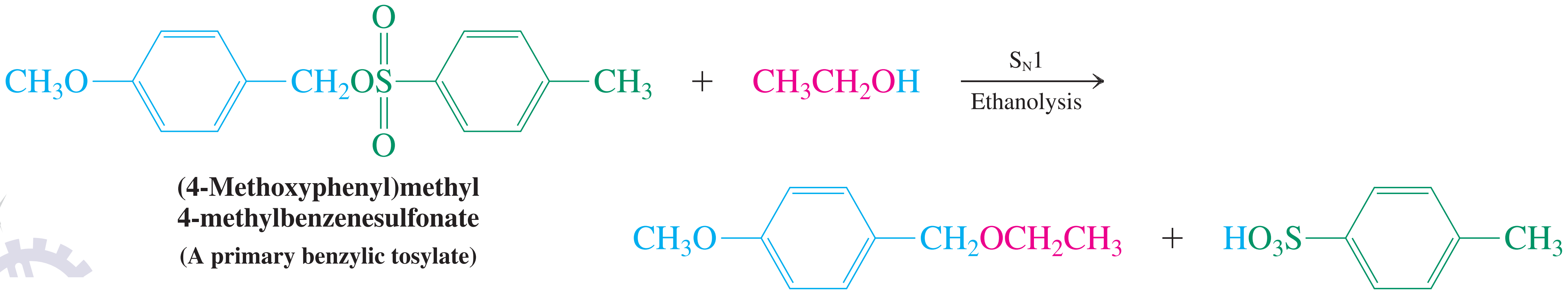


Benzylic resonance can affect strongly the reactivity of benzylic halides and sulfonates in nucleophilic displacements.

For example, the 4-methylbenzenesulfonate (tosylate) of 4-methoxyphenylmethanol (4-methoxybenzyl alcohol) reacts with solvent ethanol rapidly via an S_N1 mechanism.

This reaction is an example of solvolysis, specifically ethanolysis.

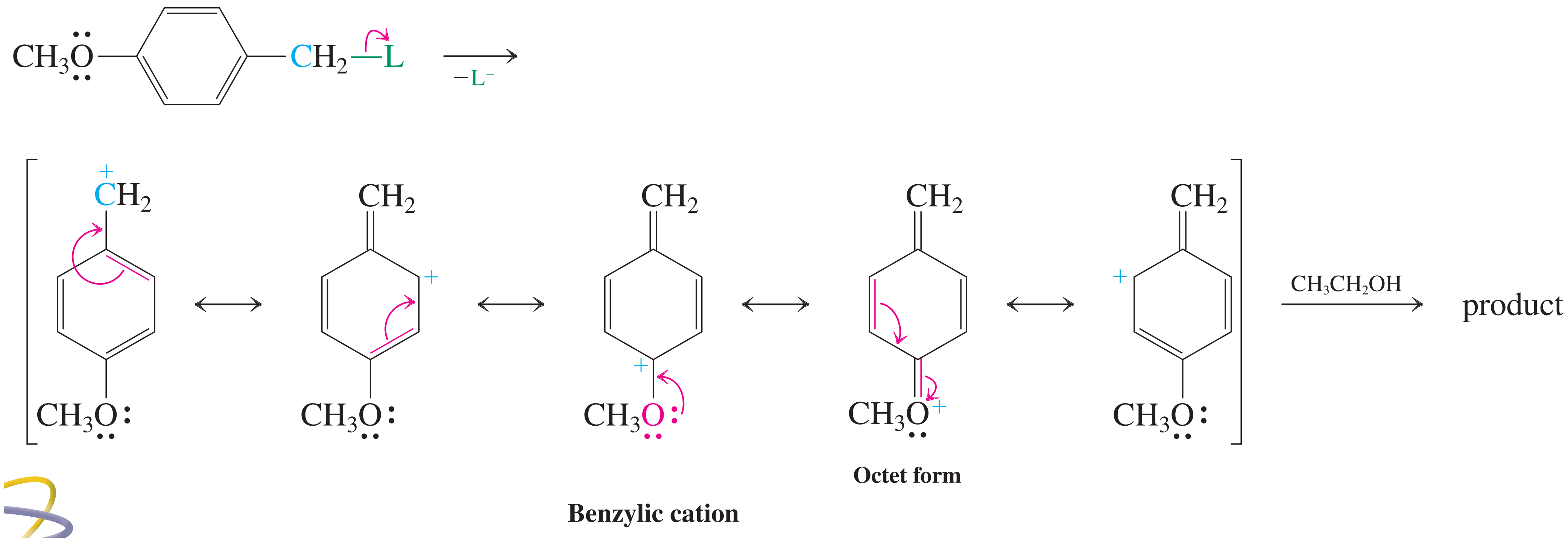
The delocalization of the positive charge of the benzylic cation through the benzene ring, allows for relatively facile dissociation of the starting sulfonate.



(4-Methoxyphenyl)methyl 4-methylbenzenesulfonate
(A primary benzylic tosylate)

1-(Ethoxymethyl)-4-methoxybenzene

Mechanism of Benzylic Unimolecular Nucleophilic Substitution

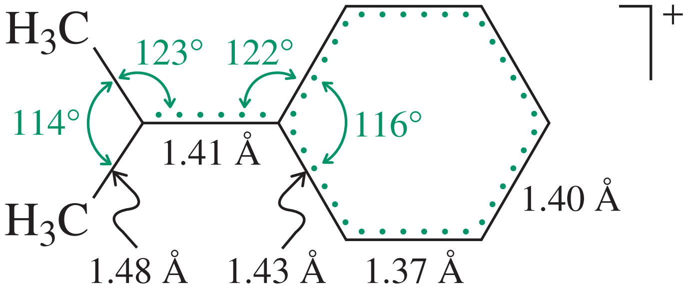


The above S_N1 reaction is facilitated by the presence of the para methoxy substituent, which allows for extra stabilization of the positive charge.

In the absence of this substituent, S_N2 processes may dominate. Thus, the parent benzyl halides and sulfonates undergo preferential and unusually rapid S_N2 displacements, even under solvolytic conditions, and particularly in the presence of good nucleophiles.

Several benzylic cations are stable enough to be isolable.

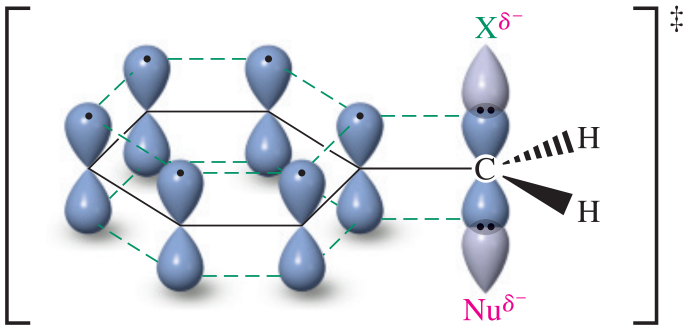
For example, the X-ray structure of the 2-phenyl-2-propyl cation (as its SbF_6^- salt) was obtained in 1997 and shows the phenyl–C bond (1.41 Å) to be intermediate in length between those of pure single (1.54 Å) and double bonds (1.33 Å), in addition to the expected planar framework and trigonal arrangement of all *sp*^{2} carbons, as expected for a delocalized benzylic system.

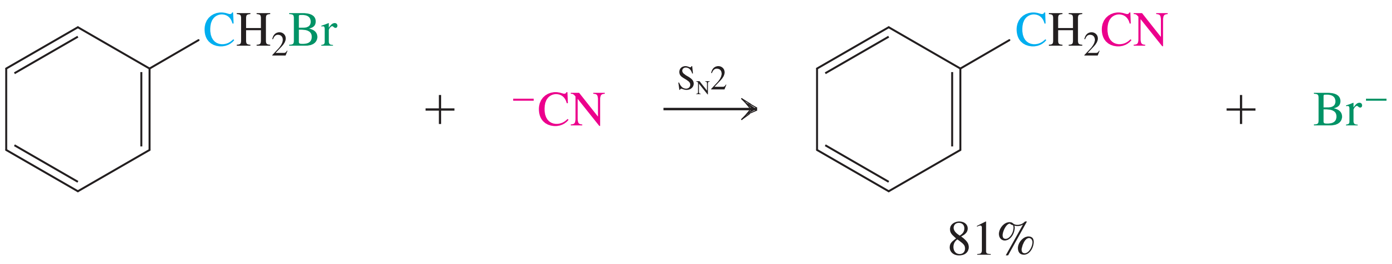


As in allylic S_N2 reactions, two factors contribute to this acceleration.

(1) benzylic carbon is made relatively more electrophilic by the neighboring *sp*²-hybridized phenyl carbon (as opposed to *sp*³-hybridized ones).

(2) stabilization of the S_N2 transition state by overlap with the benzene **π** system.





(Bromomethyl)benzene
(Benzyl bromide)

Phenylethanenitrile
(Phenylacetonitrile)

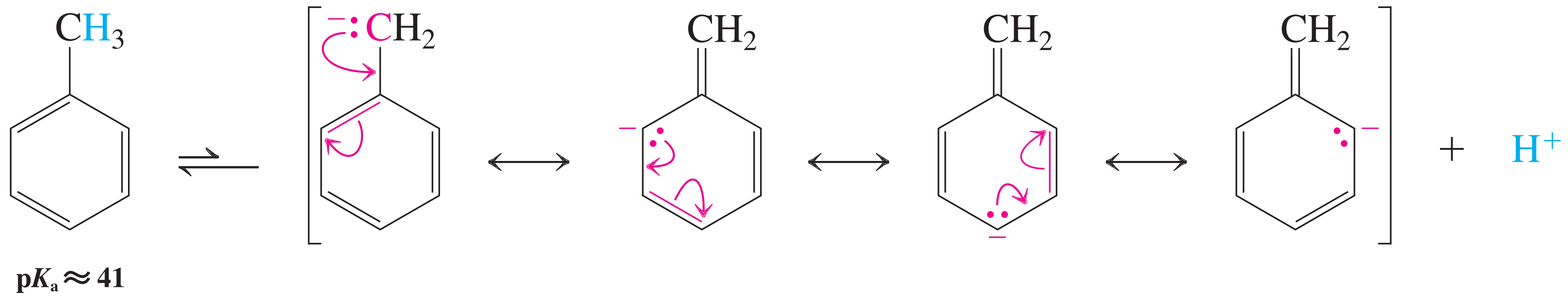
(∼ 100 times faster than S_N2 reactions of primary bromoalkanes)

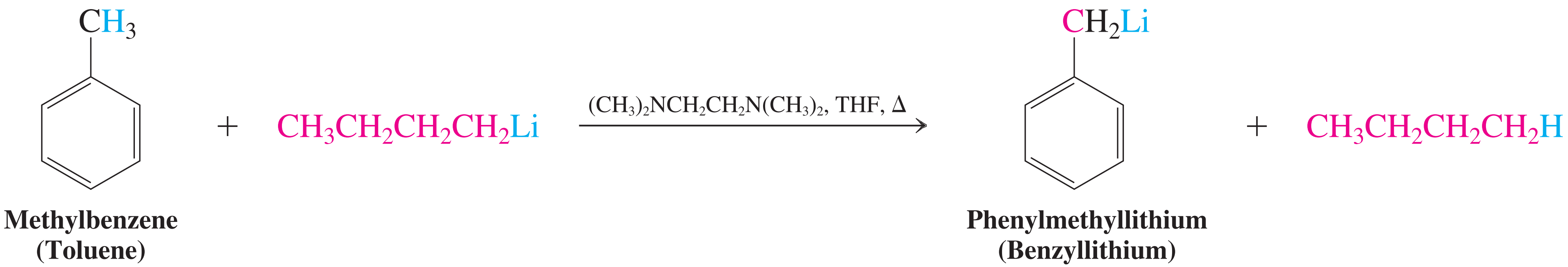
Resonance in benzylic anions makes benzylic hydrogens relatively acidic

A negative charge adjacent to a benzene ring, as in the benzyl anion, is stabilized by conjugation.

The acidity of methylbenzene (toluene; pK_a ≈ 41) is considerably greater than that of ethane (pK_a ≈ 50) and comparable to that of propene (pK_a ≈ 40).

Toluene can be deprotonated by butyllithium to generate phenylmethyllithium.





22-2 BENZYLIC OXIDATIONS AND REDUCTIONS

Because it is aromatic, the benzene ring is quite unreactive. While it does undergo electrophilic aromatic substitutions, reactions that dismantle the aromatic six-electron circuit, such as oxidations and reductions, are much more difficult to achieve.

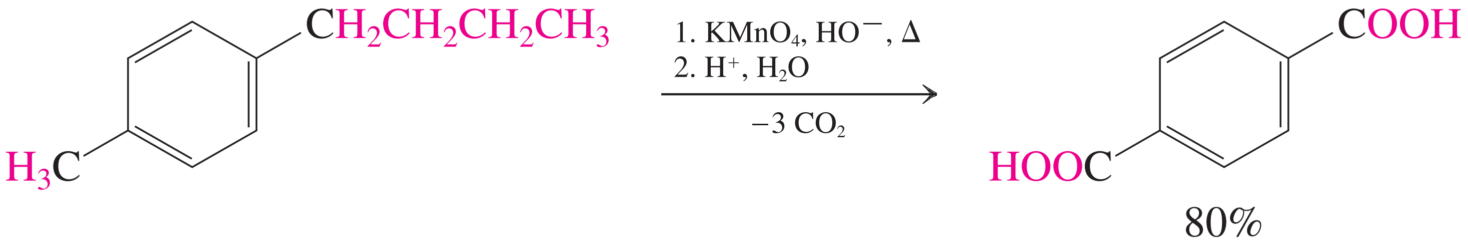
In contrast, such transformations occur with comparative ease when taking place at *benzylic* positions.

Oxidation of alkyl-substituted benzenes leads to aromatic ketones and acids

Reagents such as hot $KMnO_4$ and $Na_2Cr_2O_7$ may oxidize alkylbenzenes all the way to benzoic acids.

Benzylic carbon–carbon bonds are cleaved in this process, which usually requires at least one benzylic C–H bond to be present in the starting material (i.e., tertiary alkylbenzenes are inert).

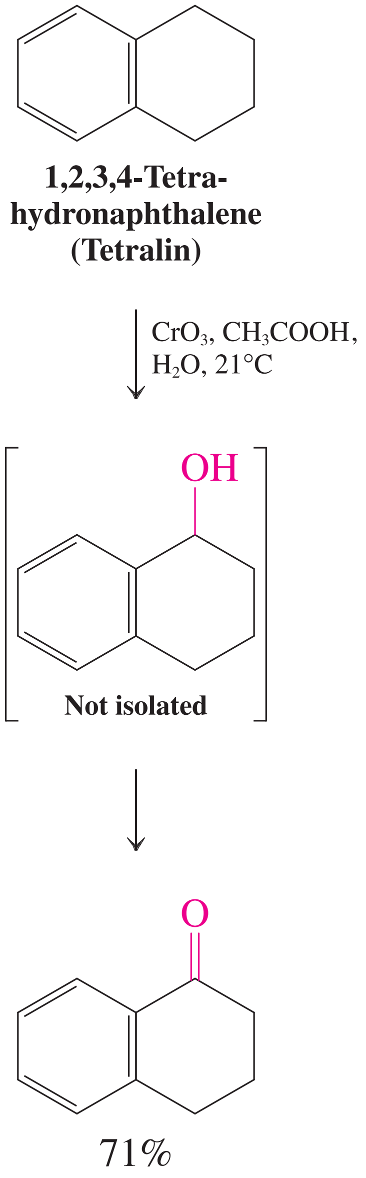
Complete Benzylic Oxidations of Alkyl Chains



1-Butyl-4-methylbenzene

1,4-Benzenedicarboxylic acid (Terephthalic acid)

The reaction proceeds through first the benzylic alcohol and then the ketone, at which stage it can be stopped under milder conditions.

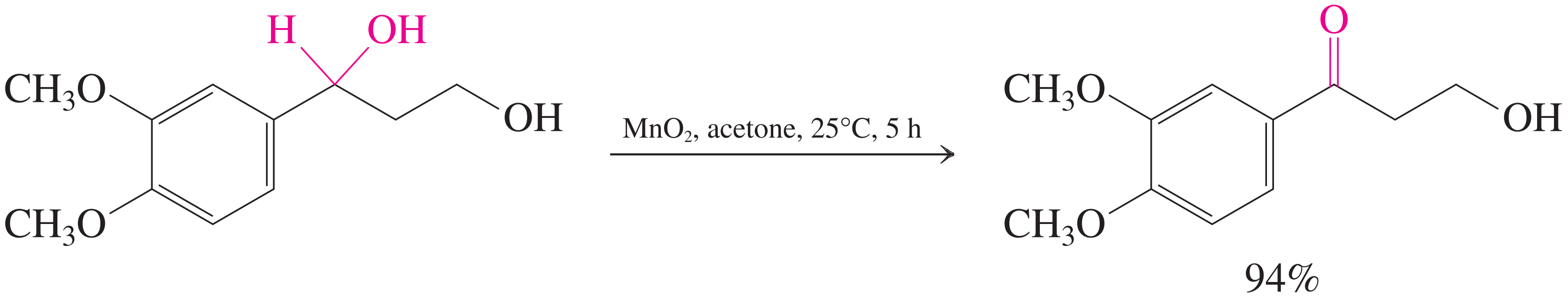


1-Oxo-1,2,3,4-tetrahydronaphthalene (1-Tetralone)

The special reactivity of the benzylic position is also seen in the mild conditions required for the oxidation of benzylic alcohols to the corresponding carbonyl compounds.

For example, manganese dioxide, MnO_2, performs this oxidation selectively in the presence of other (nonbenzylic) hydroxy groups. (Recall that MnO_2 was used in the conversion of allylic alcohols into **α**,**β**-unsaturated aldehydes and ketones.)

Selective Oxidation of a Benzylic Alcohol with Manganese Dioxide

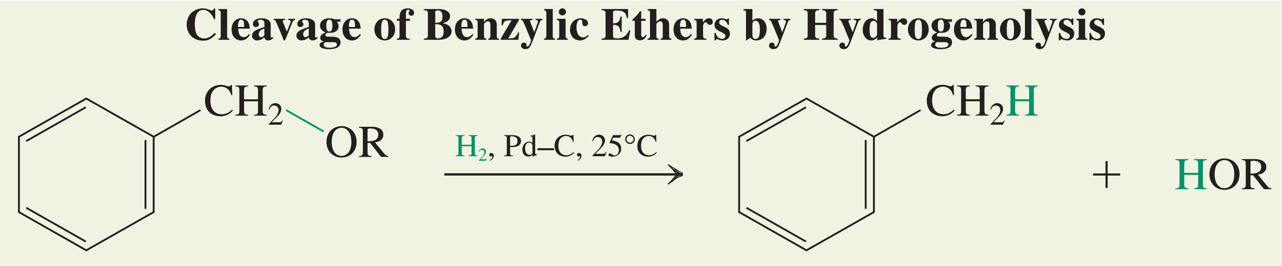


Benzylic ethers are cleaved by hydrogenolysis

Exposure of benzylic alcohols, ethers, or esters to hydrogen in the presence of metal catalysts results in rupture of the reactive benzylic carbon–oxygen bond.

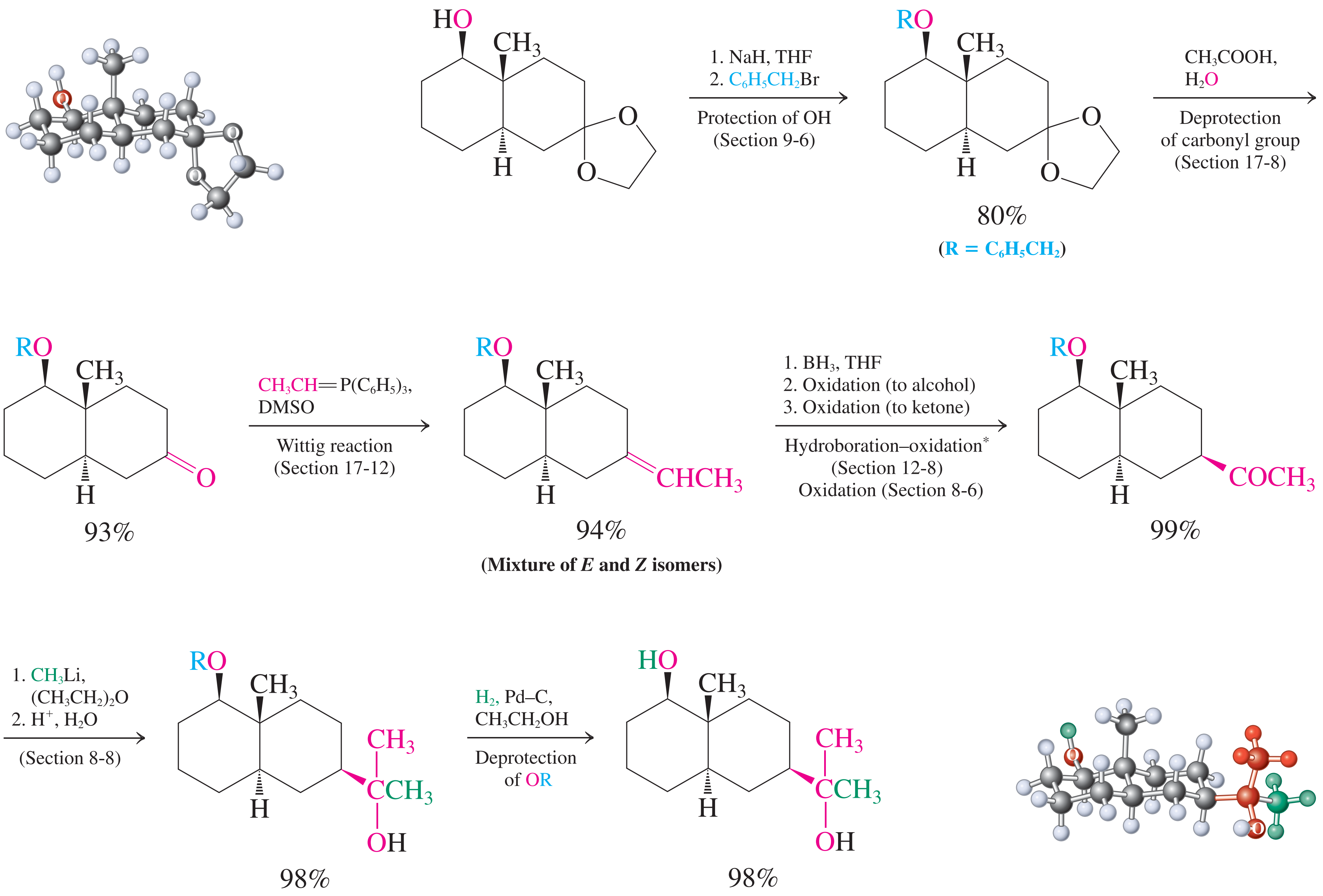
This transformation is an example of **hydrogenolysis,** cleavage of a **σ** bond by catalytically activated hydrogen.

Hydrogenolysis is not possible for ordinary alcohols, ethers, and esters. Therefore, the benzyl substituent is a valuable protecting group for hydroxy functions.



The following scheme shows its use in part of a synthesis of a compound in the eudesmane class of volatile plant oils, which includes substances of importance in both medicine and perfumery.

Phenylmethyl Protection in a Complex Synthesis



1. NaH, THF
2. $C_6H_5CH_2Br$

Protection of OH (Section 9-6)

80%

(R = $C_6H_5CH_2$)

CH_3COOH, H_2O

Deprotection of carbonyl group (Section 17-8)

93%

$CH_3CH{=}P(C_6H_5)_3$, DMSO

Wittig reaction (Section 17-12)

94%

(Mixture of *E* and *Z* isomers)

1. BH_3, THF
2. Oxidation (to alcohol)
3. Oxidation (to ketone)

Hydroboration–oxidation* (Section 12-8)
Oxidation (Section 8-6)

99%

1. CH_3Li, $(CH_3CH_2)_2O$
2. H^+, H_2O

(Section 8-8)

98%

H_2, Pd–C, CH_3CH_2OH

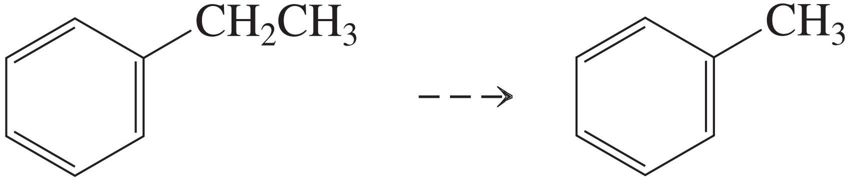
Deprotection of OR

98%

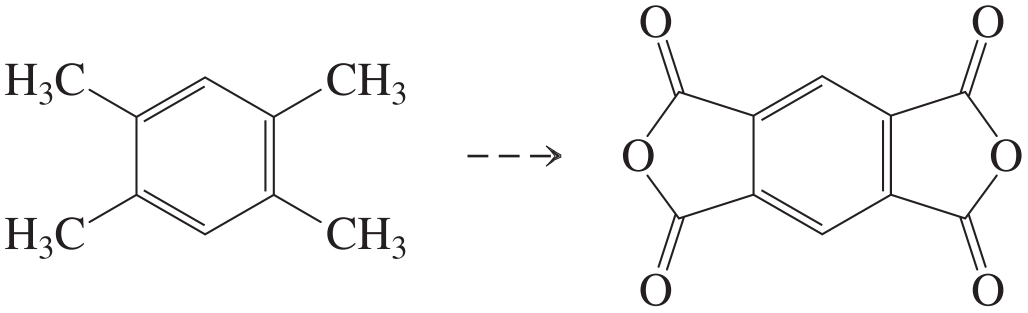
Exercise 22-5

Write synthetic schemes that would connect the following starting materials with their products.

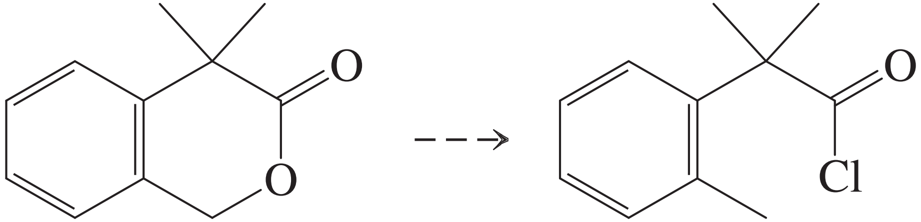
(a)



(b)



(c)

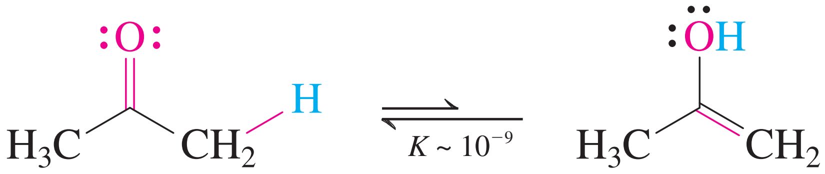


22-3 NAMES AND PROPERTIES OF PHENOLS

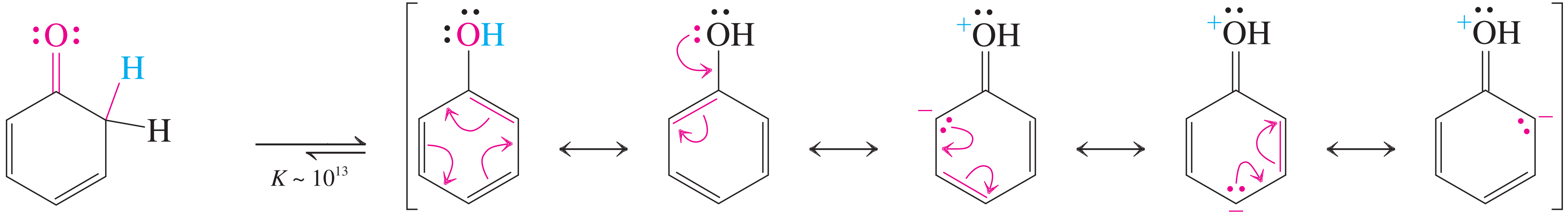
Arenes substituted by hydroxy groups are called **phenols**. The **π** system of the benzene ring overlaps with an occupied *p* orbital on the oxygen atom, a situation resulting in delocalization similar to that found in benzylic anions.

As one result of this extended conjugation, phenols possess an unusual, enolic structure. Enols are usually unstable, and tautomerize easily to the corresponding ketones because of the relatively strong carbonyl bond.

Phenols prefer the enol to the keto form because the aromatic character of the benzene ring is preserved.



Acetone **2-Propenol**



2,4-Cyclohexadienone **Phenol**

Phenols and their ethers are ubiquitous in nature; some derivatives have medicinal and herbicidal applications, whereas others are important industrial materials.

Phenols are hydroxyarenes

Phenol itself was formerly known as carbolic acid. It forms colorless needles (m.p. 41 ^{o}C), has a characteristic odor, and is somewhat soluble in water.

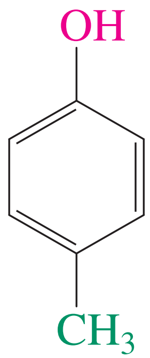
Aqueous solutions of it (or its methyl-substituted derivatives) are applied as disinfectants, but its main use is for the preparation of polymers (phenolic resins).

Pure phenol causes severe skin burns and is toxic; deaths have been reported from the ingestion of as little as 1 g. Fatal poisoning may also result from absorption through the skin.

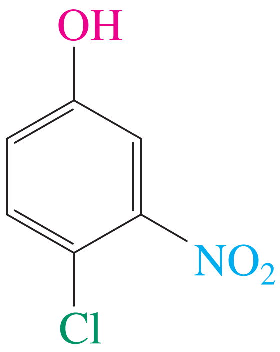
Substituted phenols are named as phenols, benzenediols, or benzenetriols, although some common names are accepted by IUPAC. These substances find uses in the photography, dyeing, and tanning industries.

The compound bisphenol A is an important monomer in the synthesis of epoxyresins and polycarbonates, materials that are widely employed in the manufacture of durable plastic materials, food packaging, dental sealants, and coatings inside beverage cans.

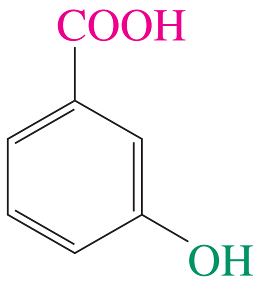
Phenols containing the higher-ranking carboxylic acid functionality are called **hydroxybenzoic acids.** Many have common names. Phenyl ethers are named as **alkoxybenzenes.** As a substituent, C_6H_5O is called **phenoxy.**



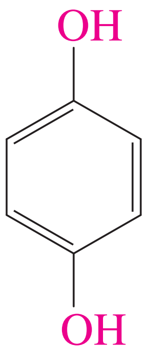
4-Methylphenol
(*p*-Cresol)



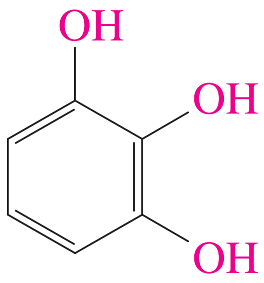
4-Chloro-
3-nitrophenol



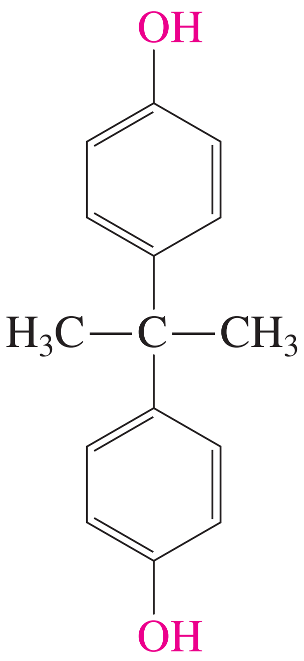
3-Hydroxybenz-
oic acid
(*m*-Hydroxybenzoic acid)



1,4-Benzenediol
(Hydroquinone)

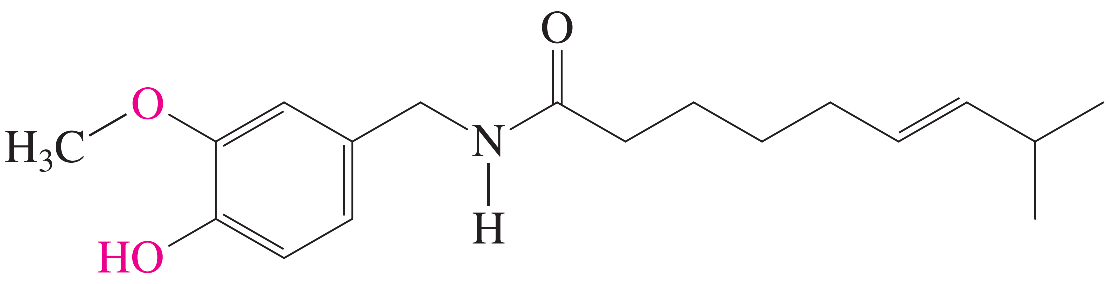


1,2,3-Benzenetriol
(Pyrogallol)



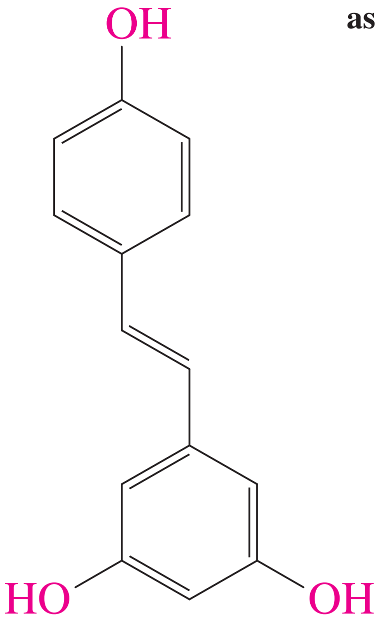
Bisphenol A

Many examples of phenol derivatives, particularly those exhibiting physiological activity.



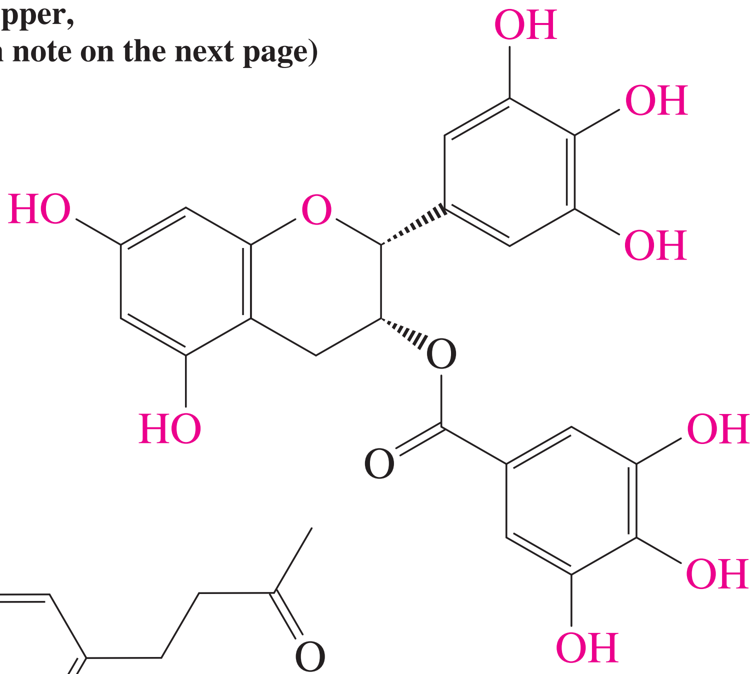
Capsaicin

(Active ingredient in hot pepper,
as in jalapeño or cayenne pepper; see margin note on the next page)



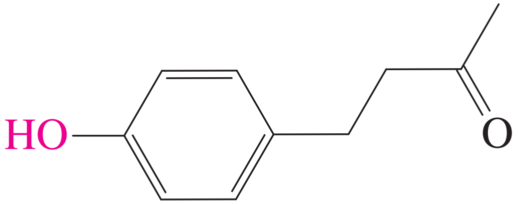
Resveratrol

(Cancer chemopreventive
from grapes; see also
Real Life 22-1)



Epigallocatechin-3 gallate

(Cancer chemopreventive
from green tea)



4-(4-Hydroxyphenyl)-2-butanone

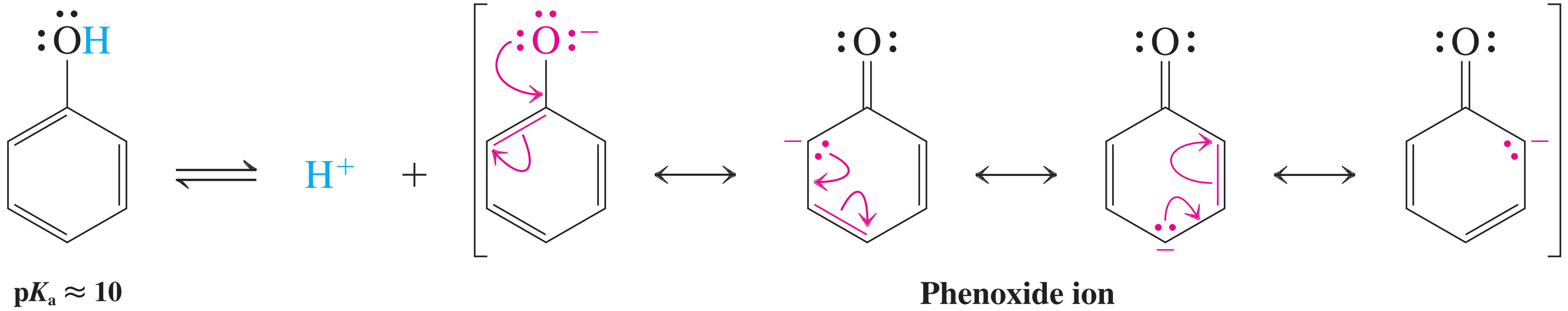
(Flavor of raspberries)

Phenols are unusually acidic

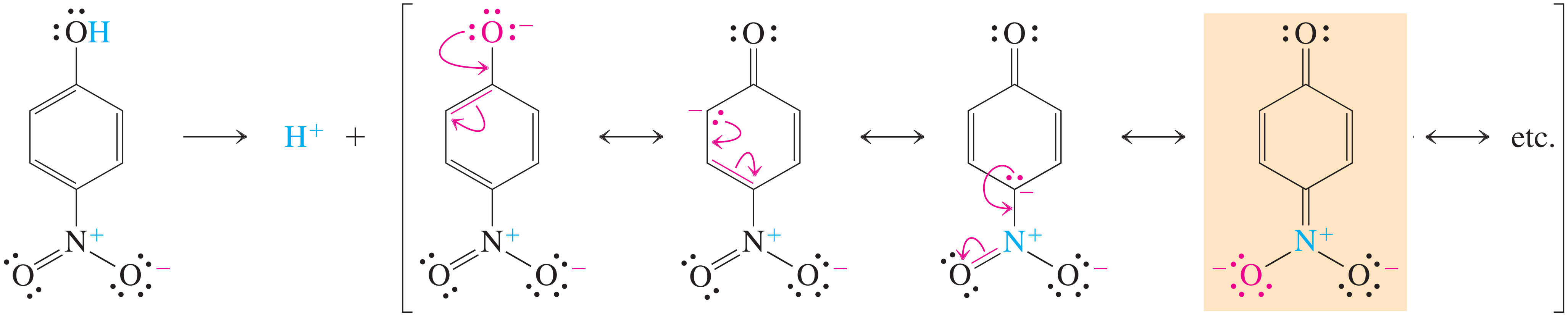
Phenols have pK_a values that range from 8 to 10. Even though they are less acidic than carboxylic acids (pK_a = 3–5), they are stronger than alkanols (pK_a = 16–18).

The reason is **resonance**: The negative charge in the conjugate base, called the **phenoxide ion,** is stabilized by delocalization into the ring.

Acidity of Phenol



The acidity of phenols is greatly affected by substituents that are capable of resonance. 4-Nitrophenol (*p*-nitrophenol), for example, has a pK_a of 7.15.



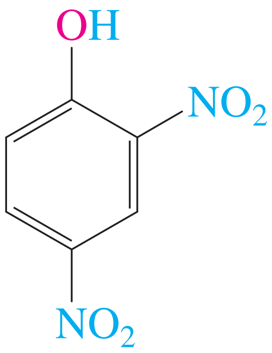
pK_a = 7.15

Negative charge delocalized into the nitro group

The 2-isomer has similar acidity (pK_a = 7.22), whereas nitrosubstitution at C3 results in a pK_a of 8.39. Multiple nitration increases the acidity to that of carboxylic or even mineral acids.

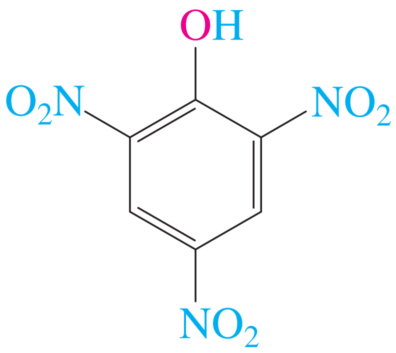
Electron-donating substituents have the opposite effect, raising the pK_a.

The oxygen in phenol and its ethers is also weakly basic, in the case of ethers giving rise to acid-catalyzed cleavage.



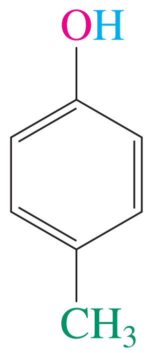
2,4-Dinitrophenol

pK_a = 4.09



2,4,6-Trinitrophenol (Picric acid)

pK_a = 0.25



4-Methylphenol (*p*-Cresol)

pK_a = 10.26