Organic Chemistry III

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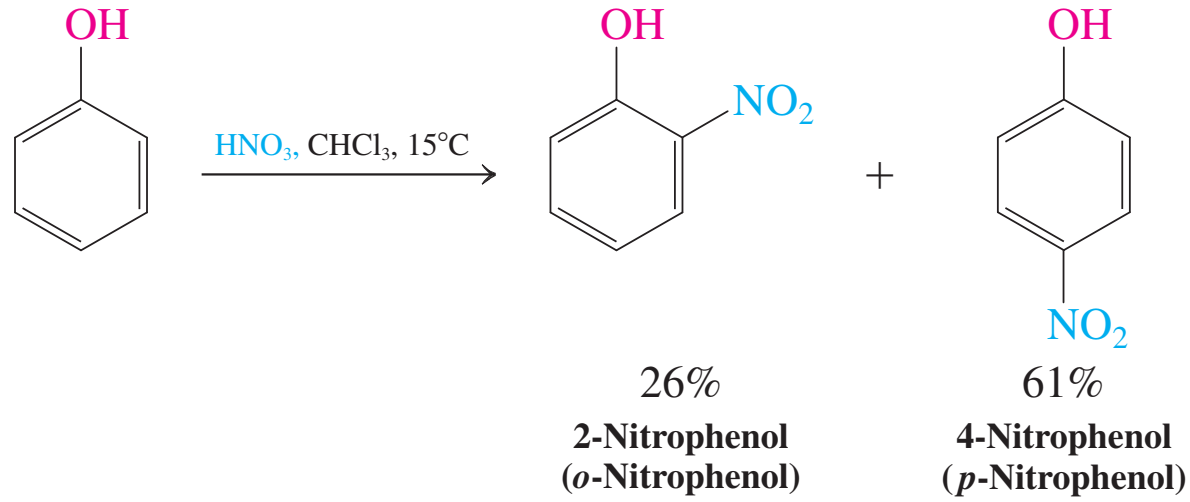
By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

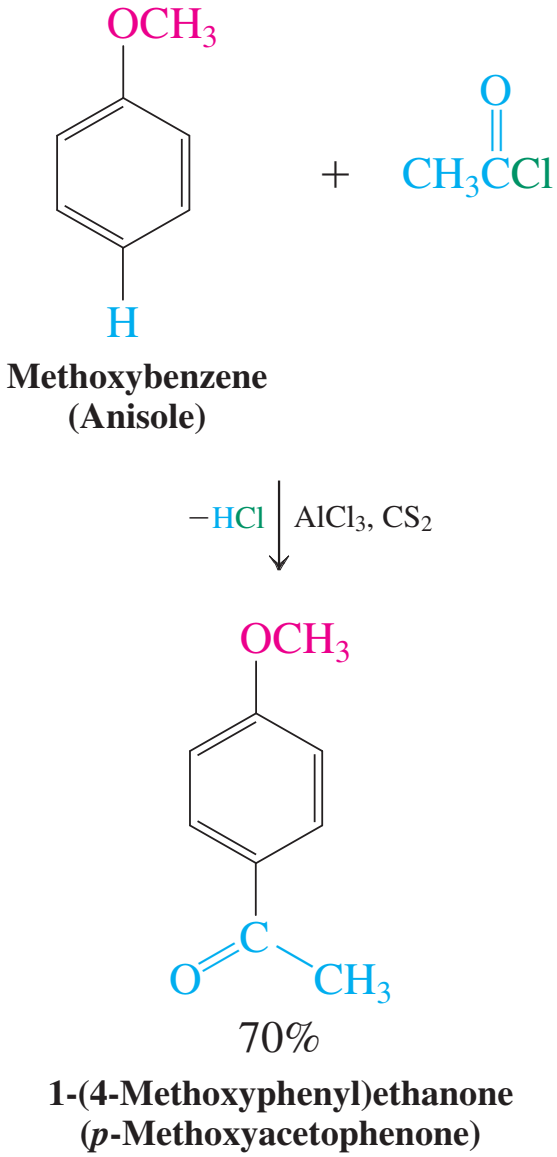
22-6 ELECTROPHILIC SUBSTITUTION OF PHENOLS

The aromatic ring in phenols is also a center of reactivity. The interaction between the OH group and the ring strongly activates the *ortho* and *para* positions toward electrophilic substitution.

For example, even dilute nitric acid causes nitration.

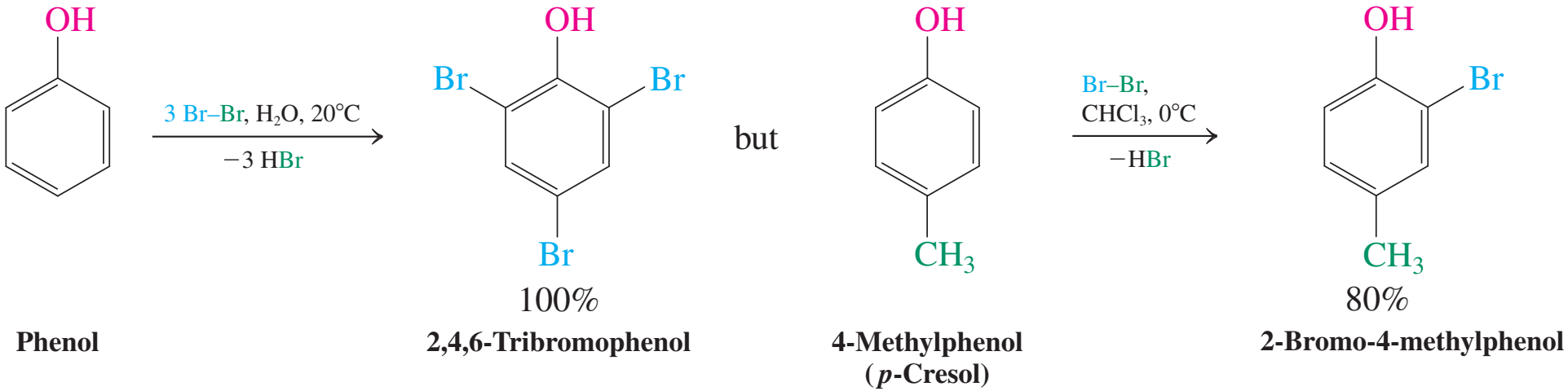


Friedel-Crafts acylation of phenols is complicated by ester formation and is better carried out on ether derivatives of phenol.



Phenols are halogenated so readily that a catalyst is not required, and multiple halogenations are frequently observed.

Tribromination occurs in water at 20 °C, but the reaction can be controlled to produce the monohalogenation product through the use of a lower temperature and a less polar solvent.



Phenol

100%

2,4,6-Tribromophenol

4-Methylphenol (*p*-Cresol)

80%

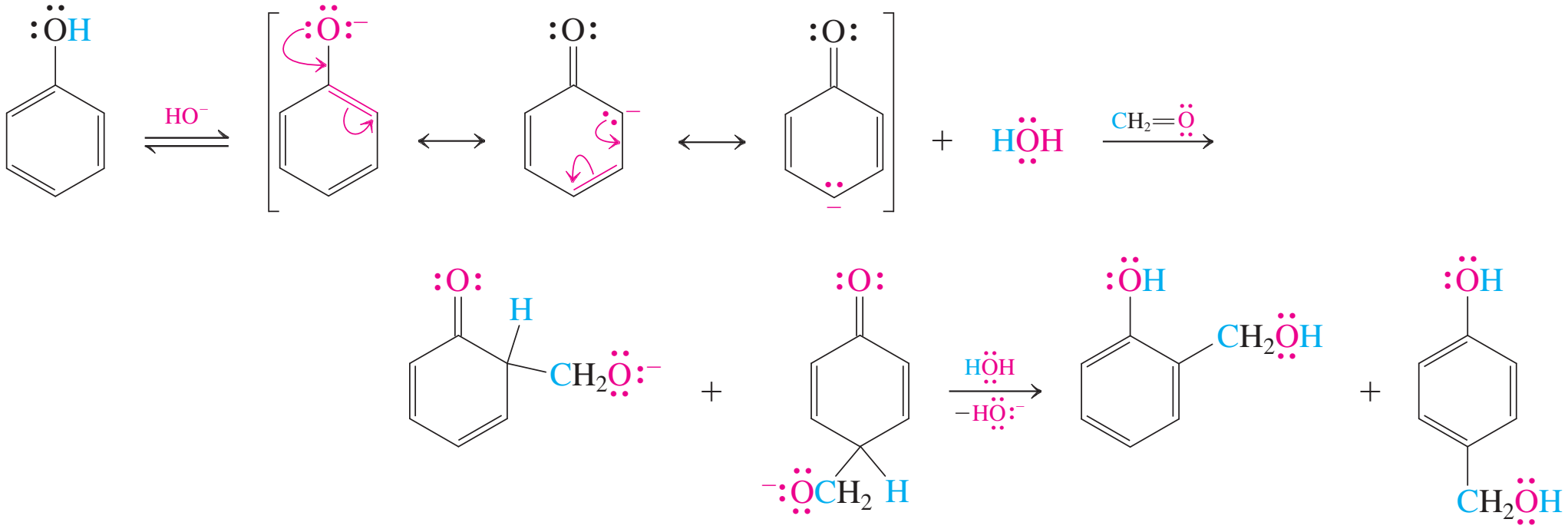
2-Bromo-4-methylphenol

Electrophilic attack at the *para* position is frequently dominant because of steric effects. However, it is normal to obtain mixtures resulting from both *ortho* and *para* substitutions, and their compositions are highly dependent on reagents and reaction conditions.

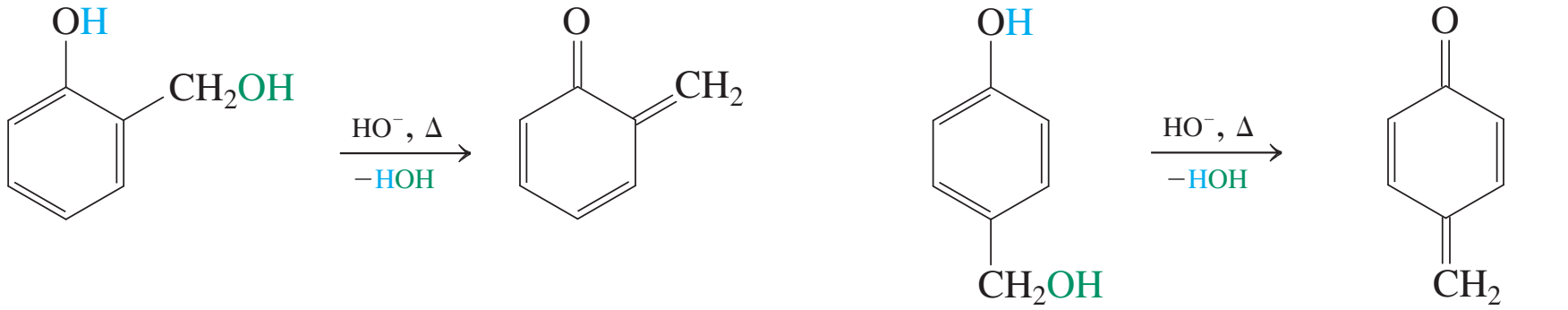
Under basic conditions, phenols can undergo electrophilic substitution, even with very mild electrophiles, through intermediate phenoxide ions. An industrially important application is the reaction with formaldehyde, which leads to *o*- and *p*-hydroxymethylation.

Mechanistically, these processes may be considered enolate condensations, much like the aldol reaction.

Hydroxymethylation of Phenol



The initial aldol products are unstable: They dehydrate on heating, giving reactive intermediates called **quinomethanes.**



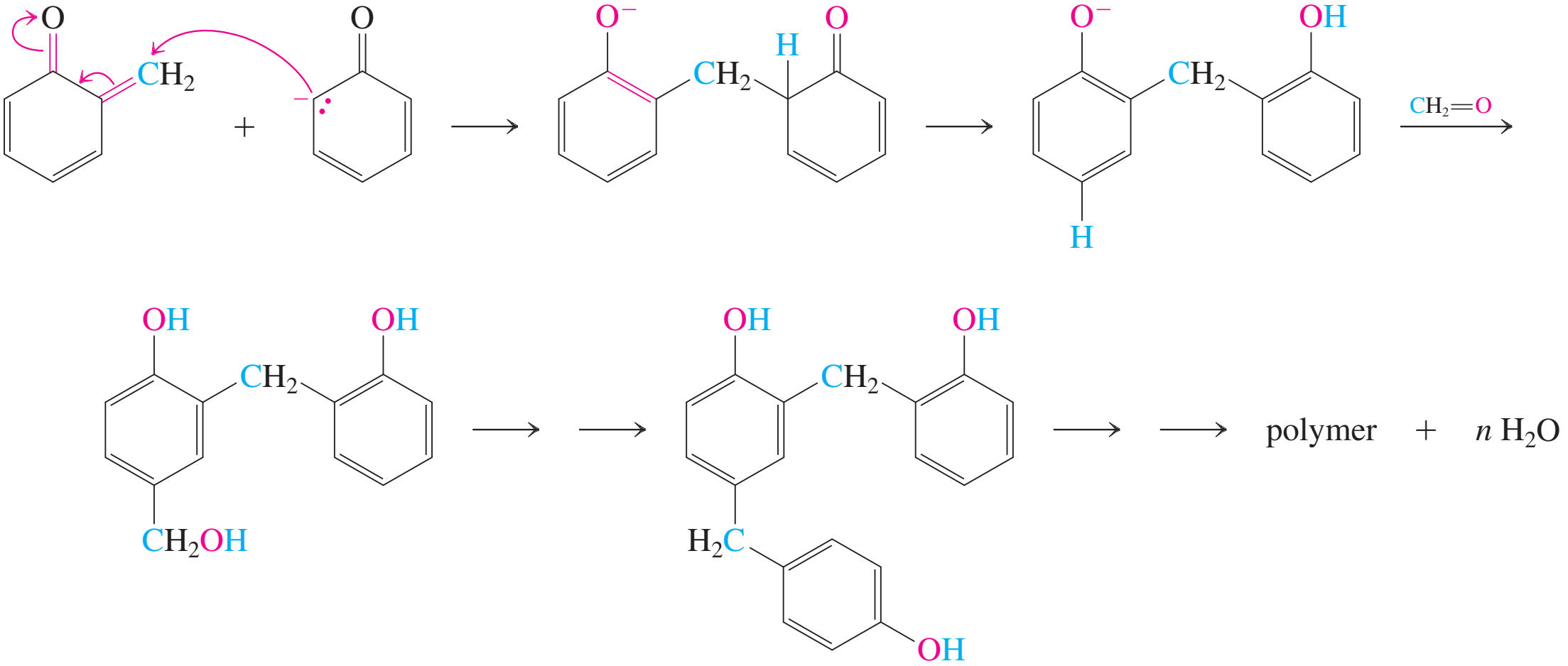
o-Quinomethane

p-Quinomethane

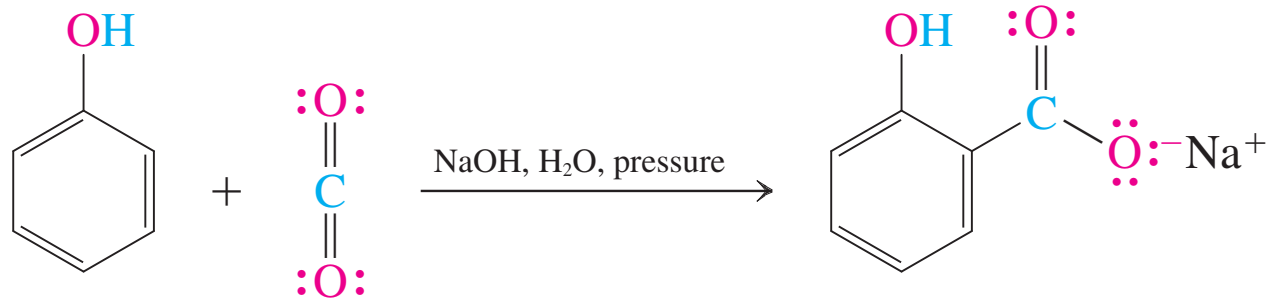
Because quinomethanes are **α**,**β**-unsaturated carbonyl compounds, they may undergo Michael additions with excess phenoxide ion. The resulting phenols can be hydroxymethylated again and the entire process repeated.

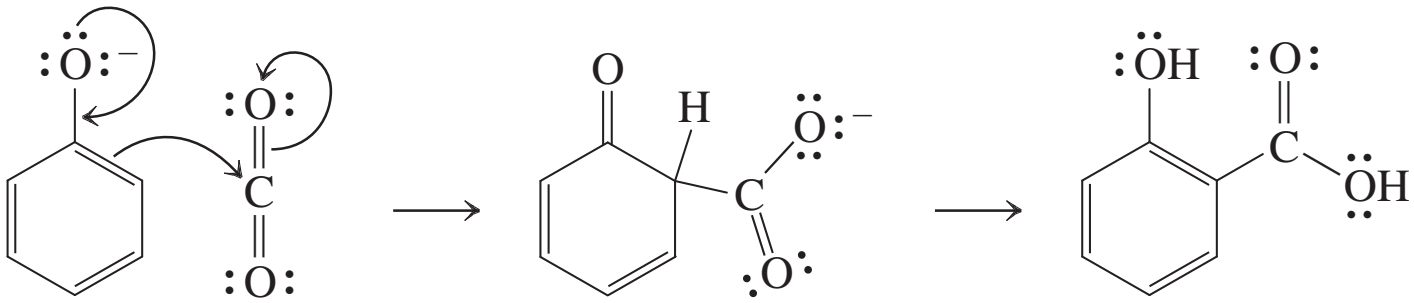
Eventually, a complex phenol– formaldehyde copolymer, also called a **phenolic resin** (e.g., Bakelite), is formed. Their major uses are in plywood (45%), insulation (14%), molding compounds (9%), fibrous and granulated wood (9%), and laminates (8%).

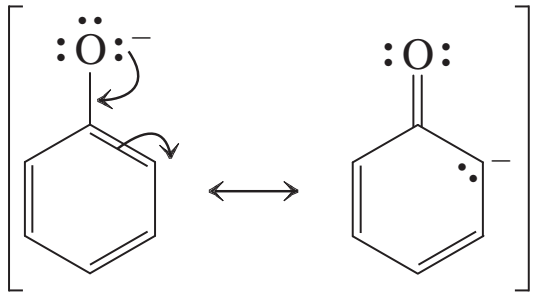
Phenolic Resin Synthesis



In the **Kolbe-Schmitt reaction,** phenoxide attacks carbon dioxide to furnish the salt of 2-hydroxybenzoic acid (*o*-hydroxybenzoic acid, salicylic acid, precursor to aspirin).



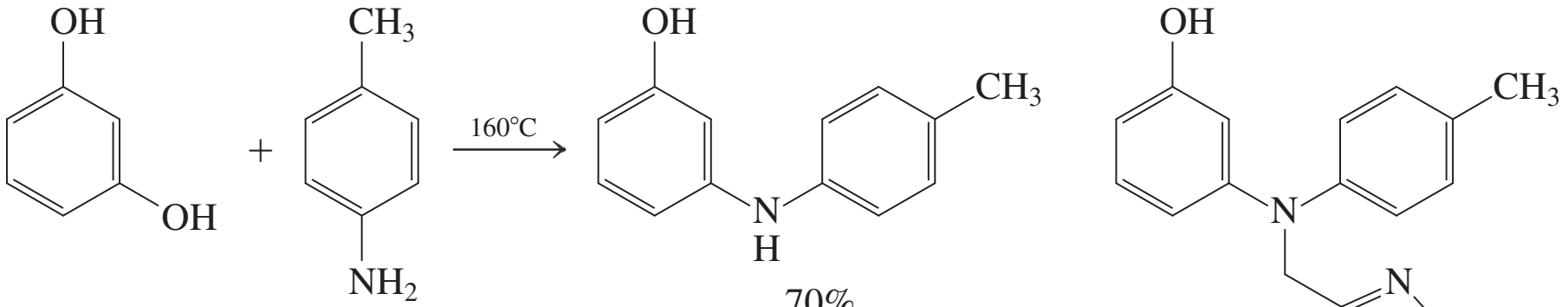




Phenoxide ion

Exercise 22-22

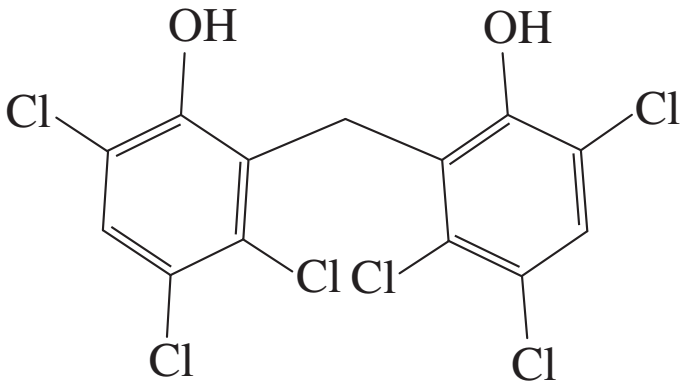
Phentolamine (as a water-soluble methanesulfonic acid salt) is an antihypertensive that has recently been introduced into dentistry: It cuts in half the time taken to recover from the numbing effect of local anesthetics. The key step in its preparation dates from 1886, the reaction shown below. What is its mechanism? (**Caution:** This is not a nucleophilic aromatic substitution. **Hint:** Think keto–enol tautomerism).



Phentolamine

Exercise 22-23

Hexachlorophene is a skin germicide formerly used in soaps. It is prepared in one step from 2,4,5-trichlorophenol and formaldehyde in the presence of sulfuric acid. How does this reaction proceed? (**Hint:** Formulate an acid-catalyzed hydroxymethylation for the first step.)



Hexachlorophene

22-8 OXIDATION OF PHENOLS: BENZOQUINONES

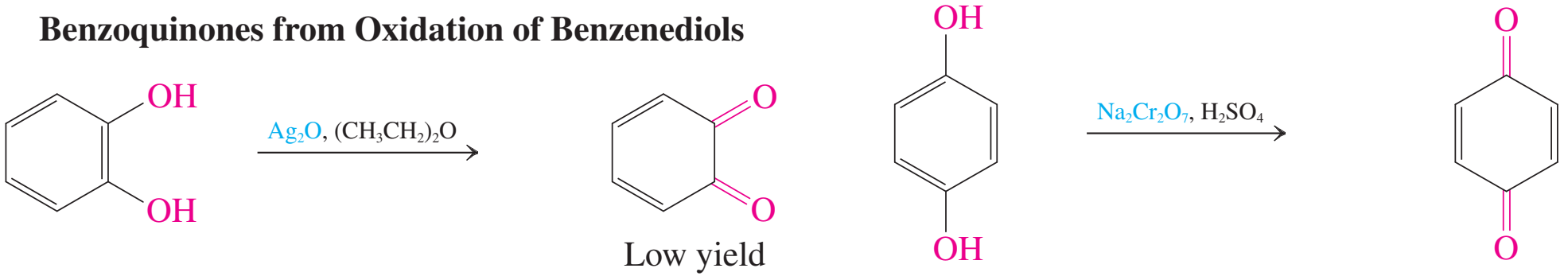
Phenols can be oxidized to carbonyl derivatives by one-electron transfer mechanisms, resulting in a new class of cyclic diketones, called **benzoquinones.**

Benzoquinones and benzenediols are redox couples

The phenols, 1,2- and 1,4-benzenediol (for which the respective common names catechol and hydroquinone are retained by IUPAC) are oxidized to the corresponding diketones, *ortho*- and *para*-benzoquinone, by a variety of oxidizing agents, such as sodium dichromate or silver oxide.

Yields can be variable when the resulting diones are reactive, as in the case of *o*-benzoquinone, which partly decomposes under the conditions of its formation.

Benzoquinones from Oxidation of Benzenediols

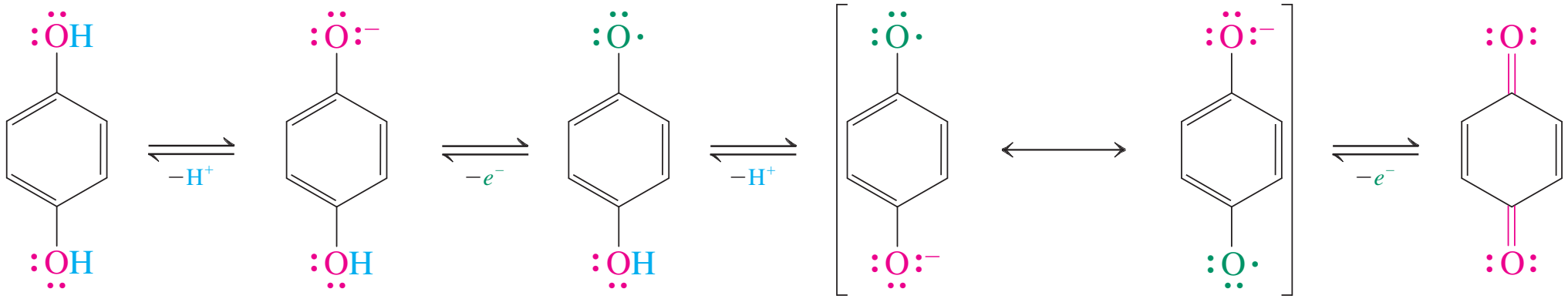


The redox process that interconverts hydroquinone and *p*-benzoquinone can be visualized as a sequence of proton and electron transfers.

Initial deprotonation gives a phenoxide ion, which is transformed into a **phenoxy radical** by one-electron oxidation. Proton dissociation from the remaining OH group furnishes a **semiquinone radical anion,** and a second one-electron oxidation step leads to the benzoquinone.

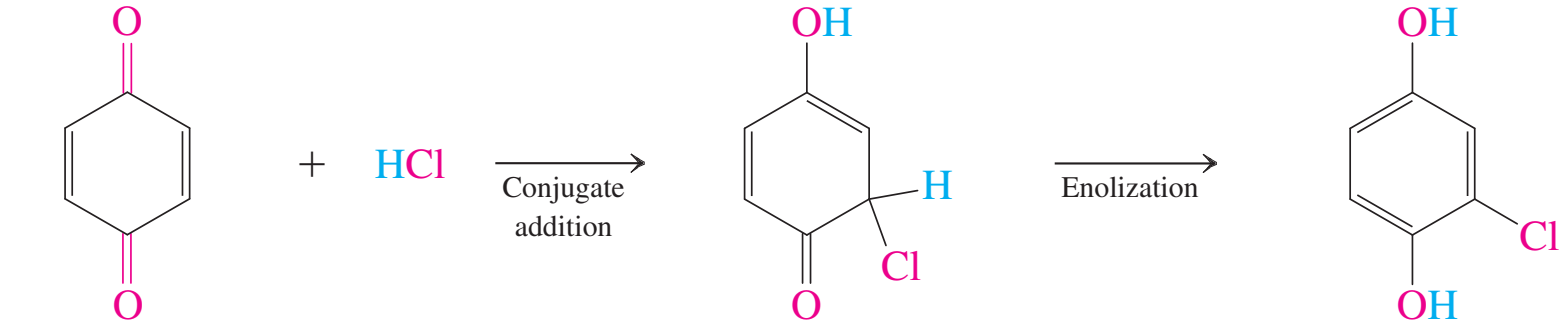
All of the intermediate species in this sequence benefit from considerable resonance stabilization.

Redox Relation Between *p*-Benzoquinone and Hydroquinone



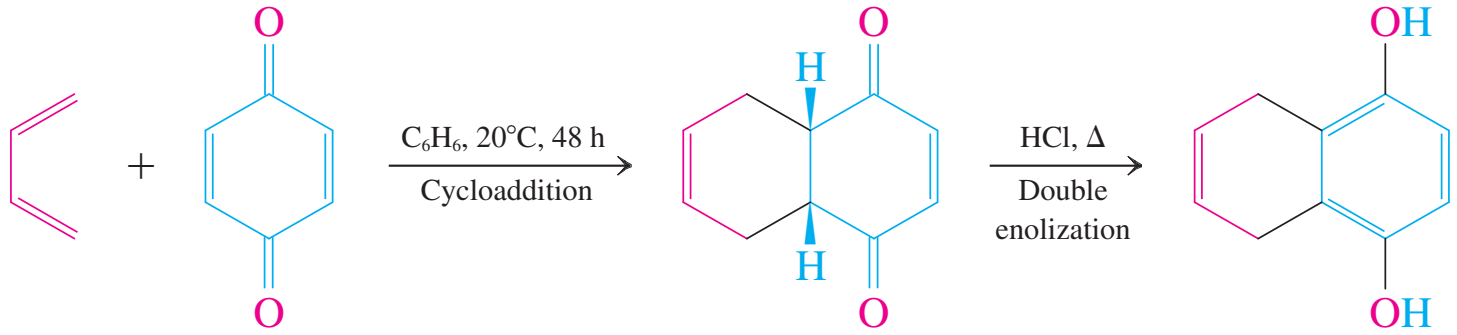
The enone units in *p*-benzoquinones undergo conjugate and Diels-Alder additions

p-Benzoquinones function as reactive **α,β**-unsaturated ketones in conjugate additions. Hydrogen chloride adds to give an intermediate hydroxy dienone that enolizes to the aromatic 2-chloro-1,4-benzenediol.



***p*-Benzoquinone** | **6-Chloro-4-hydroxy-2,4-cyclohexadienone** | **2-Chloro-1,4-benzenediol**

The double bonds also undergo cycloadditions to dienes. The initial cyclo-adduct tautomerizes with acid to the aromatic system.



88% overall

22-9 OXIDATION-REDUCTION PROCESSES IN NATURE

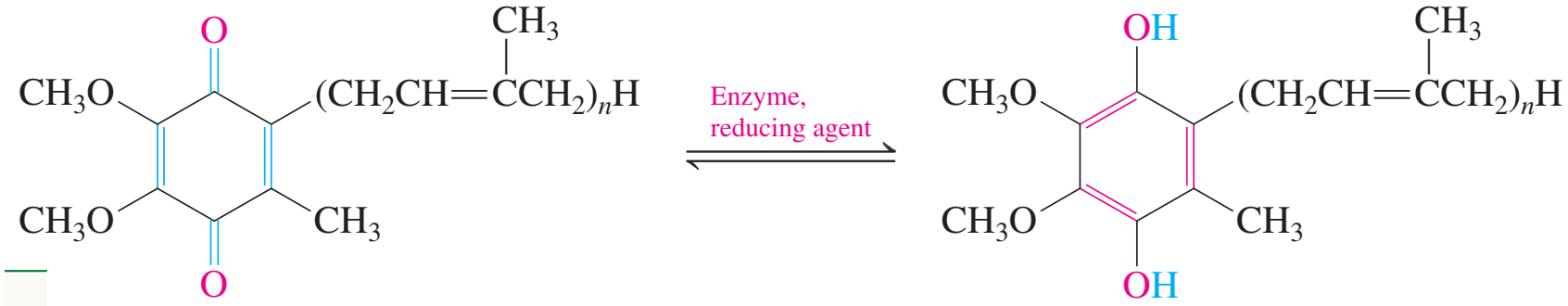
Chemical processes involving hydroquinones and *p*-benzoquinones that occur in nature. Oxygen can engage in reactions that cause damage to biomolecules. Natural **antioxidants** inhibit these transformations, as do several synthetic preservatives.

Ubiquinones mediate the biological reduction of oxygen to water

Nature makes use of the benzoquinone–hydroquinone redox couple in reversible oxidation reactions. These processes are part of the complicated cascade by which oxygen is used in biochemical degradations.

An important series of compounds used for this purpose are the **ubiquinones** (a name coined to indicate their ubiquitous presence in nature), also collectively called **coenzyme Q (CoQ,** or simply **Q).** The ubiquinones are substituted *p*-benzoquinone derivatives bearing a side chain made up of 2-methylbutadiene units (isoprene). An enzyme system that utilizes NADH converts CoQ into its reduced form (QH_2).

QH_2 participates in a chain of redox reactions with electron-transporting iron-containing proteins called **cytochromes**. The reduction of Fe^{3+} to Fe^{2+} in cytochrome *b* by QH_2 begins a sequence of electron transfers involving six different proteins. The chain ends with reduction of O_2 to water by addition of four electrons and four protons.



Ubiquinones (n = 6, 8, 10)
(Coenzyme Q)

Reduced form of coenzyme Q
(Reduced Q, or QH_2)

Phenol derivatives protect cell membranes from oxidative damage

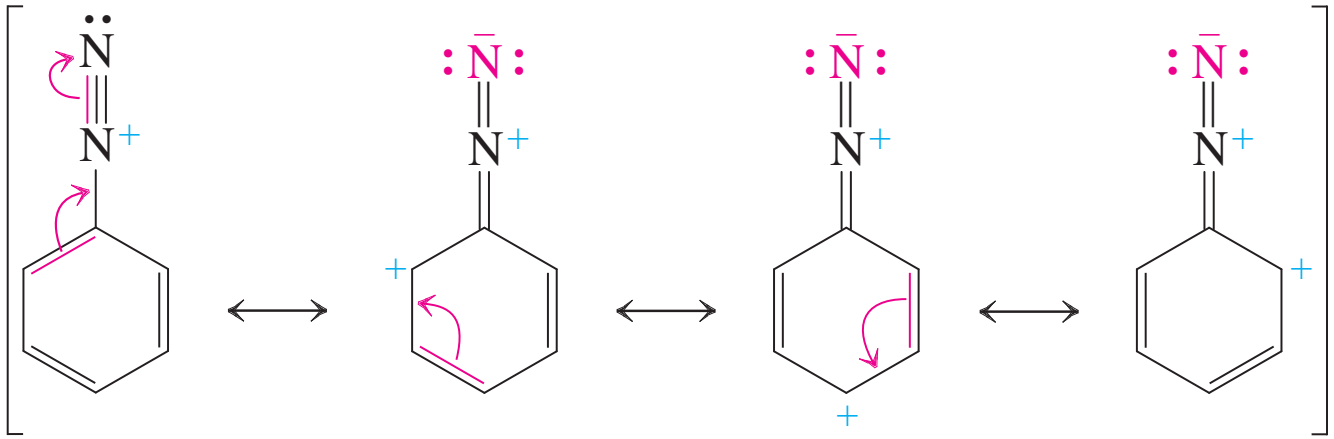
The biochemical conversion of oxygen into water includes several intermediates, including **superoxide,** $O_2^{\cdot -}$, the product of one-electron reduction, and **hydroxy radical,** ·OH, which arises from cleavage of H_2O_2. Both are highly reactive species capable of initiating reactions that damage organic molecules of biological importance. An example is the phosphoglyceride, a cell-membrane component derived from the unsaturated fatty acid *cis*,*cis*-octadeca-9,12-dienoic acid (linoleic acid).

22-10 ARENEDIAZONIUM SALTS

N-nitrosation of primary benzenamines (anilines) furnishes arenediazonium salts, which can be used in the synthesis of phenols.

Arenediazonium salts are stabilized by resonance of the π electrons in the diazo function with those of the aromatic ring.

They are converted into haloarenes, arenecarbonitriles, and other aromatic derivatives through replacement of nitrogen by the appropriate nucleophile.



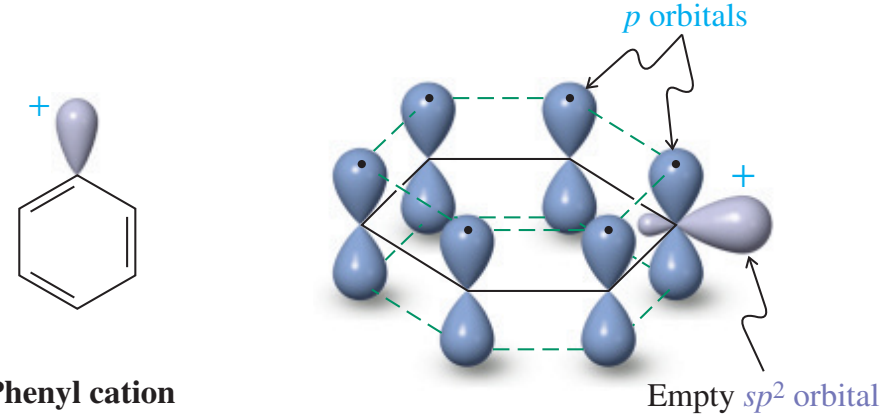
At elevated temperatures (>50 °C), nitrogen extrusion does take place to form the very reactive phenyl cation. When this is done in aqueous solution, phenols are produced.

Why is the phenyl cation so reactive?

The empty orbital associated with the positive charge is one of the sp^2 hybrids aligned in *perpendicular* fashion to the π framework that normally produces aromatic resonance stabilization.

Hence, this orbital cannot overlap with the π bonds, and the positive charge cannot be delocalized. Moreover, the cationic carbon would prefer *sp* hybridization, an arrangement precluded by the rigid frame of the benzene ring.

We used a similar argument to explain the difficulty in deprotonating benzene to the corresponding phenyl anion.

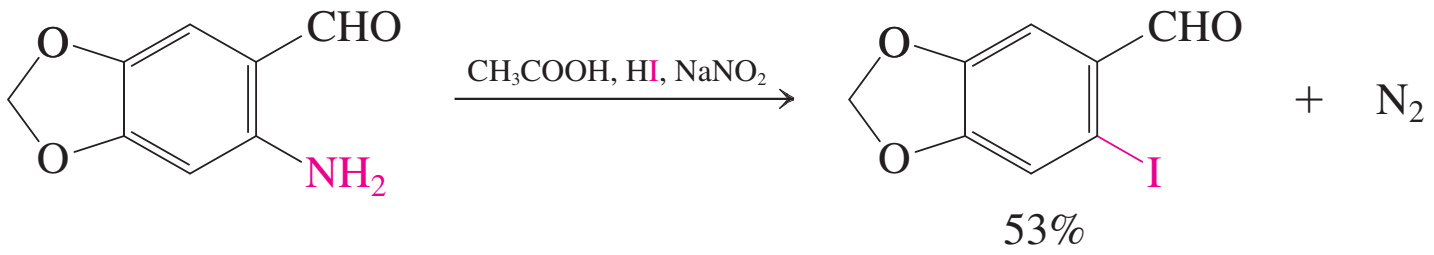


Arenediazonium salts can be converted into other substituted benzenes

When arenediazonium salts are decomposed in the presence of nucleophiles other than water, the corresponding substituted benzenes are formed.

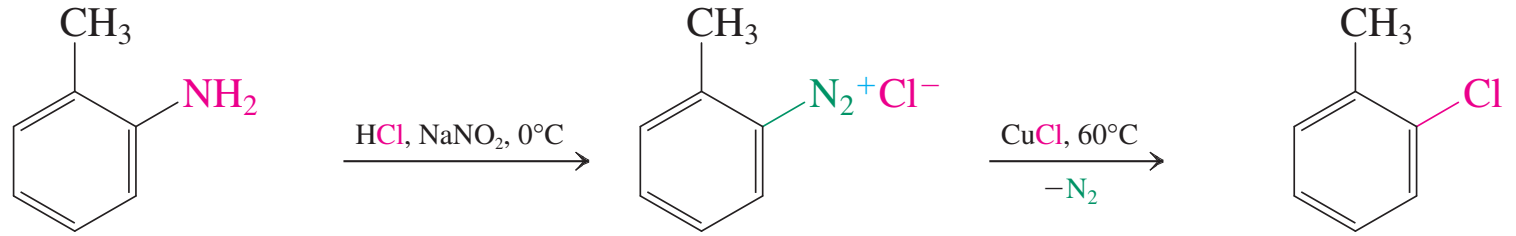
For example, diazotization of arenamines (anilines) in the presence of hydrogen iodide results in the corresponding iodoarenes.

Attempts to obtain other haloarenes in this way are frequently complicated by side reactions.



One solution to this problem is the **Sandmeyer reaction,** which makes use of the fact that the exchange of the nitrogen substituent for halogen is considerably facilitated by the presence of cuprous [Cu(I)] salts. The detailed mechanism of this process is complex, and radicals are participants.

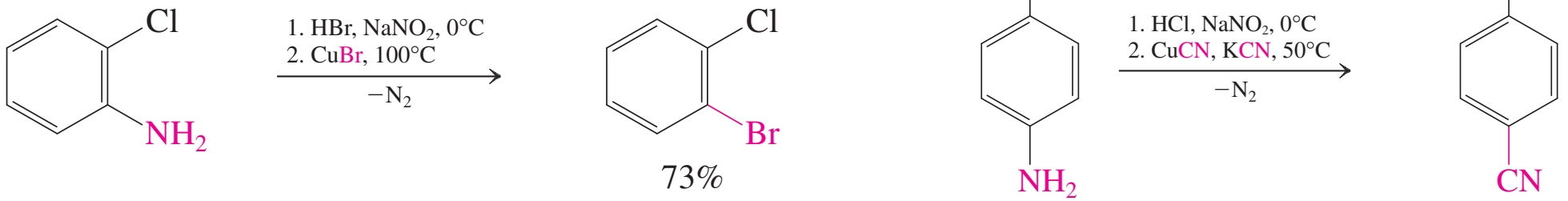
Addition of cuprous cyanide, CuCN, to the diazonium salt in the presence of excess potassium cyanide gives aromatic nitriles.



79% overall

2-Methylbenzenamine (*o*-Methylaniline)

1-Chloro-2-methylbenzene (*o*-Chlorotoluene)



73%

70%

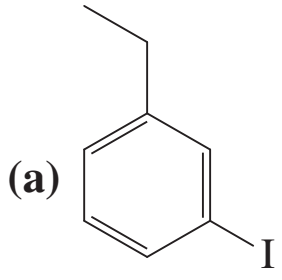
2-Chlorobenzenamine (*o*-Chloroaniline)

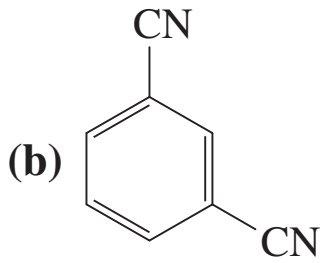
1-Bromo-2-chlorobenzene (*o*-Bromochlorobenzene)

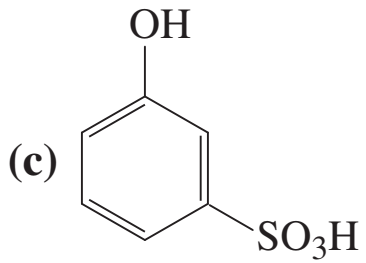
4-Methylbenzonitrile (*p*-Tolunitrile)

Exercise 22-30

Propose syntheses of the following compounds, starting from benzene.





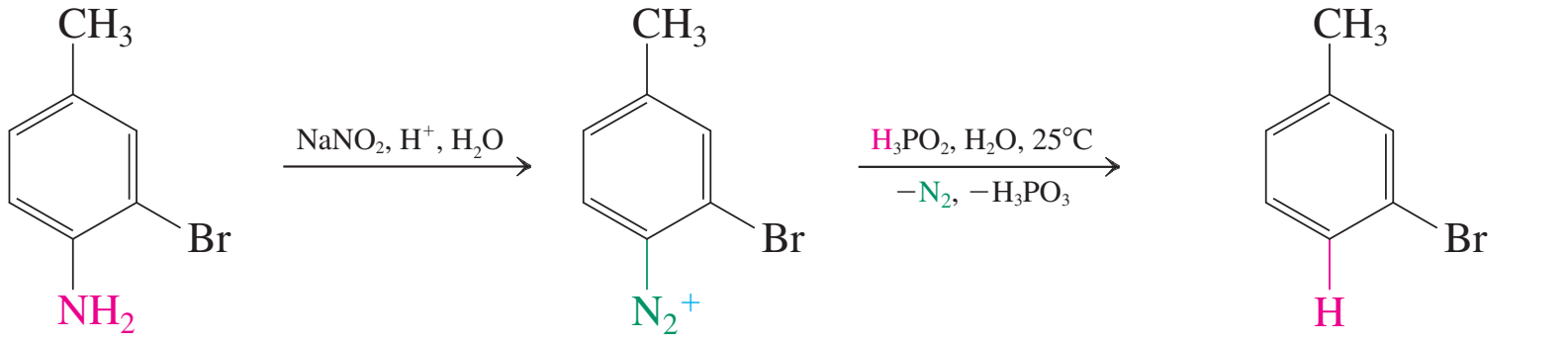


The diazonium group can be removed by reducing agents. The sequence diazotization–reduction is a way to replace the amino group in arenamines (anilines) with hydrogen.

The reducing agent employed is aqueous hypophosphorous acid, H_3PO_2.

This method is especially useful in syntheses in which an amino group is used as a removable directing substituent in electrophilic aromatic substitution.

Reductive Removal of a Diazonium Group



85%

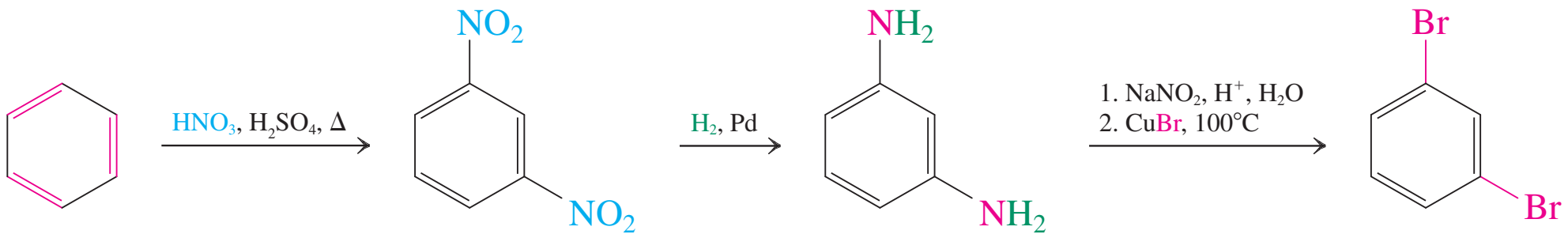
1-Bromo-3-methylbenzene
(*m*-Bromotoluene)

Another application of diazotization in synthetic strategy is illustrated in the synthesis of 1,3-dibromobenzene (*m*-dibromobenzene). Direct electrophilic bromination of benzene is not feasible for this purpose; after the first bromine has been introduced, the second will attack *ortho* or *para*.

What is required is a *meta*-directing substituent that can be transformed eventually into bromine. The nitro group is such a substituent. Double nitration of benzene furnishes 1,3-dinitrobenzene (*m*-dinitrobenzene).

Reduction leads to the benzenediamine, which is then converted into the dihalo derivative.

Synthesis of 1,3-Dibromobenzene by Using a Diazotization Strategy



22-11 ELECTROPHILIC SUBSTITUTION WITH ARENEDIAZONIUM SALTS: DIAZO COUPLING

Being positively charged, arenediazonium ions are electrophilic. Although they are not very reactive in this capacity, they can accomplish electrophilic aromatic substitution when the substrate is an activated arene, such as phenol or benzenamine (aniline).

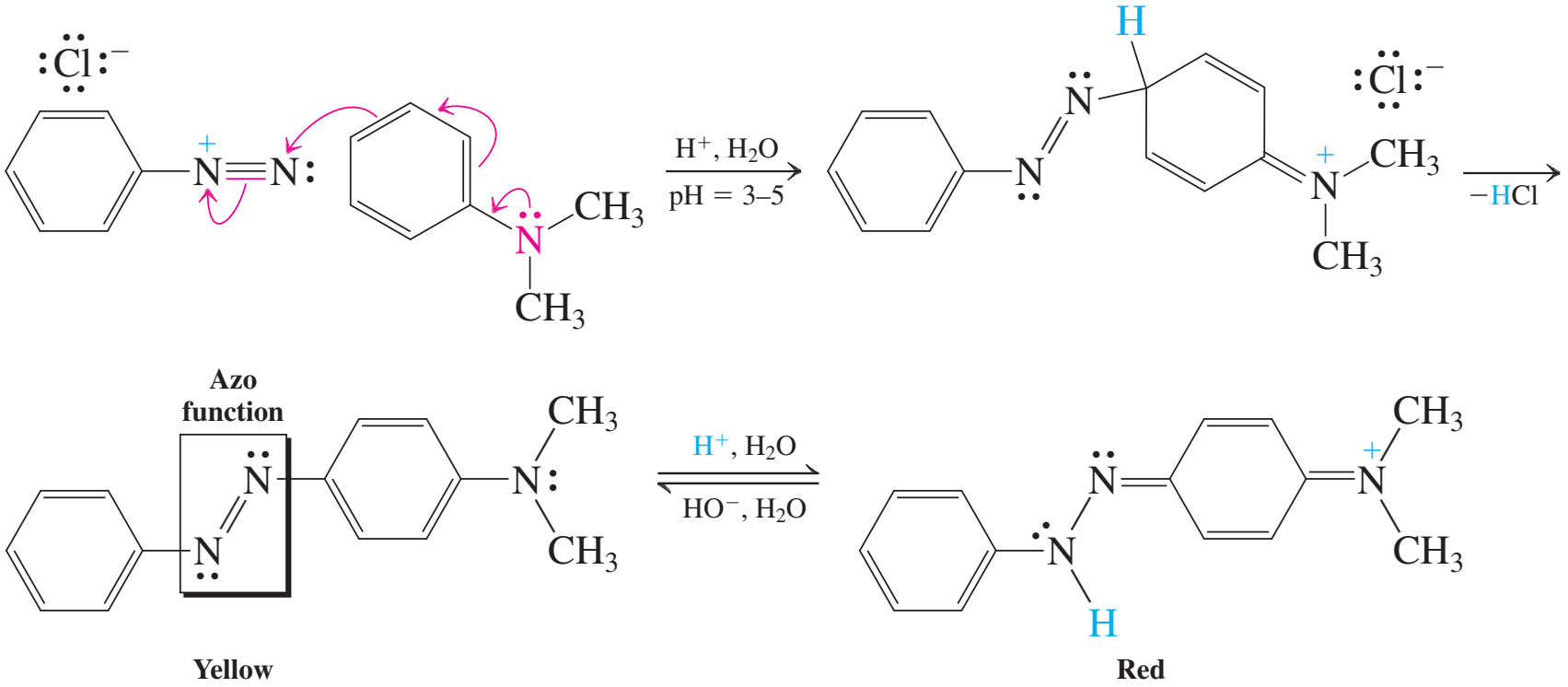
This reaction, called **diazo coupling,** leads to highly colored compounds called **azo dyes.**

For example, reaction of *N*,*N*-dimethylbenzenamine (*N*,*N*-dimethylaniline) with benzenediazonium chloride gives the brilliant orange dye Butter Yellow.

This compound was once used as a food coloring agent but has been declared a suspect carcinogen by the Food and Drug Administration.

Like many azo dyes, it is employed as a pH indicator, yellow above pH = 4.0, red below pH = 2.9. The reason for the color change is the protonation of one of the diazo nitrogens at low pH to generate a resonance-stabilized cation.

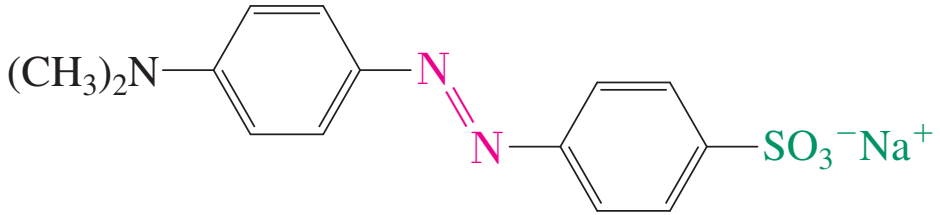
By UV-visible spectroscopy, the two colors of Butter Yellow are manifested in absorptions at λ_{max} = 420 nm (yellow) and 520 nm (red), respectively.

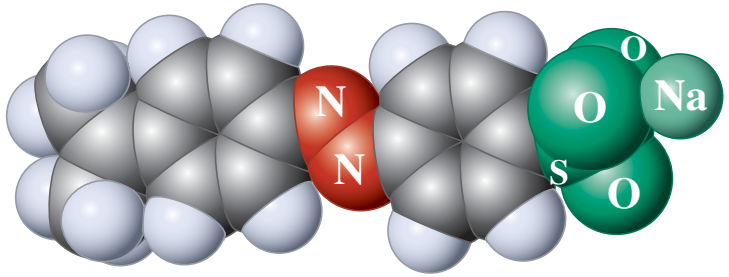


4-Dimethylaminoazobenzene
(*p*-Dimethylaminoazobenzene, Butter Yellow)

Dyes used in the clothing industry usually contain sulfonic acid groups that impart water solubility and allow the dye molecule to attach itself ionically to charged sites on the polymer framework of the textile.

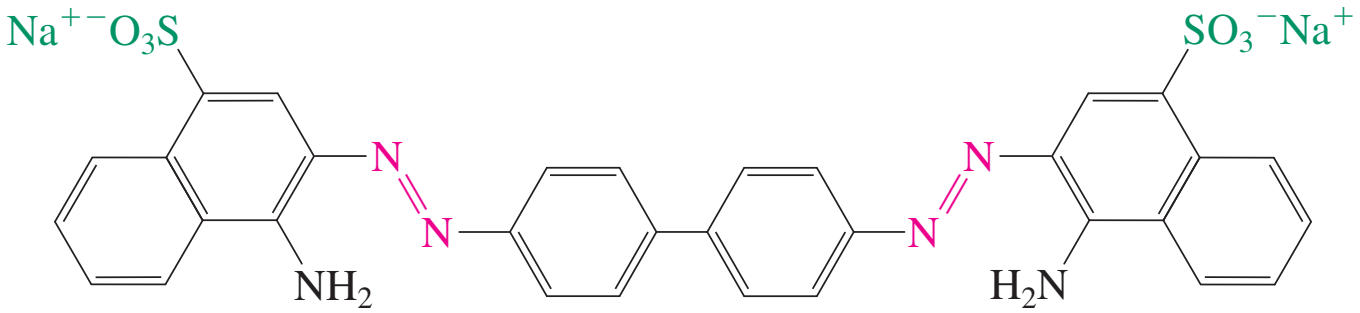
Industrial Dyes





Methyl Orange

pH ≤ 3.1, red; λ_{max} = 520 nm
pH ≥ 4.4, yellow; λ_{max} = 450 nm



Congo Red

pH ≤ 3.0, blue-violet; λ_{max} = 590 nm
pH ≥ 5.2, red; λ_{max} = 497 nm