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OpenCourseWare (2023)

CHEMISTRY II

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Organic Compounds:

Alcohols, Phenols, Ethers, Carbonyl compounds, Carboxylic acids, and Amines

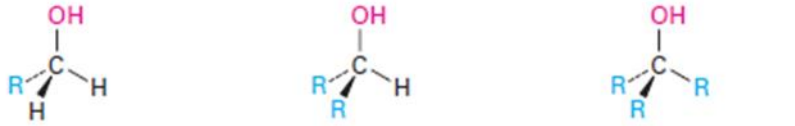
1. ALCOHOLS AND PHENOLS

When the term "alcohol" is mentioned, the immediate association is typically with ethanol, the alcohol found in alcoholic beverages. On a related note, phenol, characterized by its aromatic ring, is prevalent among the contaminants found in wastewater.

Alcohols and phenols can be conceptualized as organic derivatives of water, where one of the water hydrogens is substituted by an organic group: H_2O versus R-OH and Ar-OH. In practical terms, "alcohol" is reserved for compounds where the OH group is attached to a saturated, sp^3-hybridized carbon atom, while those with the OH group bonded to a vinylic, sp^2-hybridized carbon are termed enols.

Alcohols are widespread and boast diverse applications in both the industrial and pharmaceutical realms. Methanol, for example, holds significant industrial importance. Historically derived from heating wood without air, earning it the name "wood alcohol," today, around 40 million metric tons of methanol are produced annually worldwide. Most of this production involves the catalytic reduction of carbon monoxide with hydrogen gas. Despite its industrial significance, methanol poses a threat to human health, causing blindness in small doses (15 mL) and death in larger quantities (100–250 mL). Industrially, it serves as both a solvent and a starting material for producing formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).

Alcohols are categorized as primary (1°), secondary (2°), or tertiary (3°), based on the number of organic groups attached to the carbon carrying the hydroxyl moiety.



A primary (1°) alcohol **A secondary (2°) alcohol** **A tertiary (3°) alcohol**

Firstly, choose the longest carbon chain containing the hydroxyl group and generate the parent name by substituting the -e ending of the corresponding alkane with -**ol**. Removing -e is executed to avoid consecutive vowels; for instance, propanol is favored over propaneol. Then, begin numbering the alkane chain from the end closest to the hydroxyl group. Finally, assign numbers to substituents based on their positions in the chain, and articulate the name by listing the substituents alphabetically, indicating the position to which the OH is bonded. It's noteworthy that when naming cis-1,4-cyclohexanediol, the final -e of cyclohexane remains intact because the succeeding letter, d, is not a vowel; hence, it is cyclohexanediol rather than cyclohexandiol. Similar to the naming conventions for alkenes, the latest IUPAC recommendations position the locant immediately before the suffix instead of preceding the parent in the nomenclature.

2-Methyl-2-pentanol (New: 2-Methylpentan-2-ol)

***cis*-1,4-Cyclohexanediol** (New: *cis*-Cyclohexane-1,4-diol)

3-Phenyl-2-butanol (New: 3-Phenylbutan-2-ol)

Figure 1. Examples of alcohols.

1.1. Physical properties of Alcohols and Phenols

The hydroxy functional group significantly influences the physical properties of alcohols, shaping their molecular structure and facilitating hydrogen bonding. Alcohols and phenols share a nearly identical geometry around the oxygen atom with water, featuring an approximately tetrahedral R-O-H bond angle (e.g., 108.5° in methanol) and sp^3-hybridized oxygen. Similar to water, their higher-than-expected boiling points are attributed to hydrogen bonding, where a positively polarized OH hydrogen atom is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together. This intermolecular attraction raises the boiling temperature, exemplified by the higher boiling point of 1-propanol than butane and chloroethane despite similar molecular weights.

The hydrophobic nature of nonpolar alkanes, labeled as such due to their poor solvation in water, contrasts with the hydrophilic behavior of polar substituents like the OH group. Alcohols with larger hydrophobic alkyl portions exhibit lower solubility in water while displaying increased solubility in nonpolar solvents. Notably, the water-like structure of lower alcohols, such as methanol and ethanol, makes them effective solvents for polar compounds and salts. This characteristic renders alcohols popular protic solvents in the SN^2 reaction.

The versatile nature of alcohols, crucial for various applications, stems from their dual role as both acids and bases (Figure 2). In their role as weak bases, they undergo reversible protonation by strong acids, forming oxonium ions (ROH_2^+). Instead, weak acids dissociate slightly in dilute aqueous solutions, donating a proton to water and generating H_3O+ along with an alkoxide ion (RO^-) or a phenoxide ion (ArO^-). This dual behavior as both acids and bases further underscores the versatile chemical properties of alcohols and phenols.

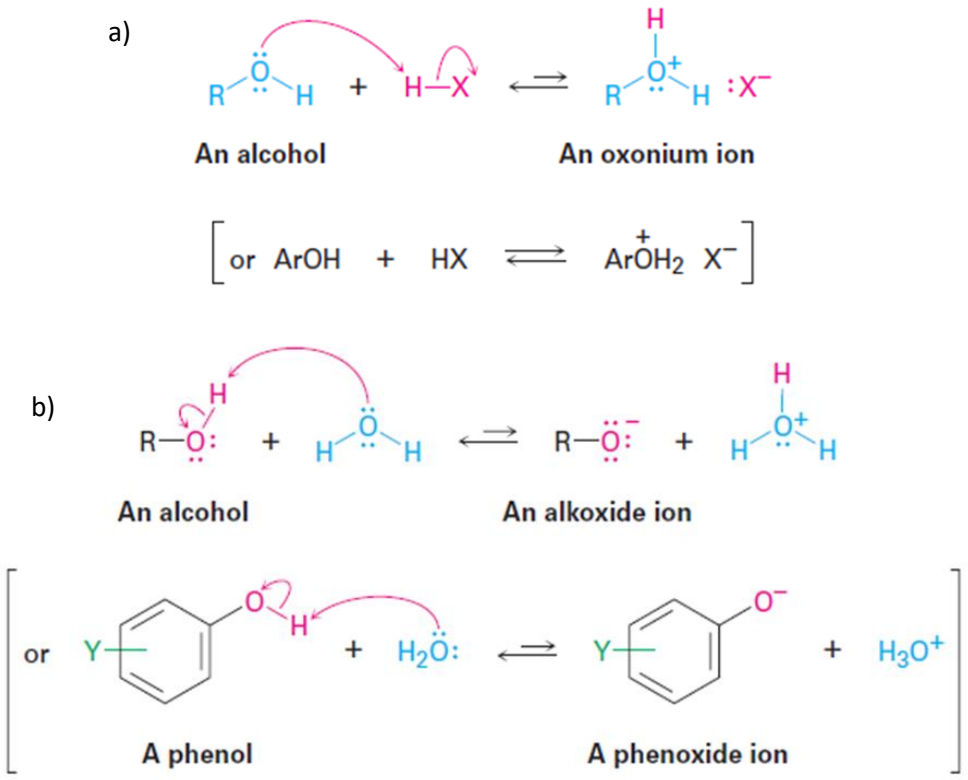


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Figure 2. a) Alcohols as weak bases; b) alcohols and phenols as weak acids.

The acidity of alcohols in water is quantified by the equilibrium constant K. Comparing pKa values for alcohols with those of minerals and other strong acids reveals that, like water, alcohols are relatively weak acids. Nonetheless, their acidity surpasses that of alkanes and haloalkanes significantly. The underlying reason for the acidity of alcohols, in contrast to the non-acidic nature of alkanes and haloalkanes, is the notably high electronegativity of the oxygen atom to which the proton is attached. This electronegativity stabilizes the negative charge of the resulting alkoxide ion.

Compounds with a smaller Ka and a larger pKa exhibit reduced acidity, while those with a larger Ka and a smaller pKa are more acidic. Examining the data in the Table1, it becomes apparent that simple alcohols, such as methanol and ethanol, possess acidity levels comparable to water, while the more intricately substituted tert-butyl alcohol demonstrates somewhat weaker acidity.

Table 1. Acidity constants of some alcohols and phenols.

Compound	pK_a	
$(CH_3)_3COH$	18.00	Weaker acid
CH_3CH_2OH	16.00	
H_2O	15.74	
CH_3OH	15.54	
CF_3CH_2OH	12.43	
p-Aminophenol	10.46	
CH_3SH	10.3	
p-Methylphenol	10.17	
Phenol	9.89	
p-Chlorophenol	9.38	
p-Nitrophenol	7.15	Stronger acid

The influence of alkyl substitution on alcohol acidity primarily arises from the solvation of the alkoxide ion formed during acid dissociation. The ease with which the alkoxide ion is solvated by water dictates its stability, energetic favorability, and, consequently, the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is readily accessible and easily solvated by water. In contrast, the oxygen atom of a hindered alkoxide ion, like that from tert-butyl alcohol, is less accessible and, therefore less stabilized.

Inductive effects also play a pivotal role in determining alcohol acidities. Electron-withdrawing halogen substituents, for instance, stabilize an alkoxide ion by dispersing the charge over a larger volume, enhancing the acidity of the alcohol. A comparison between ethanol (pK_a 16.00) and 2,2,2-trifluoroethanol (pK_a 12.43), or between tert-butyl alcohol (pK_a 18.0) and nonafluoro-tert-butyl alcohol (pK_a 5.4), illustrates this impact. The table demonstrates an almost million-fold variation in alcohol acidity. It reveals a decreasing acidity trend (increasing pK_a) from methanol to primary, secondary, and tertiary systems. This order is attributed to the alkoxide's steric interference with solvation and hydrogen bonding. Disruption of these processes leads to an elevation in pK_a.

Phenols exhibit heightened acidity compared to alcohols due to the resonance stabilization of the phenoxide anion (Figure 3). The delocalization of the negative charge across the aromatic ring's *ortho* and *para* positions enhances the phenoxide anion's stability relative to undissociated phenol, resulting in a lower ΔG° for dissociation.

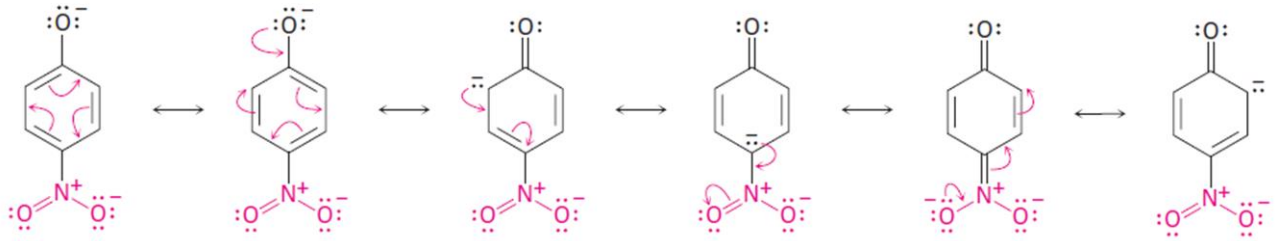

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Figure 3. Delocalization of the negative charge over the *ortho* and *para* positions of the aromatic ring in phenols.

The acidity of substituted phenols can vary depending on whether the substituent is electron-withdrawing or electron-donating. Phenols with an electron-withdrawing substituent tend to be more acidic because these substituents facilitate the delocalization of the negative charge. On the other hand, phenols with an electron-donating substituent are less acidic as these substituents concentrate the negative charge. This acidifying effect of an electron-withdrawing substituent is particularly evident in phenols with a nitro group at the *ortho* or *para* position.

1.2. Synthesis of Alcohols and Phenols

Alcohols play a pivotal role in organic chemistry, holding a central position due to their versatility. They can be synthesized from various compounds such as alkenes, alkyl halides, ketones, esters, and aldehydes, among others, and are equally versatile in their potential transformations into various compounds.

The primary method for alcohol synthesis, both in laboratory settings and within living organisms, involves the reduction of carbonyl compounds. Similar to how the reduction of an alkene incorporates hydrogen into a C=C bond to form an alkane, reducing a carbonyl compound adds hydrogen to a C=O bond, forming an alcohol. This versatile process encompasses reducing various carbonyl compounds, including aldehydes, ketones, carboxylic acids, and esters.

Aldehydes readily undergo reduction to produce primary alcohols, while ketones yield secondary alcohols upon reduction (Figure 4). Numerous reagents are employed in laboratory reductions of aldehydes and ketones, with sodium borohydride ($NaBH_4$) being a popular choice due to its safety and ease of handling. Sodium borohydride, a white crystalline solid, can be weighed openly in the atmosphere and utilized in either water or alcohol solutions. Another commonly used reducing agent is lithium aluminum hydride ($LiAlH_4$), soluble in ether and tetrahydrofuran. Although more reactive than $NaBH_4$, $LiAlH_4$ is also more hazardous, reacting violently with water and undergoing explosive decomposition when heated above 120 °C. The reduction mechanisms involve the addition of a nucleophilic hydride ion ($:H^-$) to the positively polarized carbon atom of the carbonyl group. The initial product is an alkoxide ion, subsequently protonated by H_3O^+ in a second step to yield the final alcohol product.

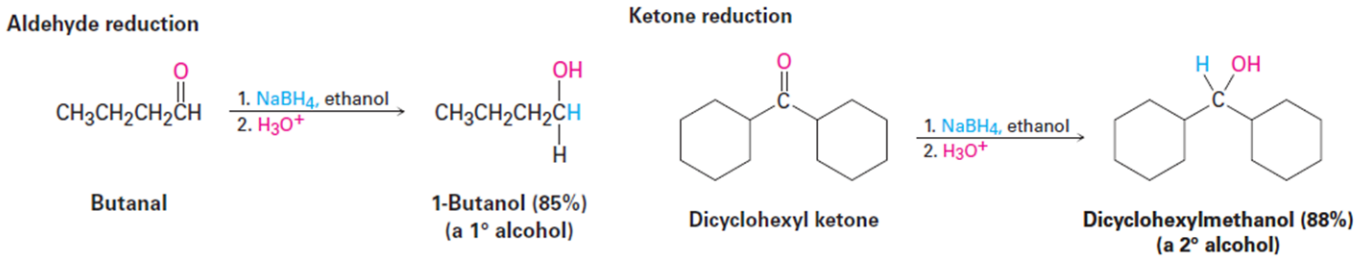

Figure 4. Synthesis of alcohols from aldehyde and ketone reduction.

Carboxylic acids and esters are reduced to yield primary alcohols, albeit at a slower rate compared to the reduction of aldehydes and ketones (Figure 5). While $NaBH_4$ is sluggish in reducing esters and ineffective in reducing carboxylic acids, the more reactive $LiAlH_4$ is commonly employed for these reductions. All carbonyl groups, encompassing acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Notably, one hydrogen atom is added to the carbonyl carbon during aldehyde and ketone reductions, whereas carboxylic acid and ester reductions introduce two hydrogens.

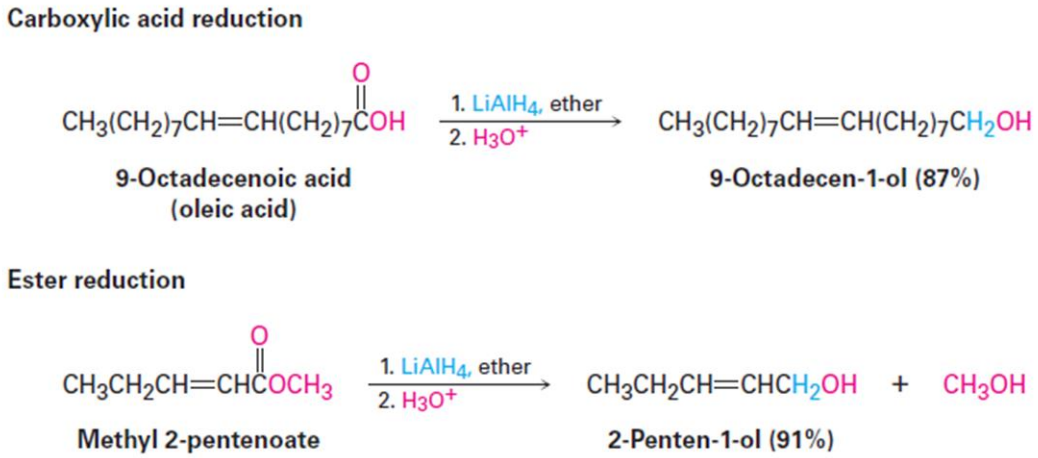

Figure 5. Synthesis of alcohols from carboxylic acid and ester reduction.

Grignard reagents (RMgX), derived from the reaction of organohalides with magnesium, react with carbonyl compounds similarly to hydride reducing agents. This reaction involves the addition of a carbanion nucleophile to the C=O bond. These organometallic reagents, particularly those of magnesium and lithium, serve as powerful tools in reactions where the negatively polarized alkyl group acts as a nucleophile. They can attack the carbonyl group to produce alcohols upon aqueous work-up, forming a new carbon–carbon bond in the process. Grignard reagents produce primary, secondary, and tertiary alcohols.

Following the flow of electrons elucidates the reaction mechanism (Figure 6). The nucleophilic alkyl group in the organometallic compound attacks the carbonyl carbon, generating a new carbon–carbon linkage. Simultaneously, an electron pair from the alkyl group induces a shift of two electrons from the double bond onto the oxygen, forming a metal alkoxide. The addition of a dilute aqueous acid completes the reaction by hydrolyzing the metal–oxygen bond, exemplifying aqueous workup.

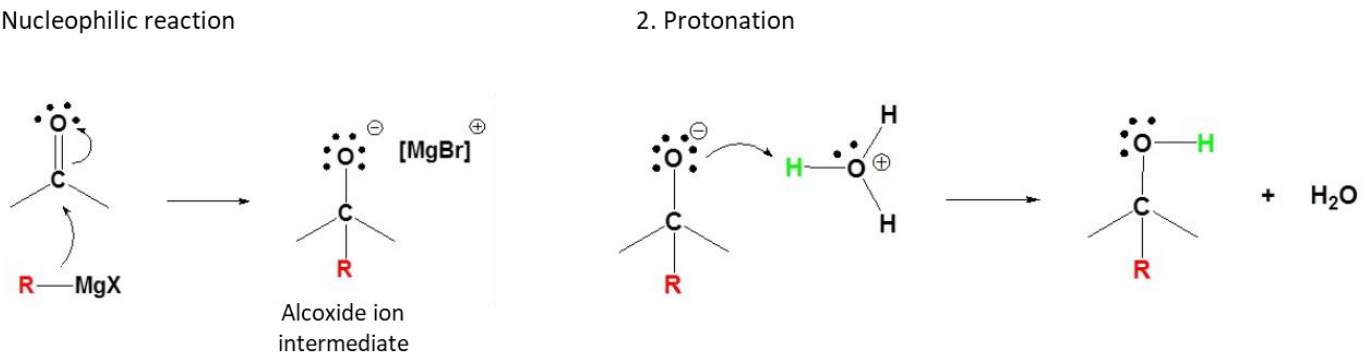

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Figure 6. Mechanism of Grignard reagents to obtain alcohols from carbonyl compounds.

For an extended period, phenol was produced using the Dow process, wherein chlorobenzene underwent a reaction with NaOH at elevated temperatures and pressures. However, a contemporary approach has emerged involving the synthesis of phenol from isopropylbenzene, commonly referred to as cumene (Figure 7). In this method, cumene undergoes benzylic oxidation with air at high temperatures through a radical mechanism, forming cumene hydroperoxide. The subsequent treatment with acid transforms cumene hydroperoxide into phenol and acetone. This process stands out for its efficiency as it concurrently generates two valuable chemicals, phenol and acetone.

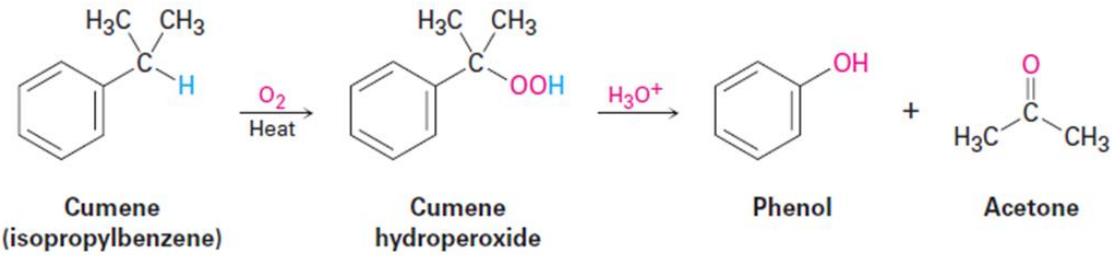

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Figure 7. Synthesis of phenol from cumene.

The reaction mechanism involves the protonation of the hydroperoxy group on the terminal oxygen atom, resulting in the formation of an oxonium ion (Figure 8). Subsequently, rearrangement occurs through the migration of the phenyl ring from carbon to oxygen, leading to the expulsion of water and the generation of a carbocation. The nucleophilic addition of water to the carbocation yields another oxonium ion, which further rearranges through a proton shift from one oxygen atom to another. The elimination of phenol produces acetone as a co-product, and the acid catalyst is regenerated in the process.

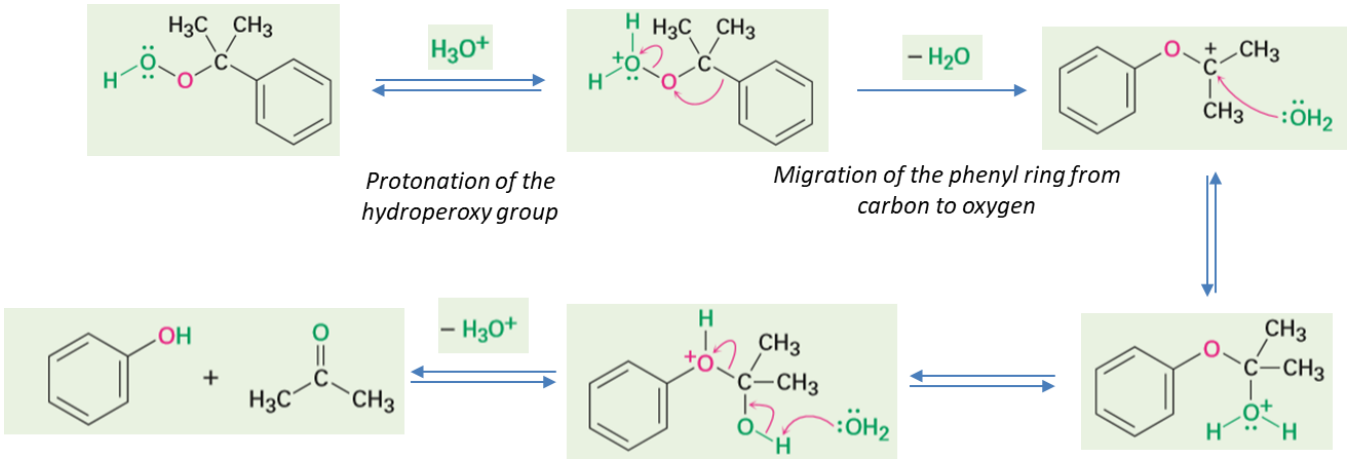

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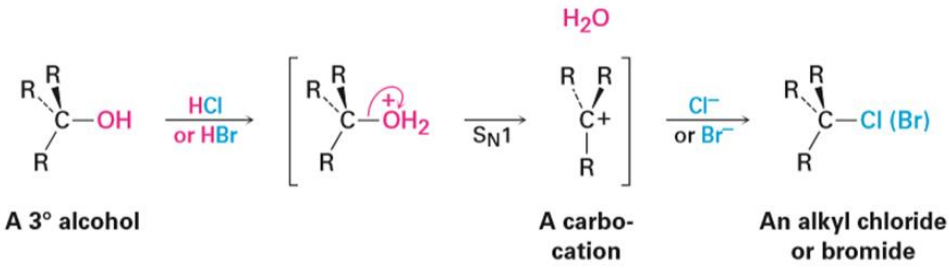
Figure 8. Mechanism of the synthesis of phenol described in Figure 7.

1.3. Reactivity of Alcohols and Phenols

Tertiary alcohols undergo reactions with either HCl or HBr at 0 °C via an S_N1 mechanism involving a carbocation intermediate (Figure 9). The S_N1 mechanism unfolds as follows: acid protonates the hydroxyl oxygen atom, causing the expulsion of water and generating a carbocation. This carbocation subsequently reacts with a nucleophilic halide ion, yielding the desired alkyl halide product. Conversely, primary and secondary alcohols exhibit greater resistance to acid, making them more suitably converted into halides through treatment with either $SOCl_2$ or PBr_3 using an S_N2 mechanism (Figure 9). The -OH group transforms into a more effective leaving group, either a chlorosulfite (-OSOCl) or a dibromophosphite ($-OPBr_2$), which can be readily expelled through backside nucleophilic substitution. This strategic alteration efficiently converts primary and secondary alcohols into corresponding halides.



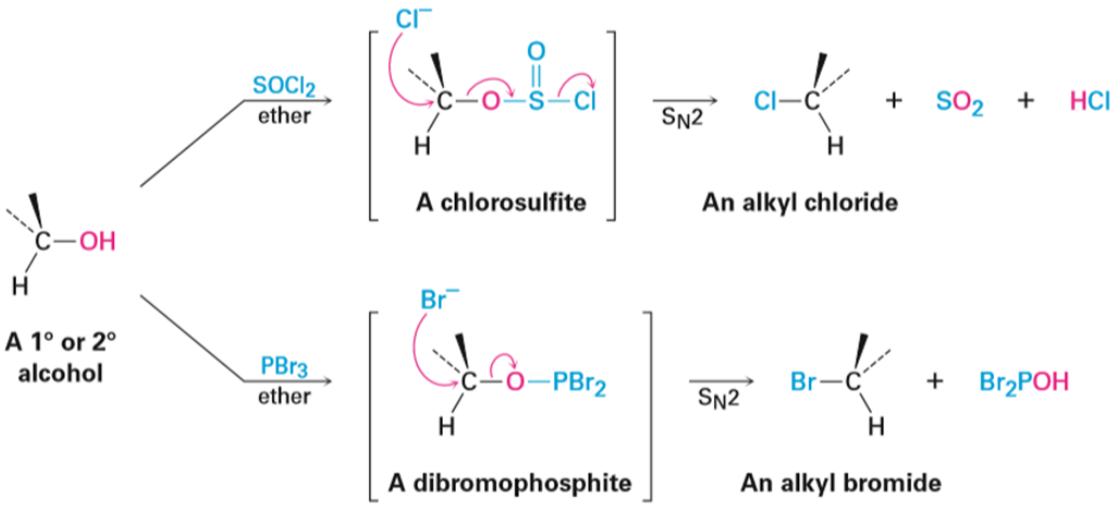


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Figure 9. Conversion of tertiary, primary, and secondary alcohols into haloalkanes.

In both laboratory settings and biological pathways, a crucial transformation of alcohols involves their dehydration to produce alkenes. Due to the significance of this reaction, several methods have been developed to facilitate dehydration. The acid-catalyzed reaction is an effective approach, especially for tertiary alcohols. For instance, subjecting 1-methylcyclohexanol to warm aqueous sulfuric acid in a solvent like tetrahydrofuran leads to the elimination of water and the formation of 1-methylcyclohexene (Figure 10). The reaction follows an E1 process, unfolding through a three-step mechanism. It initiates with the protonation of the alcohol oxygen, followed by the unimolecular elimination of water to generate a carbocation intermediate. The process concludes with removing a proton from the adjacent carbon atom.

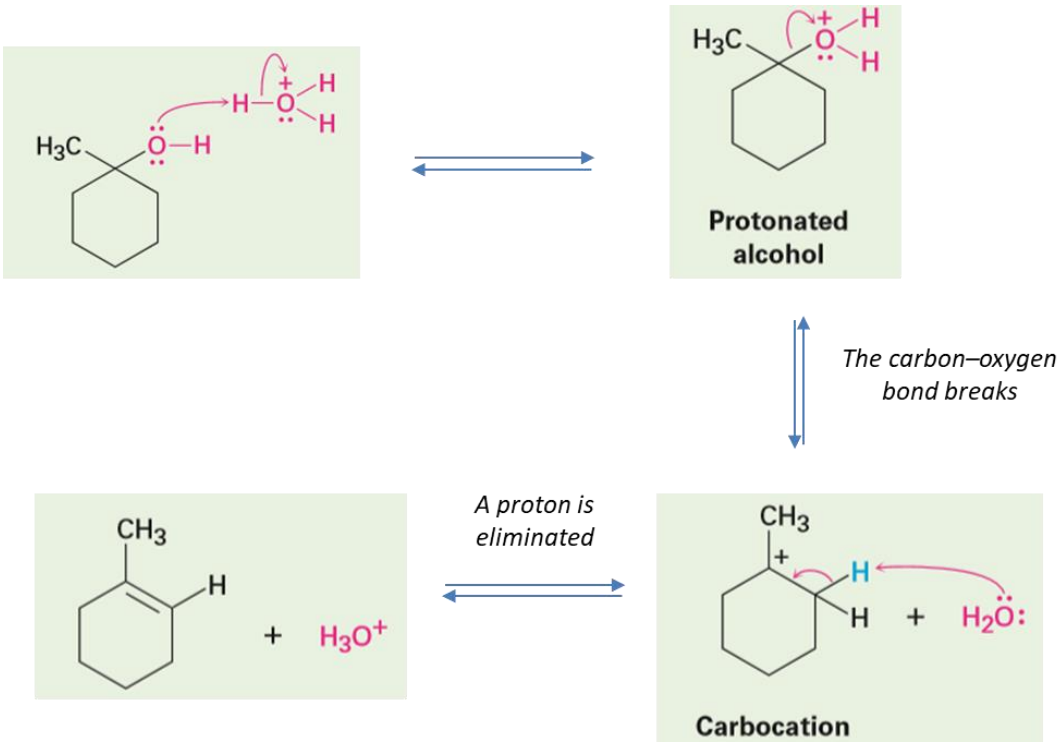

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Figure 10. Mechanism of the synthesis of alkenes from a tertiary alcohol.

The oxidation of alcohols represents a crucial chemical transformation, leading to the formation of carbonyl compounds (Figure 11)—a process inversely related to reducing carbonyl compounds into alcohols. Primary alcohols result in aldehydes or carboxylic acids upon oxidation, while secondary alcohols yield ketones. Tertiary alcohols, however, generally exhibit low reactivity towards most oxidizing agents. Various reagents, such as $KMnO_4$, CrO_3, and $Na_2Cr_2O_7$, can be employed to oxidize primary or secondary alcohols. The selection of a specific reagent hinges on factors such as cost, convenience, reaction yield, and alcohol sensitivity.

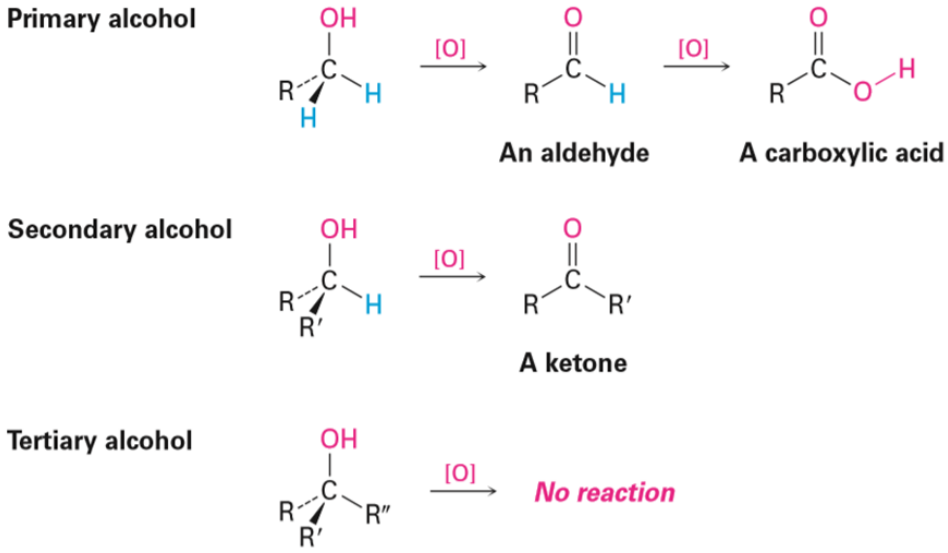

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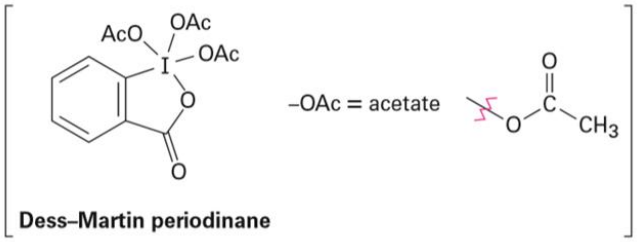
Figure 11. Oxidation of primary, secondary, and tertiary alcohols to carbonyl compounds.

The oxidation of primary alcohols can lead to either aldehydes or carboxylic acids, depending on the chosen reagents and reaction conditions. While older methods often relied on Cr(VI) reagents like CrO_3 or $Na_2Cr_2O_7$, a prevalent contemporary approach for generating aldehydes from primary alcohols in laboratory settings involves the use of the I(V)-containing Dess–Martin periodinane in a dichloromethane solvent.



The oxidation behavior of phenols diverges from that of alcohols due to the absence of a hydrogen atom on the carbon adjacent to the hydroxyl group. Consequently, the oxidation of a phenol results in the formation of a cyclohexa-2,5-diene-1,4-dione, commonly known as a quinone (Figure 12). Various oxidizing agents can facilitate this transformation, with $Na_2Cr_2O_7$ being a prevalent choice for straightforward phenols.

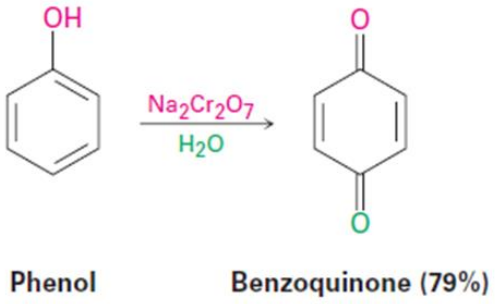


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Figure 12. Oxidation of phenol to quinone.

Quinones hold significance as a class of compounds owing to their redox or oxidation-reduction properties. They readily undergo reduction to hydroquinones (p-dihydroxybenzenes) through reagents like $NaBH_4$ and $SnCl_2$. Conversely, hydroquinones can be effortlessly reoxidized back to quinones using $Na_2Cr_2O_7$ (Figure 13).

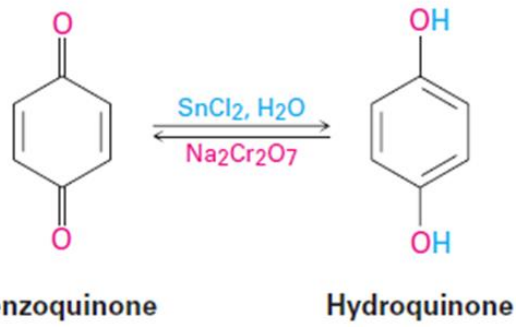

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Figure 13. Reduction of quinone to hydroquinone.

2. ETHERS

Like alcohols, ethers (R-O-R) are organic derivatives of water. Still, they exhibit a distinct structure with two organic groups bonded to the same oxygen atom instead of one. These organic groups can be alkyl, aryl, or vinylic, and the oxygen atom may be part of an open chain or a ring. One of the most well-known ethers is diethyl ether, which boasts a long history of medicinal use as an anesthetic and industrial application as a solvent. Ethers with diverse structures find utility in various applications. Anisole, for instance, is an aromatic ether with a pleasant scent commonly employed in perfumery. Tetrahydrofuran (THF), a cyclic ether, is often used as a solvent in different industrial processes.

Simple ethers without additional functional groups are named by identifying the two organic substituents and appending **ether**. However, the ether component is treated as an alkoxy substituent if other functional groups are present.

2.1. Physical Properties of Ethers

Similar to alcohols, ethers exhibit a nearly identical geometry to water. The R-O-R bonds have an approximately tetrahedral bond angle (about 112° in dimethyl ether), and the oxygen atom is sp^3-hybridized. The electronegative nature of the oxygen atom imparts a slight dipole moment to ethers, and their boiling points are typically slightly higher than those of comparable alkanes.

Ethers, in general, are relatively stable and unreactive, but some ethers can react slowly with oxygen in the air, forming peroxides—compounds that contain an O-O bond. Peroxides derived from low-molecular-weight ethers like diisopropyl ether and tetrahydrofuran are explosive and highly dangerous, even in small amounts. While ethers are valuable solvents in laboratory settings, they must be used cautiously and should not be stored for extended periods.

2.2. Synthesis of Ethers

The Williamson ether synthesis is the most widely used method for preparing ethers. This synthesis involves the reaction of an alkoxide ion with a primary alkyl halide or tosylate in an S_N2 reaction (Figure 14). The alkoxide ion is typically generated by the reaction of an alcohol with a strong base, such as sodium hydride (NaH).

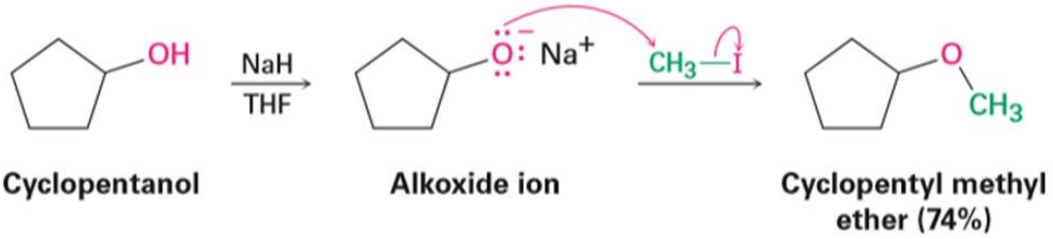

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Figure 14. Williamson ether reaction of cyclopentanol for obtaining an ether.

Given that the Williamson synthesis follows the S_N2 mechanism, it is subject to the usual constraints. Primary halides and tosylates are optimal reactants, as more hindered substrates can undergo competitive E2 elimination. Therefore, when synthesizing unsymmetrical ethers, it is advisable to react to the more hindered alkoxide partner with the less hindered halide partner rather than vice versa. For instance, the synthesis of tert-butyl methyl ether is best achieved by reacting tert-butoxide ion with iodomethane. This approach minimizes the likelihood of competitive E2 elimination and ensures the efficient and selective formation of the desired ether product.

2.3. Reactivity of Ethers

Ethers exhibit a notable inertness towards many reagents commonly used in organic chemistry, a characteristic that underscores their widespread utility as reaction solvents. Halogens, dilute acids, bases, and nucleophiles generally have little to no effect on most ethers. Ethers undergo only one truly general reaction—they can be cleaved by strong acids. Both aqueous HBr and HI are effective in this cleavage, but HCl does not cleave ethers.

Acidic ether cleavages typically involve nucleophilic substitution reactions occurring via either S_N1 or S_N2 mechanisms, depending on the substrate's structure. Ethers with only primary and secondary alkyl groups react via an S_N2 mechanism, where I_2 or Br_2 attacks the protonated ether at the less hindered site (Figure 15). This often results in selective cleavage into a single alcohol and a single alkyl halide. For example, ethyl isopropyl ether exclusively yields isopropyl alcohol and iodoethane upon cleavage by HI because nucleophilic attack by iodide ion occurs at the less hindered primary site rather than the more hindered secondary site.

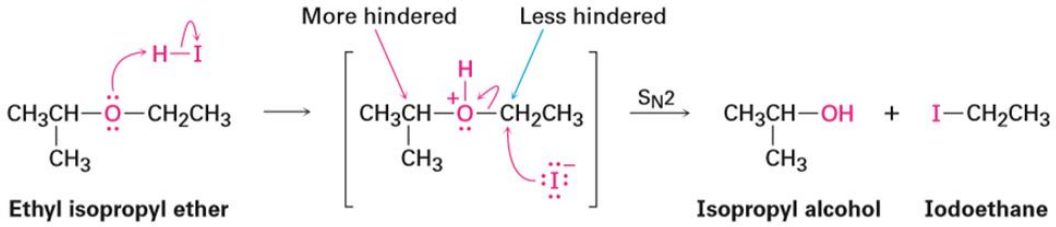

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Figure 15. Ether with primary and secondary alkyl groups react by an S_N2 mechanism.

Ethers containing a tertiary, benzylic, or allylic group can undergo cleavage via either an SN1 or E1 mechanism due to the potential formation of stable intermediate carbocations. These reactions are often rapid and take place at moderate temperatures. For instance, tert-butyl ethers react via an E1 mechanism when treated with trifluoroacetic acid at 0°C (Figure 16).

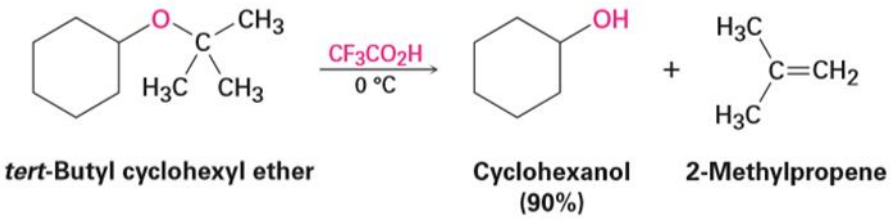

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Figure 16. Ether with a tertiary group cleave by either an S_N1 or E1 mechanism.

In contrast to the acid-induced ether cleavage reaction discussed earlier, which is generally applicable to all ethers, the Claisen rearrangement is specific to allyl aryl ethers and allyl vinyl ethers. The Claisen rearrangement involves the treatment of a phenoxide ion with 3-bromopropene (allyl bromide), resulting in a Williamson ether synthesis and forming an allyl aryl ether (Figure 17). Subsequent heating of the allyl aryl ether to 200–250 °C triggers the Claisen rearrangement, leading to an o-allylphenol. This results in the alkylation of the phenol at an ortho position.

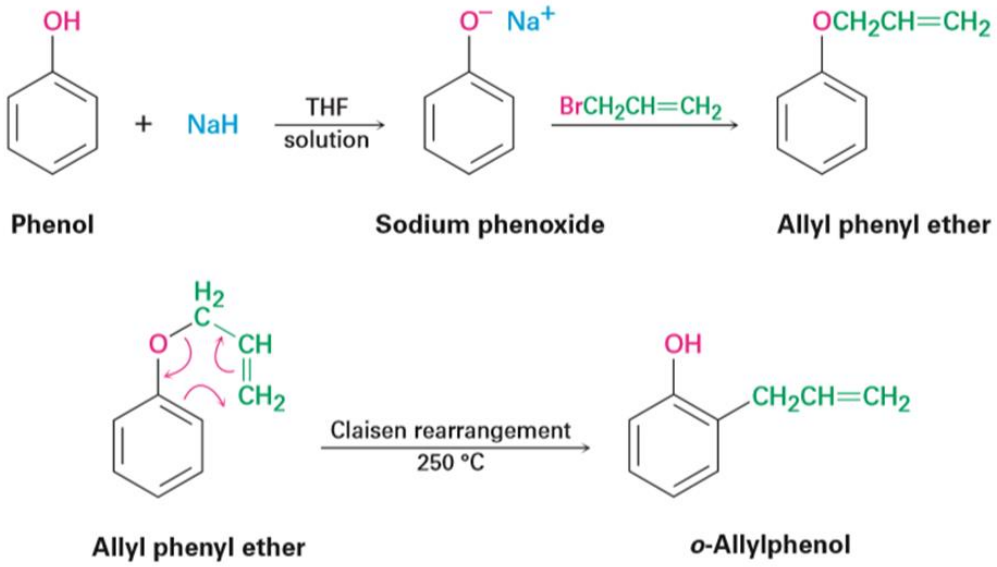

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Figure 17. Alkylation of the phenol in an ortho position through Claisen rearrangement.

A similar rearrangement occurs with allyl vinyl ethers, resulting in a so-called γ,δ-unsaturated ketone or aldehyde. The Claisen rearrangement takes place in a single step through a pericyclic mechanism, involving a reorganization of bonding electrons through a six-membered, cyclic transition state.

3. CARBONYL COMPOUNDS

Aldehydes (RCHO) and ketones (R_2CO) represent some of the most prevalent compounds found in nature. Living organisms often require substances such as aldehydes or ketones for essential processes. For example, the coenzyme pyridoxal phosphate is an aldehyde involved in numerous metabolic reactions. At the same time, the steroid hormone hydrocortisone, a ketone, is secreted by the adrenal glands to regulate the metabolism of fat, protein, and carbohydrates.

In the chemical industry, significant quantities of simple aldehydes and ketones are manufactured for use as solvents and as starting materials in the synthesis of various compounds. Notably, over 23 million tons of formaldehyde (H_2CO) are produced annually worldwide for applications in building insulation materials and the adhesive resin binding particle boards and plywood. Acetone, $(CH_3)_2CO$, serves as a widely utilized industrial solvent, with an annual global production of approximately 3.3 million tons.

Aldehydes receive their nomenclature by replacing the terminal -e of the corresponding alkane name with -**al**. The parent chain must incorporate the -CHO group designated as carbon 1. On the other hand, ketones are named by substituting the terminal -e of the corresponding alkane name with -**one**. The parent chain is the longest one containing the ketone group, and numbering begins closer to the carbonyl carbon. Like alkenes and alcohols, the locant is positioned before the parent name in older rules but before the suffix in more recent IUPAC recommendations.

When the need arises to refer to RCO as a substituent, the term acyl group is employed, with the name ending -**yl** attached. Examples include -$COCH_3$ referred to as an acetyl group, -CHO as a formyl group, -COAr as an aroyl group, and -COC_6H_5 as a benzoyl group.

3.1. Physical Properties of the Carbonyl Group

The carbonyl group features a concise, robust, and highly polar bond. Both the carbon and oxygen within the carbonyl group undergo sp2 hybridization, aligning them in the same plane as the two additional groups on carbon, resulting in bond angles close to 120°. Perpendicular to the molecular frame are two p orbitals, one on carbon and one on oxygen, contributing to the formation of the π bond.

When comparing the electronic structure of a carbonyl group to an alkene double bond, two notable distinctions emerge. Firstly, the oxygen atom possesses two lone electron pairs situated in two sp2 hybrid orbitals. Secondly, oxygen exhibits greater electronegativity than carbon. This property triggers a discernible polarization of the carbon-oxygen double bond, with a considerable partial positive charge on carbon and an equivalent negative charge on oxygen. Consequently, the carbon becomes electrophilic, while the oxygen becomes nucleophilic and slightly basic. This polarization is depicted through a polar resonance form for the carbonyl moiety or by representing partial charges (see Figure 18). Additionally, it is evident in the electrostatic potential map of formaldehyde, where the region around the carbon atom appears blue (positive), and the region around the oxygen appears red (negative). The partial positive charge on the carbonyl carbon renders acyl groups electron-withdrawing.

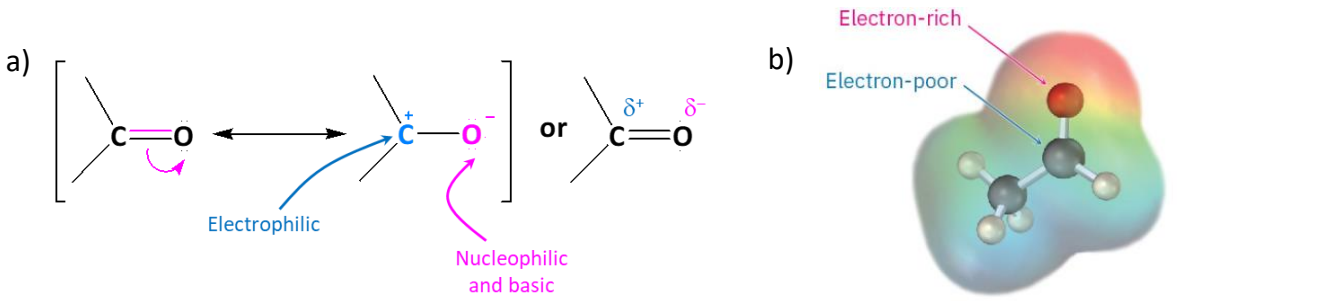

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Figure 18. a) Representation of partial charges in a carbonyl group; b) electrostatic potential map of formaldehyde.

Polarization significantly influences the physical properties of aldehydes and ketones. The polarization of the carbonyl functional group leads to higher boiling points for aldehydes and ketones when compared to hydrocarbons of similar size and molecular weight. The polarity of these molecules is evident in smaller carbonyl derivatives, like acetaldehyde and acetone, which demonstrate complete miscibility with water.

3.2. Synthesis of Ketones and Aldehydes

One of the most efficient methods for synthesizing aldehydes involves the oxidation of primary alcohols. As depicted in Figure 19, this reaction is frequently carried out using the Dess–Martin periodinane reagent in dichloromethane solvent at room temperature.

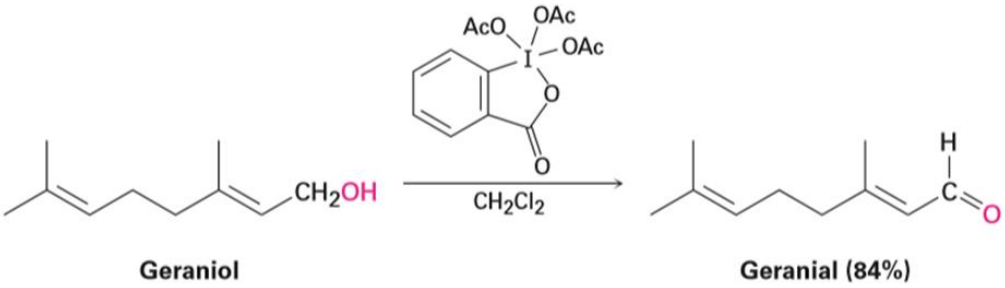

Figure 19. Synthesis of an aldehyde from a primary alcohol using the Dess-Martin periodinane reagent as an oxidant.

Generally, methods for synthesizing ketones closely mirror those for aldehydes. Secondary alcohols can be oxidized using various reagents to produce ketones. The choice of oxidant is influenced by factors such as reaction scale, cost, and the acid or base sensitivity of the alcohol. Commonly employed options include the Dess–Martin periodinane or a Cr(VI) reagent, such as CrO_3 (Figure 20).

Figure 20. Synthesis of a ketone from a secondary alcohol using CrO_3 as an oxidant.

3.3. Reactivity of Ketones and Aldehydes

3.3.1. Oxidation

Aldehydes readily undergo oxidation to form carboxylic acids, while ketones generally exhibit inertness towards oxidation. This distinction stems from their structural dissimilarity: aldehydes feature a -CHO proton susceptible to abstraction during oxidation, whereas ketones lack this characteristic.

Several oxidizing agents, such as $KMnO_4$ and hot HNO_3, can convert aldehydes into carboxylic acids. However, a more commonly selected reagent is CrO_3 in aqueous acid. This oxidation process occurs swiftly at room temperature, yielding favorable outcomes. Figure 21 illustrates that the oxidation of aldehydes involves the generation of intermediate 1,1-diols or hydrates. These hydrates result from a reversible nucleophilic addition of water to the carbonyl group. Although hydrates form to a limited extent at equilibrium, they behave like typical primary or secondary alcohols, undergoing oxidation to produce a carbonyl compound.

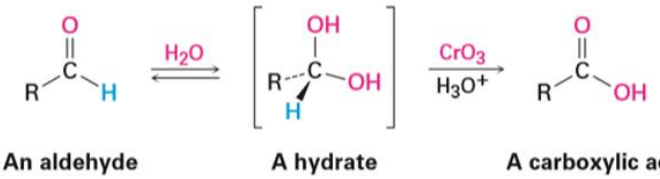

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Figure 21. Mechanism of oxidation of an aldehyde.

3.3.2. Nucleophilic Addition Reaction

The nucleophilic addition reaction is the most general reaction for aldehydes and ketones. In this process, a nucleophile, represented as $:Nu^-$, approaches the carbonyl group at an angle of approximately 105° opposite the carbonyl oxygen. A bond is formed with the electrophilic C-O carbon atom. Concurrently, rehybridization of the carbonyl carbon occurs, transitioning from sp^2 to sp^3. An electron pair from the C-O bond shifts toward the electronegative oxygen atom, forming a tetrahedral alkoxide ion intermediate. Protonation of the alkoxide, achieved by the addition of acid, then yields the final product—a neutral alcohol.

Mechanism shown in Figure 22 reports two steps. In step 1, an electron pair from the nucleophile adds to the electrophilic carbon of the carbonyl group, pushing an electron pair from the C=O bond onto oxygen. This process creates an alkoxide ion intermediate, and the carbonyl carbon undergoes rehybridization from sp^2 to sp^3. In step 2, protonation of the alkoxide anion intermediate leads to the formation of the neutral alcohol addition product.

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Figure 22. Mechanism of the nucleophilic addition reaction of a carbonyl group.

The nucleophile can exist in two forms: negatively charged ($:Nu^-$) or neutral (:Nu). However, if it is neutral, it usually carries a hydrogen atom that can subsequently be eliminated. Nucleophilic additions to aldehydes and ketones exhibit two general variations (Figure 23). In the first variation, the tetrahedral intermediate is protonated by water or acid, resulting in an alcohol as the final product. In the second variation, the carbonyl oxygen atom is protonated and then eliminated as H_2O, yielding a product with a C-Nu double bond.

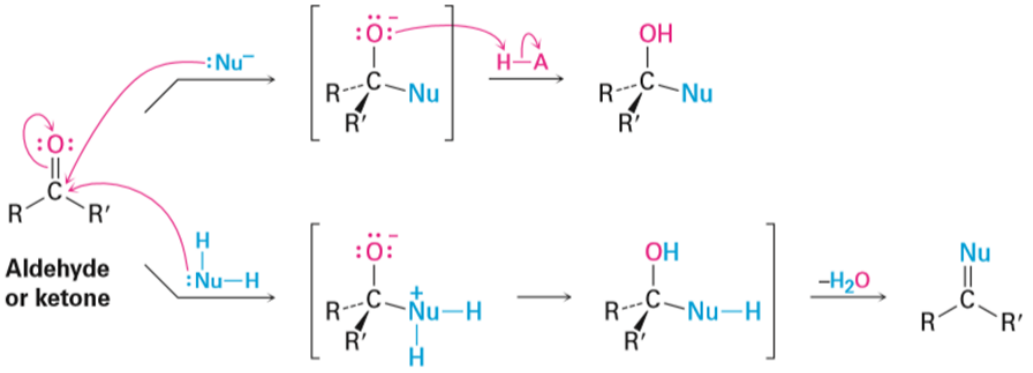

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Figure 23. Pathways for the nucleophilic addition reaction of a carbonyl group.

Aldehydes generally display higher reactivity than ketones in nucleophilic addition reactions, influenced by both steric and electronic factors. Sterically, the presence of only one large substituent bonded to the C=O carbon in an aldehyde, as opposed to two large substituents in a ketone, allows for easier nucleophile approach. Consequently, the transition state leading to the tetrahedral intermediate is less crowded and lower in energy for an aldehyde than for a ketone. Electronically, aldehydes exhibit greater reactivity than ketones due to the enhanced polarization of aldehyde carbonyl groups. This polarity difference can be understood by recalling the stability order of carbocations. A primary carbocation is higher in energy and more reactive than a secondary carbocation because it has only one alkyl group inductively stabilizing the positive charge, as opposed to two.

Nucleophilic Addition of H_2O: Hydration

Aldehydes and ketones undergo a reaction with water to form 1,1-diols, also known as geminal (gem) diols. The hydration reaction is reversible, and a gem diol can eliminate water to regenerate the aldehyde or ketone. The position of the equilibrium between a gem diol and an aldehyde or ketone depends on the structure of the carbonyl compound. Generally, the equilibrium favors the carbonyl compound due to steric reasons, but for some simple aldehydes, the gem diol is favored. For instance, an aqueous solution of formaldehyde consists of 99.9% gem diol and 0.1% aldehyde at equilibrium, while an aqueous solution of acetone consists of only about 0.1% gem diol and 99.9% ketone.

The nucleophilic addition of water to an aldehyde or ketone is slow under neutral conditions but is catalyzed by both base and acid. Mechanism of both catalyzed reactions are illustrated in Figure 24. Under basic conditions, where the nucleophile is negatively charged (OH^-), it uses a pair of electrons to form a bond with the electrophilic carbon atom of the C=O group. Simultaneously, the C=O carbon atom rehybridizes from sp^2 to sp^3, and two electrons from the C=O π bond are pushed onto the oxygen atom, forming an alkoxide ion. Protonation of the alkoxide ion by water then yields a neutral addition product plus regenerated OH^-. Under acidic conditions, the carbonyl oxygen atom is first protonated by H_3O^+ to enhance the electrophilicity of the carbonyl group. A neutral nucleophile, H_2O, then forms a bond with the carbon atom of the C=O group, and two electrons from the C=O π bond move onto the oxygen atom. This neutralizes the positive charge on oxygen while the nucleophile gains a positive charge. Finally, deprotonation by water gives the neutral addition product and regenerates the H_3O^+ catalyst.

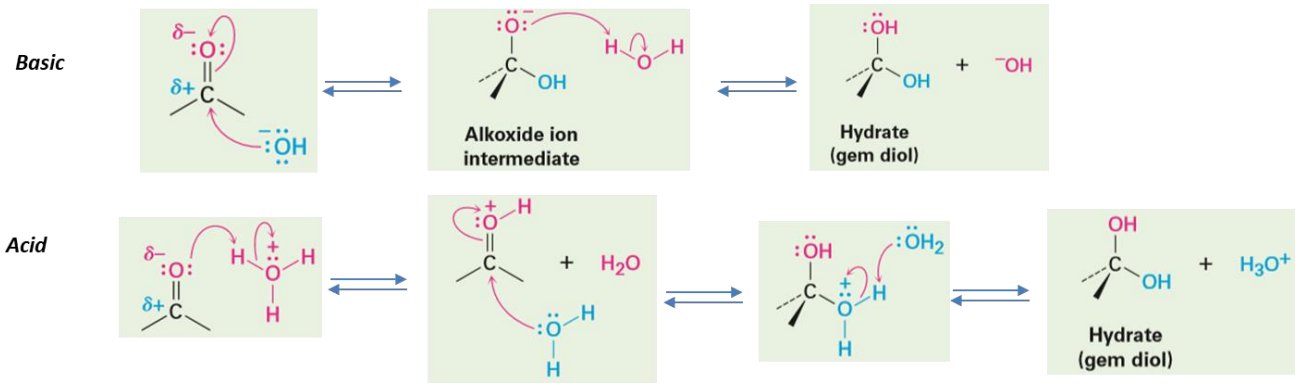

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Figure 24. Pathways for the nucleophilic addition reaction of a carbonyl group.

It's crucial to note the key difference between the base-catalyzed and acid-catalyzed reactions. The base-catalyzed reaction occurs rapidly because water is converted into a hydroxide ion, a much better nucleophile. On the other hand, the acid-catalyzed reaction takes place rapidly because the carbonyl compound is converted by protonation into a much better electrophile.

Nucleophilic Addition of Hydride: Reduction

The most prevalent method for preparing alcohols, both in laboratory settings and within living organisms, involves the reduction of carbonyl compounds. Aldehydes can be reduced using sodium borohydride ($NaBH_4$) to yield primary alcohols, while ketones undergo a similar reduction to form secondary alcohols.

Carbonyl reduction follows a typical nucleophilic addition mechanism under basic conditions (Figure 25). Although the details of carbonyl-group reductions are intricate, $LiAlH_4$ and $NaBH_4$ function as if they were donors of hydride ion nucleophile ($:H^-$). The alkoxide ion intermediate initially formed is subsequently protonated by adding aqueous acid. The reaction is effectively irreversible since the reverse process would necessitate the expulsion of a very poor leaving group.

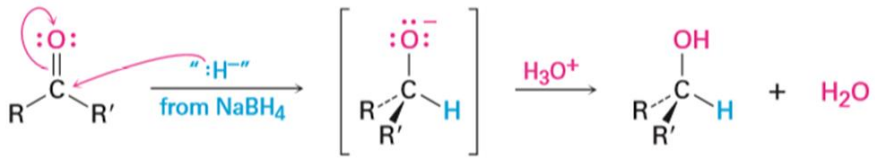

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Figure 25. Reduction of a carbonyl group by nucleophilic addition of hydride.

Nucleophilic Addition of Grignard Reagents

Just as aldehydes and ketones undergo nucleophilic addition with hydride ions to produce alcohols, they similarly experience this addition with Grignard reagent nucleophiles, represented as R'MgX. When reacting with Grignard reagents in ether solution, aldehydes yield secondary alcohols, while ketones give rise to tertiary alcohols.

A Grignard reaction initiates with an acid–base complexation involving Mg^{2+} and the carbonyl oxygen atom of the aldehyde or ketone. This complexation enhances the electrophilicity of the carbonyl group. Nucleophilic addition of $:R^-$ then generates a tetrahedral magnesium alkoxide intermediate. Protonation, achieved by adding water or diluting aqueous acid in a separate step, yields the final neutral alcohol product. Mechanism is shown in Figure 26. Like reduction, Grignard additions are effectively irreversible, as a carbanion is too poor a leaving group to be expelled in a reversal step.

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Figure 26. Mechanism of the Grignard reaction.

4. CARBOXYLIC ACIDS

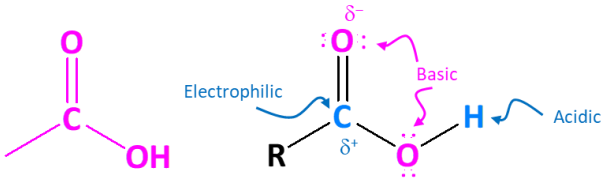
Carboxylic acids are distinguished by the presence of the carboxyl group, a functional group consisting of a hydroxyl unit attached to a carbonyl carbon. This substituent is denoted as COOH.

A multitude of carboxylic acids exists in nature. Acetic acid, with the chemical formula CH_3CO_2H, serves as the primary organic component in vinegar. Butanoic acid, $CH_3CH_2CH_2CO_2H$, is accountable for the unpleasant rancid odor in sour butter. At the same time, hexanoic acid (also known as caproic acid), $CH_3(CH_2)_4CO_2H$, contributes to the distinctive aroma associated with goats and dirty gym socks (the name is derived from the Latin word "caper," meaning “goat”). Other instances include cholic acid, a significant component of human bile, and long-chain aliphatic acids like palmitic acid, $CH_3(CH_2)_{14}CO_2H$, which serves as a biological precursor to fats and vegetable oils.

Carboxylic acids derived from open-chain alkanes are systematically named by replacing the terminal -e of the corresponding alkane name with -**oic acid**. The carbon atom attached to the $-CO_2H$ group is designated as C1. The systematic nomenclature involves the suffix- carboxylic acid for compounds with a $-CO_2H$ group bonded to a ring. In this system, the CO_2H carbon is directly attached to C1 and is not individually numbered. As a substituent, the CO_2H group is referred to as a **carboxyl group**.

4.1. Physical Properties of the Carboxy Group

Carboxylic acids are characterized by the presence of the carboxyl group. The hydrogen of the hydroxy group is acidic, the oxygens are basic and nucleophilic, and the carbonyl carbon is susceptible to nucleophilic attack.



In certain aspects, carboxylic acids share similarities with both ketones and alcohols. Like ketones, the carboxyl carbon is sp^2-hybridized, resulting in planar carboxylic acid groups with –C=O and O=C-O bond angles of approximately 120°. Similarly, carboxylic acids exhibit a strong association, akin to alcohols, due to hydrogen bonding. Most carboxylic acids exist as cyclic dimers held together by two hydrogen bonds. This robust hydrogen bonding significantly influences boiling points, making carboxylic acids exhibit much higher boiling points than the corresponding alcohols. Carboxylic acids have relatively high melting and boiling points because they form hydrogen bonds in solid and liquid states. For example, acetic acid has a boiling point of 117.9 °C, in contrast to 78.3 °C for ethanol, despite both compounds having two carbons.

Their name implies the most evident property of carboxylic acids: they are acidic. Consequently, they react with bases such as NaOH and $NaHCO_3$ to produce metal carboxylate salts, $RCO_2^-\ M^+$. Although carboxylic acids with more than six carbons are only slightly soluble in water, the alkali metal salts of carboxylic acids are often highly water-soluble. Purification of an acid can be achieved by extracting its salt into aqueous base, followed by reacidification and extraction of the pure acid back into an organic solvent.

Similar to other Brønsted–Lowry acids, carboxylic acids undergo slight dissociation in dilute aqueous solutions to yield H_3O^+ and the corresponding carboxylate anions, RCO_2^-. Although weaker than mineral acids, carboxylic acids are significantly stronger acids than alcohols and phenols. For example, the K_a of ethanol is approximately 10^{-16}, making ethanol a weaker acid than acetic acid by a factor of 10^{11}. The heightened acidity of carboxylic acids compared to alcohols, despite both containing -OH groups, is attributed to the difference in the dissociation products. An alcohol dissociates to yield an alkoxide ion, where the negative charge is localized on a single electronegative atom. In contrast, a carboxylic acid produces a carboxylate ion, where the negative charge is delocalized over two equivalent oxygen atoms. In resonance terms, a carboxylate ion is a stabilized resonance hybrid of two equivalent structures. The increased stability of a carboxylate ion, being lower in energy, favors its formation in the dissociation equilibrium.

The pK_a values highlight significant acidity variations among carboxylic acids. For example, trifluoroacetic acid (K_a = 0.59) is 33,000 times stronger than acetic acid ($K_a = 1.75 \times 10^{-5}$). To explain these differences, we can consider factors that influence the stability of the carboxylate anion relative to the undissociated carboxylic acid in the equilibrium process. Any factor that enhances the stability of the carboxylate anion will shift the equilibrium toward increased dissociation and result in greater acidity. In the previous example, the presence of three electron-withdrawing fluorine atoms in trifluoroacetate anion delocalizes the negative charge, stabilizing the ion and increasing the acidity of CF_3CO_2H.

Inductive effects, operating through sigma bonds and dependent on distance, show a diminishing impact as the substituent moves farther from the carboxyl group. For example, 2-chlorobutanoic acid has a pK_a of 2.86, 3-chlorobutanoic acid has a pK_a of 4.05, and 4-chlorobutanoic acid has a pK_a of 4.52, similar to that of butanoic acid itself.

In aromatic rings, electron-donating groups activate the ring toward further electrophilic substitution, while electron-withdrawing groups deactivate the ring. The same effects are observed on the acidity of substituted benzoic acids (Figure 27). The table demonstrates that an electron-donating

(activating) group like methoxy decreases acidity by destabilizing the carboxylate anion. In contrast, an electron-withdrawing (deactivating) group like nitro increases acidity by stabilizing the carboxylate anion.

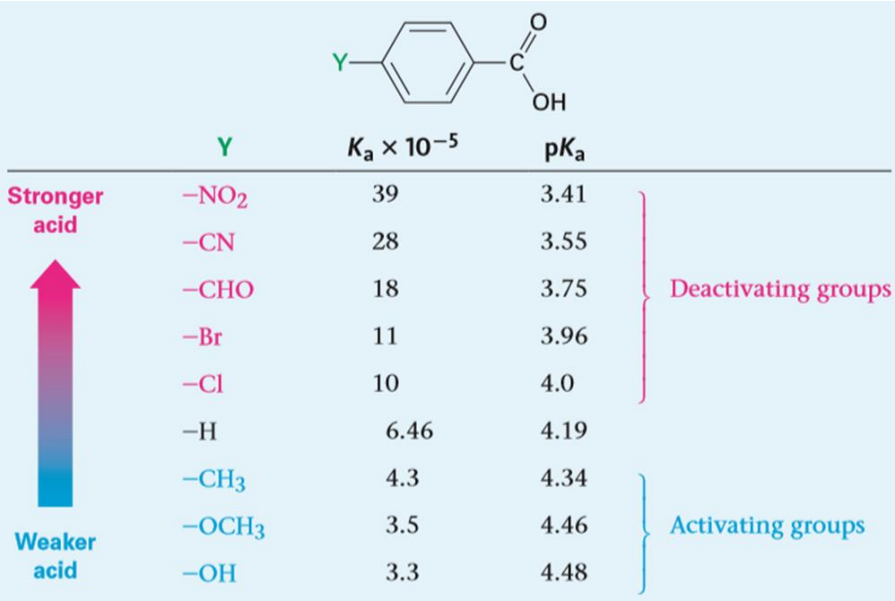


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Figure 27. Substituent effects on acidity of p-substituted benzoic acids.

4.2. Synthesis of Carboxylic Acids

4.2.1. Oxidation Reactions

The oxidation of a substituted alkylbenzene using $KMnO_4$ or $Na_2Cr_2O_7$ results in the formation of a substituted benzoic acid. It's noteworthy that both primary and secondary alkyl groups can undergo oxidation, but tertiary groups remain unaffected.

When a primary alcohol or aldehyde undergoes oxidation, it leads to the formation of a carboxylic acid. Primary alcohols are commonly oxidized using CrO_3 in aqueous acid, and aldehydes undergo a similar oxidation process.

4.2.2. Hydrolysis of Nitriles

Nitriles can be transformed into carboxylic acids through heating with aqueous acid or base. Typically, nitriles are produced through an S_N2 reaction involving a primary or secondary alkyl halide and CN^-. This establishes a two-step process: cyanide displacement followed by nitrile hydrolysis, effectively converting an alkyl halide (RBr or RCX) into a carboxylic acid (RCO_2H). It's important to note that the resulting carboxylic acid possesses one additional carbon compared to the initial alkyl halide. This synthetic route finds application in the industrial production of ibuprofen, a nonsteroidal anti-inflammatory drug.

Base-catalyzed nitrile hydrolysis proceeds through a series of steps (Figure 28): i) Nucleophilic Addition: The hydroxide ion attacks the polar C≡N triple bond, forming an imine anion through nucleophilic addition; ii) Protonation and Catalyst Regeneration: The imine anion is then protonated by water, resulting in the formation of a hydroxyimine. This step also regenerates the base catalyst, completing a catalytic

cycle; iii) Tautomerization: The hydroxyimine undergoes tautomerization, a process similar to the tautomerization of an enol to a ketone. This transformation yields an amide; iv) Further Hydrolysis: The amide undergoes further hydrolysis, ultimately giving rise to the anion of a carboxylic acid.

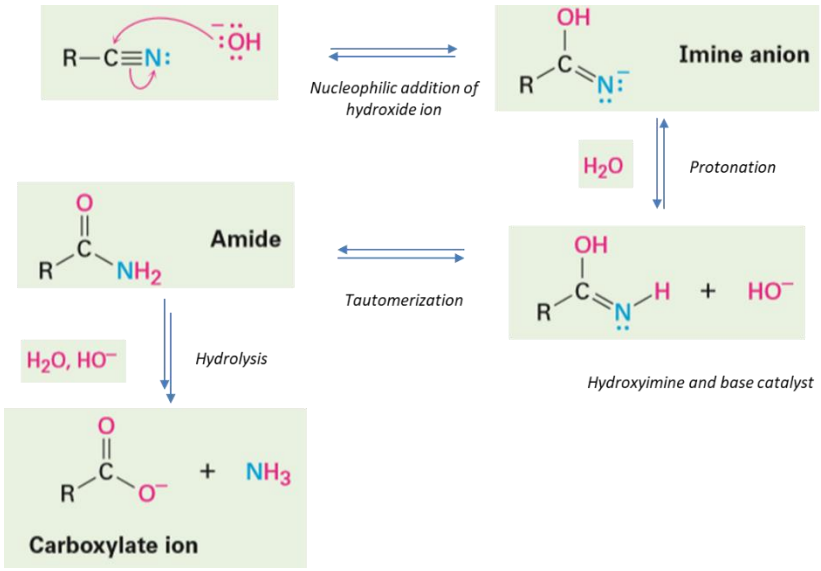

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Figure 28. Conversion of a nitrile to a carboxylic acid ion through a base-catalyzed pathway.

4.2.3. Carboxylation of Grignard Reagents

An alternative method for synthesizing carboxylic acids involves the reaction of a Grignard reagent with carbon dioxide, resulting in the formation of a metal carboxylate. Subsequent protonation of the carboxylate yields the desired carboxylic acid. This carboxylation reaction is typically carried out by introducing dry CO_2 gas into a Grignard reagent solution.

In Figure 29 is illustrated the synthesis of a carboxylic acid by Grignard reagent. The process involves the nucleophilic addition of the organomagnesium halide (Grignard reagent) to the carbon dioxide's carbonyl group, resembling a typical nucleophilic carbonyl addition reaction. Following the formation of the metal carboxylate, protonation is achieved by introducing aqueous hydrochloric acid (HCl) in a separate step. This protonation step converts the metal carboxylate into the free carboxylic acid.

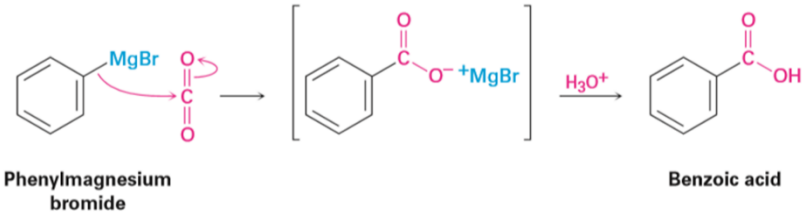

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Figure 29. Synthesis of benzoic acid by carboxylation of Grignard reagent.

4.3. Reactivity of Carboxylic Acids

Carboxylic acids exhibit similarities to both alcohols and ketones, contributing to their versatile reactivity. Similar to alcohols, carboxylic acids can undergo deprotonation, resulting in the formation of anions. These carboxylate anions serve as potent nucleophiles, participating in S_N2 reactions.

On the other hand, like ketones, carboxylic acids can undergo nucleophilic addition reactions in the carbonyl group. This characteristic makes them react with various nucleophiles like ketones.

It's worth noting that carboxylic acids possess distinct reactivity that sets them apart from alcohols and ketones. Deprotonation of carboxylic acids is contingent on their acidity, a topic explored in the initial part of this discussion. The acidity of carboxylic acids is crucial in determining their ability to donate a proton and form carboxylate anions. Moreover, the reduction of carboxylic acids is recognized as an effective means of converting carboxylic acids into alcohols through a reduction process.

4.3.1. Alpha Substitution Reactions

Alpha-substitution reactions take place at the alpha position, which is the carbon position adjacent to the carbonyl group. In these reactions, a hydrogen atom at the alpha position is replaced by an electrophile denoted as E. This substitution occurs via intermediates known as enols or enolate ions. Let's delve into the details of these two chemical species.

A carbonyl compound featuring a hydrogen atom on its alpha carbon exists in equilibrium with its corresponding enol isomer. This spontaneous interchange between two isomers, often involving hydrogen repositioning, is termed tautomerism (Figure 30). The term originates from the Greek words "tauto" meaning "the same," and "meros," meaning "part." The individual keto and enol isomers are collectively referred to as tautomers. It's important to distinguish between tautomers and resonance forms. Tautomers are constitutional isomers, representing different compounds with distinct structures, while resonance forms are alternative representations of a single compound. Tautomers exhibit variations in atom arrangement, whereas resonance forms differ solely in the position of their π and nonbonding electrons.

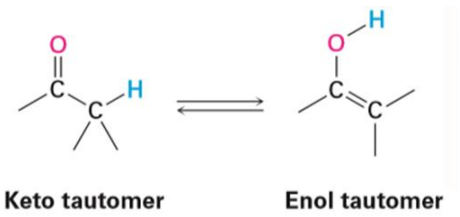

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Figure 30. Keto-enol tautomerism.

At equilibrium, most monocarbonyl compounds predominantly exist in their keto form, and isolating the pure enol is often challenging. The percentage of enol tautomer is even lower for carboxylic acids, esters, and amides. Stabilization through conjugation or intramolecular hydrogen bond formation sometimes allows the enol to predominate, as seen in 2,4-pentanedione, which is approximately 76% enol

tautomer. Despite their limited presence at equilibrium, enols significantly impact the reactivity of carbonyl compounds due to their high reactivity.

Both acids and bases catalyze the keto-enol tautomerism of carbonyl compounds. Acid catalysis involves protonation of the carbonyl oxygen, forming an intermediate cation that loses an H^+ from its alpha carbon, resulting in a neutral enol. This proton loss is analogous to the process in an E1 reaction where a carbocation loses H+ to form an alkene. Base-catalyzed enol formation occurs because the carbonyl group renders the hydrogens on the alpha carbon weakly acidic. Consequently, a carbonyl compound can act as an acid, donating one of its alpha hydrogens to a sufficiently strong base. The resulting resonance-stabilized anion, an enolate ion, undergoes protonation to yield a neutral compound. Protonation on the alpha carbon regenerates the keto tautomer, causing no net change. However, an enol tautomer is formed if protonation occurs on the oxygen atom.

Enols, characterized by electron-rich double bonds, exhibit a chemistry like nucleophiles and engage with electrophiles like alkenes. However, due to resonance electron donation from a lone pair on the neighboring oxygen, enols surpass alkenes in electron density and reactivity. Compared to alkene reactions with electrophiles (E1), enol reactions share the initial addition step. Yet, the subsequent pathway diverges. Instead of forming an addition product through reaction with a nucleophile, the intermediate cation in enol reactions loses the -OH proton, resulting in an alpha-substituted carbonyl compound (Figure 31).

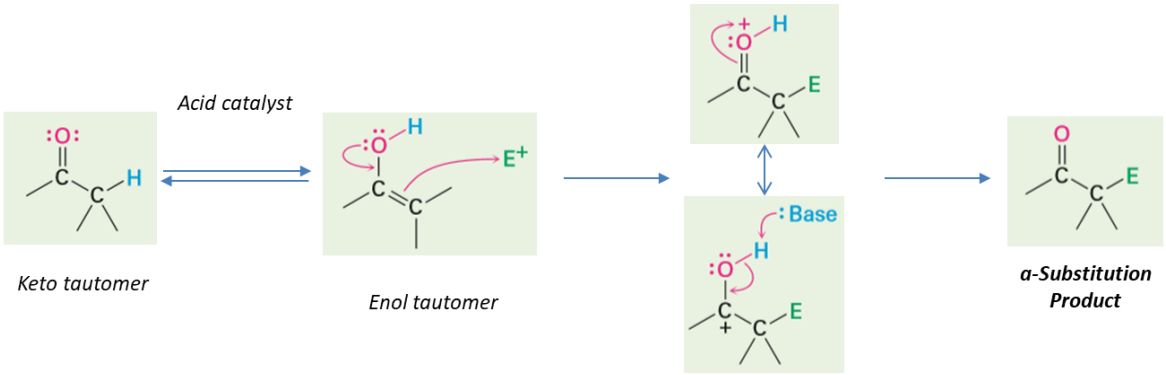

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Figure 31. Mechanism of alpha-substitution reactions.

4.3.2. Nucleophilic Acyl Substitution

A carboxylic acid's direct nucleophilic acyl substitution encounters difficulty due to the poor leaving group nature of -OH. Consequently, reactivity enhancement is often necessary, achieved either by utilizing a strong acid catalyst to protonate the carboxyl group and improve its accepting capability or by converting -OH into a more favorable leaving group. Under suitable conditions, acid chlorides, anhydrides, esters, and amides can all be derived from carboxylic acids through nucleophilic acyl substitution reactions.

In laboratory settings, carboxylic acids are transformed into acid chlorides by treating them with thionyl chloride, $SOCl_2$ (Figure 32). This reaction follows a nucleophilic acyl substitution pathway, wherein the carboxylic acid undergoes conversion into an acyl chlorosulfite intermediate. This substitution replaces

the -OH group with a considerably better leaving group. The chlorosulfite then reacts with a nucleophilic chloride ion, analogous to the process involving an alcohol and $SOCl_2$ to yield an alkyl chloride.

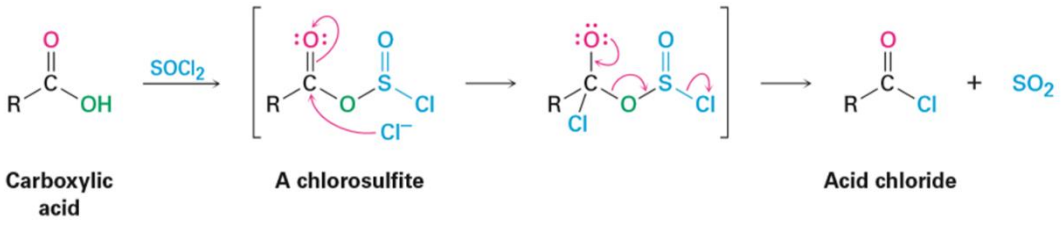

Figure 32. Nucleophilic acyl substitution pathway through conversion into acid chloride.

Esters can be synthesized through an acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol, known as the Fischer esterification reaction. However, this method is limited to synthesizing methyl, ethyl, propyl, and butyl esters due to the necessity of using excess liquid alcohol as a solvent.

The Fischer esterification reaction mechanism involves protonation of the carbonyl oxygen, enhancing the carboxylic acid's reactivity (Figure 33). Subsequent steps include nucleophilic attack by alcohol, yielding a tetrahedral intermediate, followed by proton transfer and water expulsion to regenerate the acid catalyst and produce the ester product. The net result of Fischer esterification is substituting an -OH group by -OR', where all steps are reversible, and the reaction equilibrium constant is typically close to 1. The direction of the reaction can be controlled by adjusting reaction conditions, favoring ester formation with a large excess of alcohol or carboxylic acid formation with a large excess of water.

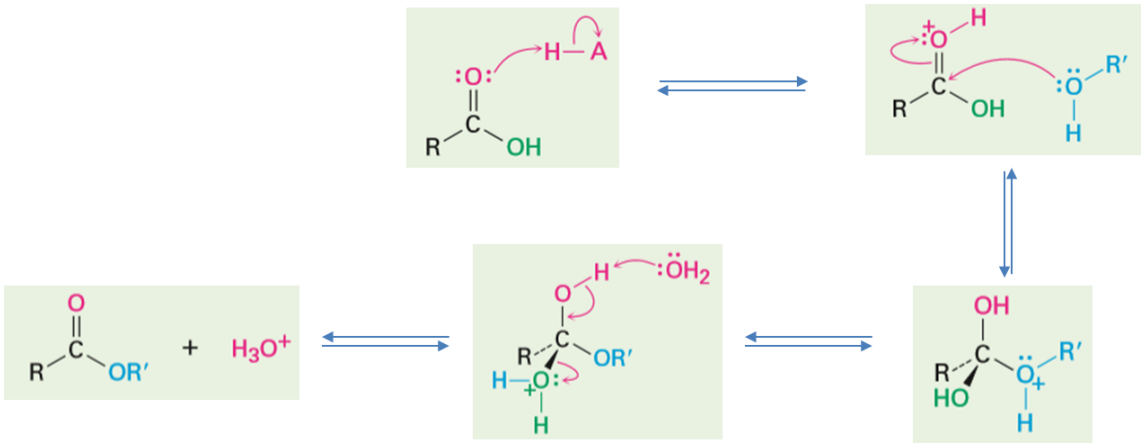

Figure 33. Mechanism of Fischer esterification.

5. AMINES

Amines are prevalent in various living organisms. Examples include trimethylamine, present in animal tissues and contributing to the characteristic smell of fish; nicotine, a substance found in tobacco; and cocaine, a stimulant naturally occurring in the leaves of the South American coca bush. Furthermore,

amino acids serve as the fundamental constituents for constructing all proteins, and cyclic amine bases play crucial roles in nucleic acids.

Amines are classified in two main types: alkyl-substituted amines (alkylamines) and aryl-substituted amines (arylamines). Despite sharing similarities in their chemistry, there are noteworthy distinctions between these two classes. Amines are categorized as primary (RNH_2), secondary (R_2NH), or tertiary (R_3N) based on the number of organic substituents linked to nitrogen. Compounds with a nitrogen atom bearing four attached groups carry a formal positive charge known as quaternary ammonium salts. Aromatic amines are referred to as anilines, and when the benzene ring carries multiple amino groups, they are named benzenediamines, -triamines, and so forth. For secondary and tertiary amines, the largest alkyl substituent on nitrogen dictates the alkanamine stem, and additional groups are denoted as *N*-substituents.

Naming conventions for primary amines vary in the IUPAC system:

- Simple amines receive the suffix -**amine** added to the alkyl substituent name. For instance, $C_6H_5NH_2$ is phenylamine, commonly known as aniline.
- Amines with more than one functional group consider -NH2 as an amino substituent on the parent molecule, with the amine function having the lowest precedence among functional groups.
- Symmetrical secondary and tertiary amines are named using the di- or tri- prefix along with the alkyl group.
- Unsymmetrically substituted secondary and tertiary amines are named as *N*-substituted primary amines. The largest alkyl group serves as the parent name, and the other alkyl groups are considered *N*-substituents due to their attachment to nitrogen.

5.1. Physical and Chemical Properties of Amines

The bonding within alkylamines closely resembles that of ammonia. The nitrogen atom is sp^3-hybridized, forming a regular tetrahedron where the three substituents occupy three corners, and the lone pair of electrons occupy the fourth. Correspondingly, the C-N-C bond angles approximate the tetrahedral value of 109°. In the case of trimethylamine, the C-N-C bond angle measures 108°, and the C-N bond length is 147 pm.

Tetrahedral geometry renders an amine with three distinct substituents on nitrogen chiral. The suggestion arises from the tetrahedral arrangement, which implies chirality when three different substituents are present, the lone electron pair serving as the fourth. Despite this potential chirality, isolating chiral amines proves challenging because the enantiomeric forms rapidly interconvert through pyramidal inversion, analogous to the inversion of an alkyl halide in an S_N2 reaction. This inversion involves a momentary rehybridization of the nitrogen atom to planar, sp^2 geometry, followed by rehybridization of the planar intermediate to tetrahedral, sp^3 geometry (Figure 34). The barrier to inversion is approximately 25 kJ/mol (6 kcal/mol), only twice the barrier to rotation about a C-C single bond. Consequently, maintaining enantiomerically pure di- or trialkylamines at room temperature is impossible when the nitrogen atom serves as the sole stereocenter, leading to the absence of optical activity.

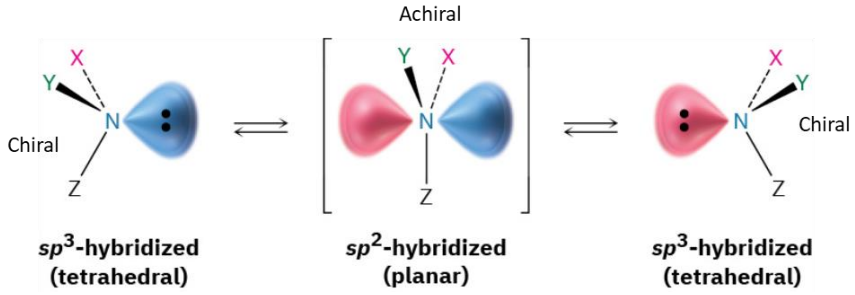

Figure 34. Inversion of chiral amines.

Primary and secondary amines exhibit hydrogen bonding and strong association, resulting in higher boiling points than alkanes of similar molecular weight. For instance, diethylamine (M_W = 73 g/mol) boils at 56.3 °C, while pentane (M_W = 72 g/mol) boils at 36.1 °C. Amines, being less electronegative than oxygen, form weaker hydrogen bonds than alcohols, leading to lower boiling points and reduced solubility in water. Smaller amines with fewer than five carbon atoms are generally water-soluble and soluble in alcohols due to their ability to form hydrogen bonds with solvents. However, if the hydrophobic part of an amine exceeds six carbons, water solubility decreases rapidly, rendering larger amines essentially insoluble in water.

Chemically, amines are both basic and nucleophilic due to the lone pair of electrons on nitrogen. They react with acids to form acid–base salts and with electrophiles in polar reactions. The basicity of amines surpasses that of alcohols, attributed to the higher availability of the lone pair for protonation. Factors like substituents or hybridization impact the electron density of amine nitrogen, influencing basicity and the pK_a of corresponding ammonium salts. The inductive effect of alkyl groups increases basicity, but steric disruption in solution limits the regular increase in pK_a values with alkyl substitution. Amines with electron-withdrawing substituents are less basic, and due to resonance stabilization, arylamines can exhibit varying basicity based on substituents.

In contrast to straightforward alkylamines, amines featuring electron-withdrawing substituents on the nitrogen exhibit reduced basicity. Notably, aniline is significantly less basic (pK_a = 4.63) than its saturated counterpart, cyclohexanamine (pK_a = 10.66), as well as other primary amines. This diminished basicity can be attributed to two key factors. Firstly, the sp^2 hybridization of the aromatic carbon attached to the nitrogen in aniline makes this carbon relatively electron-withdrawing, thereby limiting the availability of the nitrogen lone pair for protonation. Secondly, the resonance stabilization of the system involves the delocalization of the electron pair into the aromatic π system, a resonance that is lost upon protonation.

Arylamines exhibit lower basicity than alkylamines due to the delocalization of nitrogen lone-pair electrons by interaction with the aromatic ring π electron system, making them less accessible for bonding to H+. Resonance-wise, arylamines are stabilized relative to alkylamines, boasting five resonance forms. Substituted arylamines can either enhance or diminish basicity depending on the nature of the substituent. Electron-donating substituents like $-CH_3$, $-NH_2$, and $-OCH_3$, which augment the aromatic ring's reactivity toward electrophilic substitution, correspondingly elevate the basicity of the respective arylamine. Conversely, electron-withdrawing substituents such as -Cl, $-NO_2$, and -CN, which diminish ring reactivity toward electrophilic substitution, reduce arylamine basicity.

5.2. Synthesis of Amines

We leverage a significant attribute of nitrogen in numerous molecules: its nucleophilicity. Exploiting this property allows the synthesis of amines by alkylating the nitrogen in these species, resulting in their direct formation or subsequent chemical modification.

5.2.1. Reduction of N-Compounds

- Reduction of Nitrile: A two-step process involving S_N2 displacement with CN^- followed by reduction facilitates the conversion of an alkyl halide into a primary alkylamine with an additional carbon atom.
- Reduction of Amide: In laboratory settings, carboxylic acids convert into acid chlorides through thionyl chloride ($SOCl_2$) treatment via nucleophilic acyl substitution. The reduction of amides transforms carboxylic acids and their derivatives into amines with the same carbon atom count.
- Reduction of Nitro Group: Arylamines are typically synthesized through the nitration of an aromatic starting material, followed by the reduction of the nitro group.

5.2.2. Reductive Amination

A more versatile approach to amine synthesis is the reductive amination of aldehydes and ketones, enabling the creation of primary, secondary, and tertiary amines. In this method displayed in Figure 35, the carbonyl compound interacts with an amine containing at least one N–H bond (such as NH_3 or primary/secondary amines) along with a reducing agent, resulting in the direct formation of a new alkylated amine (either primary, secondary, or tertiary) named carbinolamine. The newly formed C–N bond is established with the carbonyl carbon of the aldehyde or ketone. The process commences with the initial condensation of the amine with the carbonyl component undergoing dehydration, generating the corresponding imine (for NH_3 and primary amines) or iminium ion (for secondary amines). Analogous to the carbon-oxygen double bond in aldehydes and ketones, the carbon–nitrogen double bond in these intermediates is then reduced through simultaneous catalytic hydrogenation or by incorporating specific hydride reagents ($NaBH_4$ or H_2/Ni).

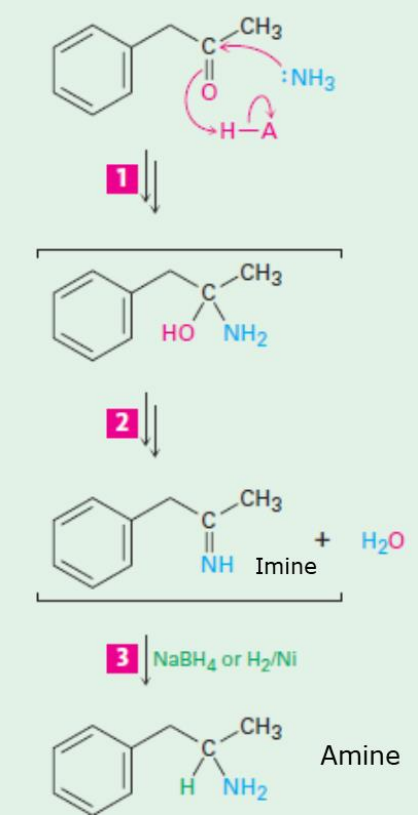

Figure 35. Mechanism of reductive amination.

5.3. Reactivity of Amines

5.3.1. Reactions of Alkylamines

Alkylations

Ammonia and other amines exhibit strong nucleophilic activity in S_N2 reactions. Consequently, the primary approach to alkylamine synthesis involves S_N2 alkylation of ammonia or an alkylamine with an alkyl halide. The resulting amine product depends on the starting materials used; ammonia yields a primary amine, while a primary amine results in a secondary amine, and so forth. Even tertiary amines readily react with alkyl halides, producing quaternary ammonium salts, $R_4N^+ X^-$. However, these reactions tend to be challenging to control as they often lead to multiple alkylations. Due to the similar reactivity of ammonia and primary amines, the initially formed monoalkylated substance frequently undergoes further reactions, yielding a mixture of products. Secondary and tertiary amines also undergo additional alkylation, albeit to a lesser extent. For instance, as shown in Figure 36, the treatment of 1-bromooctane with a twofold excess of ammonia yields a mixture containing only 45% octylamine. Doubletylation produces nearly equal amounts of dioctylamine, along with smaller quantities of trioctylamine and tetraoctylammonium bromide.

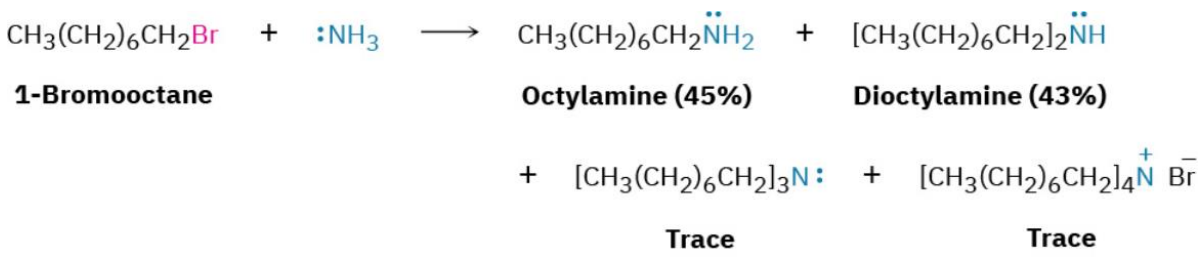

Figure 36. Multiple alkylation of 1-bromooctane with excess of ammonia.

Hofmann Elimination

Similar to alcohols, amines can undergo an elimination reaction to produce alkenes. However, due to the poor leaving ability of the amide ion (NH_2^-), it must be transformed into a more effective leaving group before the elimination reaction can proceed. The Hofmann elimination reaction addresses this challenge by subjecting an amine to complete methylation through an excess of iodomethane, forming the corresponding quaternary ammonium salt. Upon heating with a base, typically silver oxide (Ag_2O), the quaternary salt undergoes elimination to yield an alkene. Silver oxide facilitates the exchange of iodide ion for hydroxide ion in the quaternary salt, thereby providing the necessary base for the elimination process. The actual elimination step follows an E2 reaction mechanism, during which hydroxide ion removes a proton while the positively charged nitrogen atom departs, resulting in the formation of the alkene. For instance, 1-methylpentylamine can be transformed into 1-hexene using this method (Figure 37).

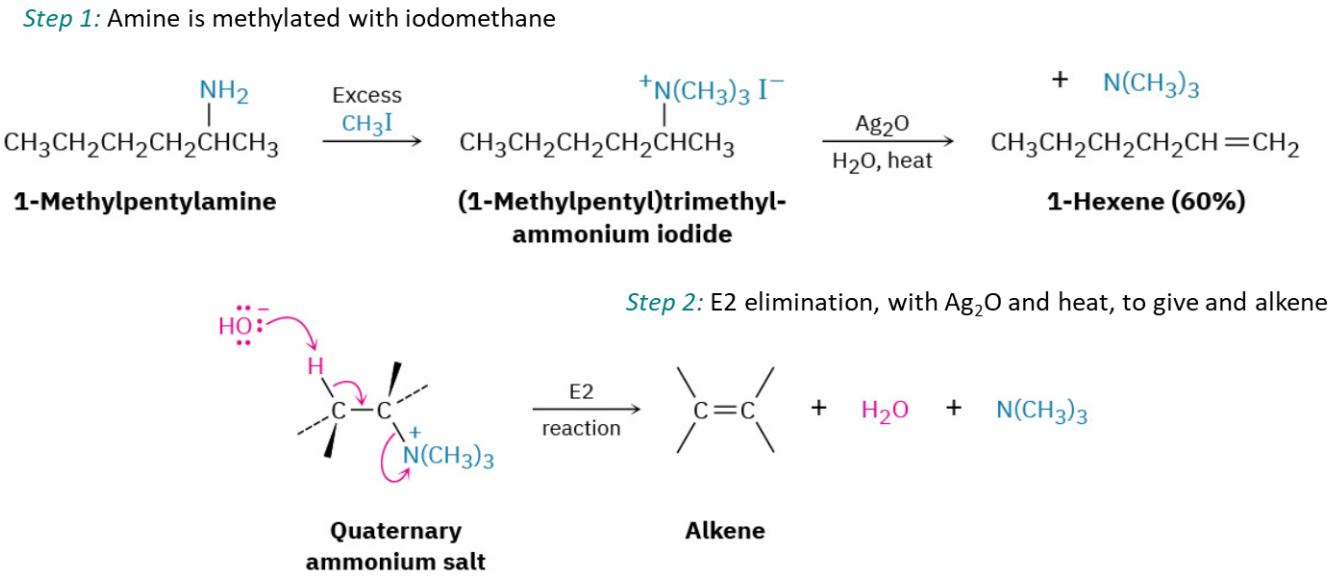

Figure 37. Hofmann elimination mechanism.

5.3.2. Reactions of Arylamines

Primary arylamines undergo a diazotization reaction when treated with nitrous acid, HNO_2, resulting in stable arenediazonium salts, denoted as Ar-$N^+{\equiv}N$ X^-. This reaction is distinctive for arylamines, as alkylamines produce highly reactive alkanediazonium products that readily lose nitrogen to form

carbocations. Unlike their alkane counterparts, arenediazonium salts exhibit stability due to resonance effects involving the π electrons in the diazo function and those of the aromatic ring. The resonance structures contain a double bond between the benzene ring and the attached nitrogen. The stability of arenediazonium salts allows for their versatile use in substitution reactions, where various nucleophiles such as halides, hydrides, cyanide, and hydroxide can replace the diazonio group (N≡N). Reactionthrough diazonium salts is illustrated in Figure 38.

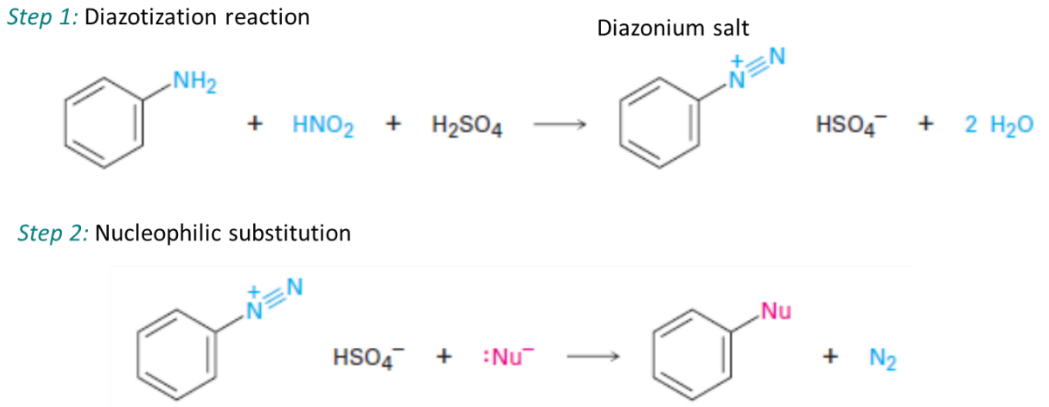

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Figure 38. Reaction through diazonium salts.

This substitution reaction, following the overall sequence of (1) nitration, (2) reduction, (3) diazotization, and (4) nucleophilic substitution, is considered one of the most adaptable methods of aromatic substitution. The Sandmeyer reaction employs copper(I) halide, CuX, to convert arenediazonium salts into aryl chlorides and bromides. In contrast, aryl iodides can be directly obtained by reacting with NaI without needing a copper(I) salt. The treatment of arenediazonium salt with CuCN yields the nitrile, which can be further transformed into various functional groups, including carboxyl. Additionally, the replacement of the diazonio group by -OH leads to the formation of phenols.