Organic Chemistry III

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21. Amines and Their Derivatives

Functional groups containing Nitrogen

Our atmosphere consists of nearly four-fifths nitrogen, N_2.

N_2 itself is relatively inert. However, in its reduced form of ammonia, NH_3, and its organic derivatives, the amines, it plays as active a role in nature.

Amines and nitrogen-bearing compounds are the most abundant organic molecules: components of the amino acids, peptides, proteins, and alkaloids.

Many amines, such as the neurotransmitters, possess powerful physiological activity; related substances have found medicinal uses as decongestants, anesthetics, sedatives, and stimulants.

Similar activity is found in cyclic amines, the nitrogen heterocycles.

In many respects, the chemistry of the amines is analogous to that of the alcohols and ethers.

All amines are basic (although primary and secondary amines can also behave as acids), they form hydrogen bonds, and they act as nucleophiles in substitution reactions.

However, there are some differences in reactivity, because nitrogen is less electronegative than oxygen.

Thus, primary and secondary amines are less acidic and form weaker hydrogen bonds than alcohols, and they are more basic and more nucleophilic.

21-1 NAMING THE AMINES

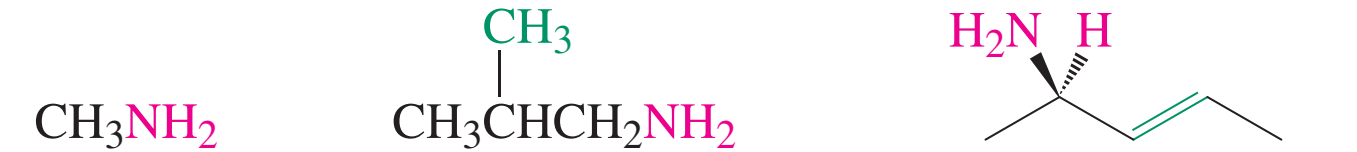
Amines are derivatives of ammonia, in which one, two, or three of the hydrogens have been replaced by alkyl or aryl groups.

In amines, the number of R substituents on nitrogen determines the amine classification: primary, secondary, and tertiary.

Ammonia **Primary amine** **Secondary amine** **Tertiary amine**

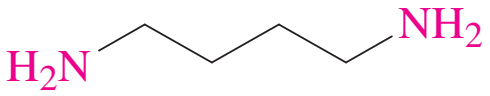
The best way to name aliphatic amines: **alkanamines,** in which the name of the alkane stem is modified by replacing the ending **-*e*** by **-amine.**

The position of the functional group is indicated by a prefix designating the carbon atom to which it is attached.

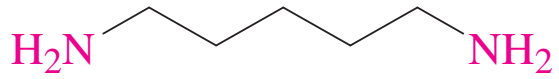


Methanamine **2-Methyl-1-propanamine** **(*R*)-*trans*-3-Penten-2-amine**

Substances with two amine functions are **diamines**. Their contribution to the smell of dead fish and rotting flesh leads to their descriptive common names.



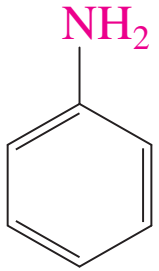
1,4-Butanediamine
(Putrescine)



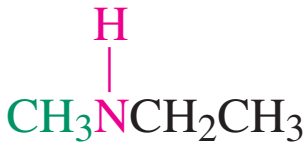
1,5-Pentanediamine
(Cadaverine)

The aromatic amines, or anilines, are called **benzenamines**.

For secondary and tertiary amines, the largest alkyl substituent on nitrogen is chosen as the alkanamine stem, and the other groups are named by using the letter *N*-, followed by the name of the additional substituent(s).



Benzenamine
(Aniline)
(A primary amine)



***N*-Methylethanamine**

(A secondary amine)

***N*,*N*-Dimethyl-1-propanamine**

(A tertiary amine)

An alternative way to name amines treats the functional group, called **amino-,** as a substituent of the alkane stem. This procedure is analogous to naming alcohols as hydroxy-alkanes.

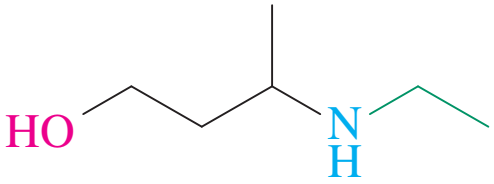
It is also used when other functional groups are present in the molecule, because the amine function has the lowest order of precedence of all functional groups discussed in this text.

$CH_3CH_2NH_2$

Aminoethane

$(CH_3)_2NCH_2CH_2CH_3$

***N,N*-Dimethylaminopropane**



3-(*N*-Ethylamino)-1-butanol

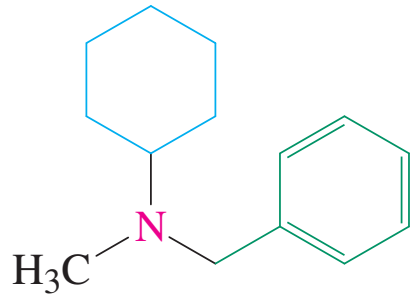
CH_3NH_2

Methylamine

$(CH_3)_3N$

Trimethylamine

Many common names are based on the term **alkylamine**, as in the naming of alkyl alcohols.



Benzylcyclohexylmethylamine

21-2 STRUCTURAL AND PHYSICAL PROPERTIES OF AMINES

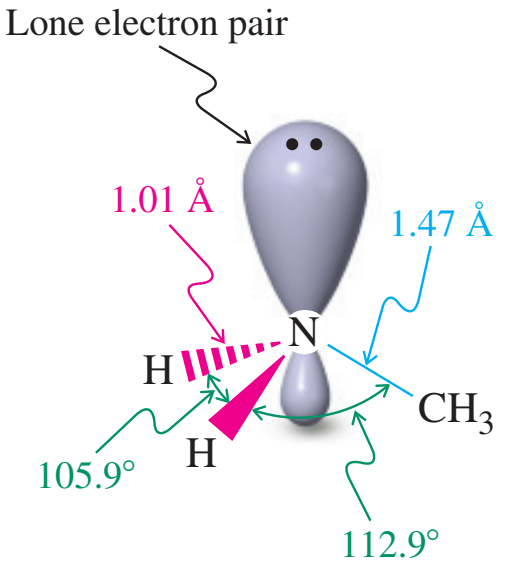
The alkanamine nitrogen is tetrahedral

Nitrogen often adopts a tetrahedral geometry, similar to carbon, but with one lone electron pair instead of a fourth bond. Thus, amines generally have tetrahedral shapes around the heteroatom.

In contrast to amides, the nitrogen orbitals in amines are very nearly sp^3 hybridized, forming an approximately tetrahedral arrangement. Three vertices of the tetrahedron are occupied by the three substituents, the fourth by the lone electron pair.

The electron pair is the source of the basic and nucleophilic properties of the amines.

The term **pyramidal** is often used to describe the geometry adopted by the nitrogen and its three substituents.



This arrangement is not rigid because of a rapid isomerization process called inversion.

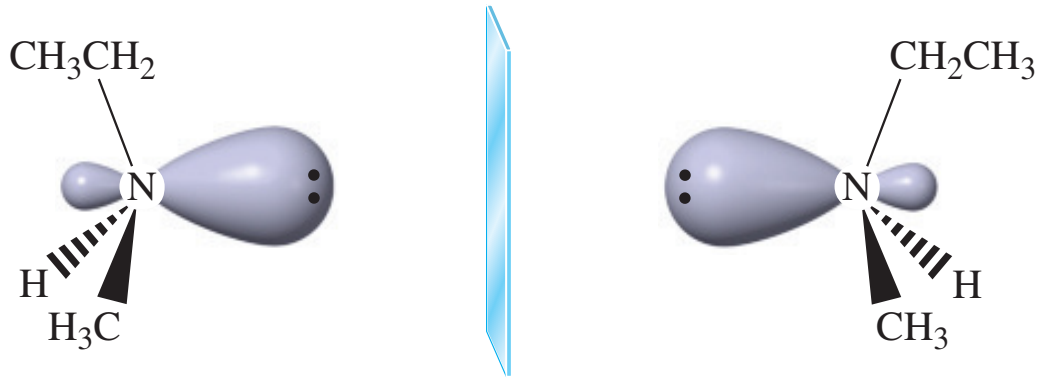
The tetrahedral geometry around an amine nitrogen suggests that it should be chiral if it bears three different substituents, the lone electron pair serving as the fourth.

The image and mirror image of such a compound are not superimposable, by analogy with carbon-based stereocenters.

However, samples of the amine prove *not* to be optically active. Why?

Amines are not configurationally stable at nitrogen, because of rapid isomerization by a process called **inversion.**

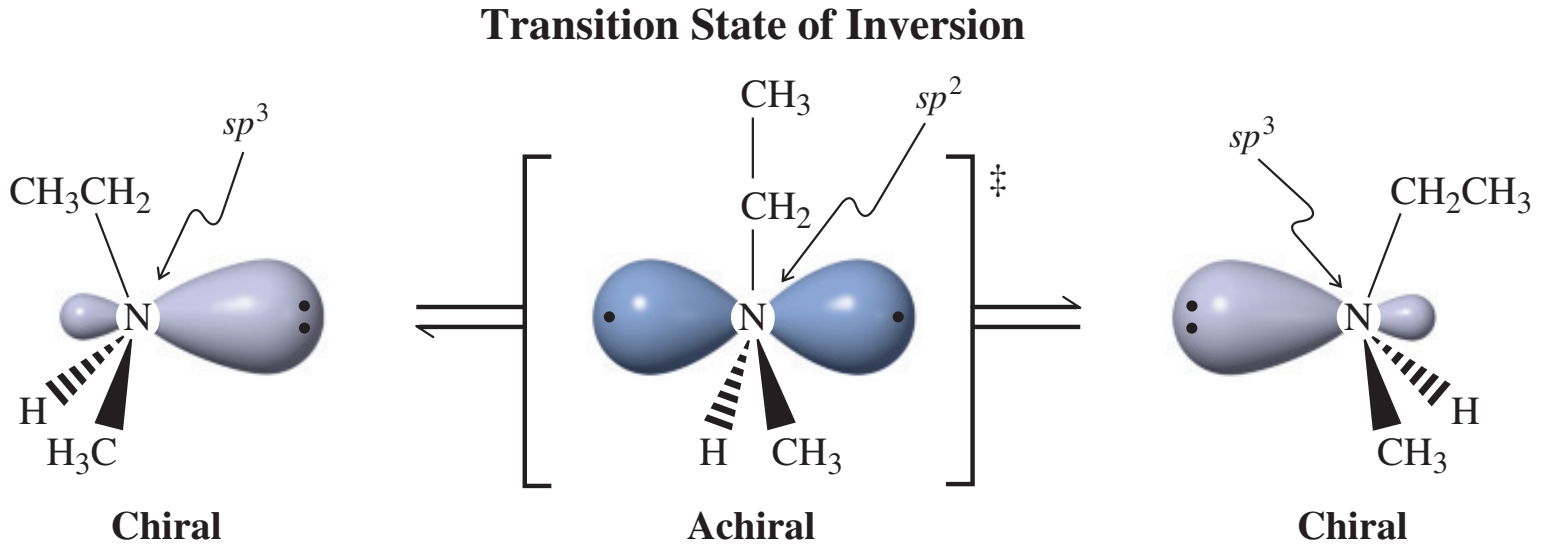
Image and Mirror Image of
***N*-Methylethanamine (Ethylmethylamine)**



The molecule passes through a transition state incorporating an sp^2-hybridized nitrogen atom. This transition state is similar to the inversion observed in S_N2 reactions.

The barrier to this motion in ordinary small amines has been measured spectroscopically and found to be between 5 and 7 kcal mol^{-1} (ca. 20–30 kJ mol^{-1}).

It is therefore impossible to keep an enantiomerically pure, simple di- or trialkylamine from racemizing at room temperature when the nitrogen atom is the only stereocenter.



Amines form weaker hydrogen bonds than alcohols do

Nitrogen is not as electronegative as oxygen, so they are weaker than the hydrogen bonds formed by alcohols. Amines have relatively low boiling points compared to alcohols.

The boiling points of the amines lie between the corresponding alkanes and alcohols.

The smaller amines are soluble in water and in alcohols because they can form hydrogen bonds to the solvent.

If the hydrophobic part of an amine exceeds six carbons, the solubility in water decreases rapidly; the larger amines are essentially insoluble in water.

Table 21-1 Physical Properties of Amines, Alcohols, and Alkanes

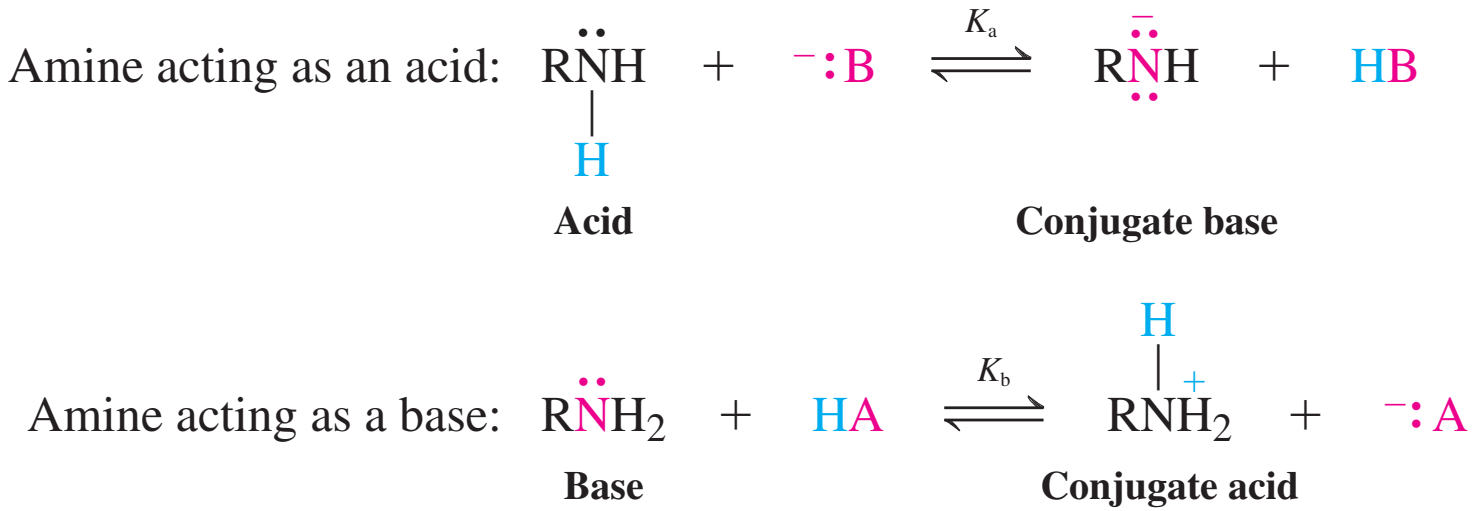
Compound	Melting point (°C)	Boiling point (°C)	Compound	Melting point (°C)	Boiling point (°C)
CH_4	−182.5	−161.7	$(CH_3)_2NH$	−93	7.4
CH_3NH_2	−93.5	−6.3	$(CH_3)_3N$	−117.2	2.9
CH_3OH	−97.5	65.0			
			$(CH_3CH_2)_2NH$	−48	56.3
CH_3CH_3	−183.3	−88.6	$(CH_3CH_2)_3N$	−114.7	89.3
$CH_3CH_2NH_2$	−81	16.6			
CH_3CH_2OH	−114.1	78.5	$(CH_3CH_2CH_2)_2NH$	−40	110
			$(CH_3CH_2CH_2)_3N$	−94	155
$CH_3CH_2CH_3$	−187.7	−42.1			
$CH_3CH_2CH_2NH_2$	−83	47.8	NH_3	−77.7	−33.4
$CH_3CH_2CH_2OH$	−126.2	97.4	H_2O	0	100

21-4 ACIDITY AND BASICITY OF AMINES

Like the alcohols, amines are both basic and acidic. Because nitrogen is less electronegative than oxygen, the acidity of amines is about 20 orders of magnitude less than that of comparable alcohols.

Conversely, the lone pair is much more available for protonation, thereby causing amines to be better bases.

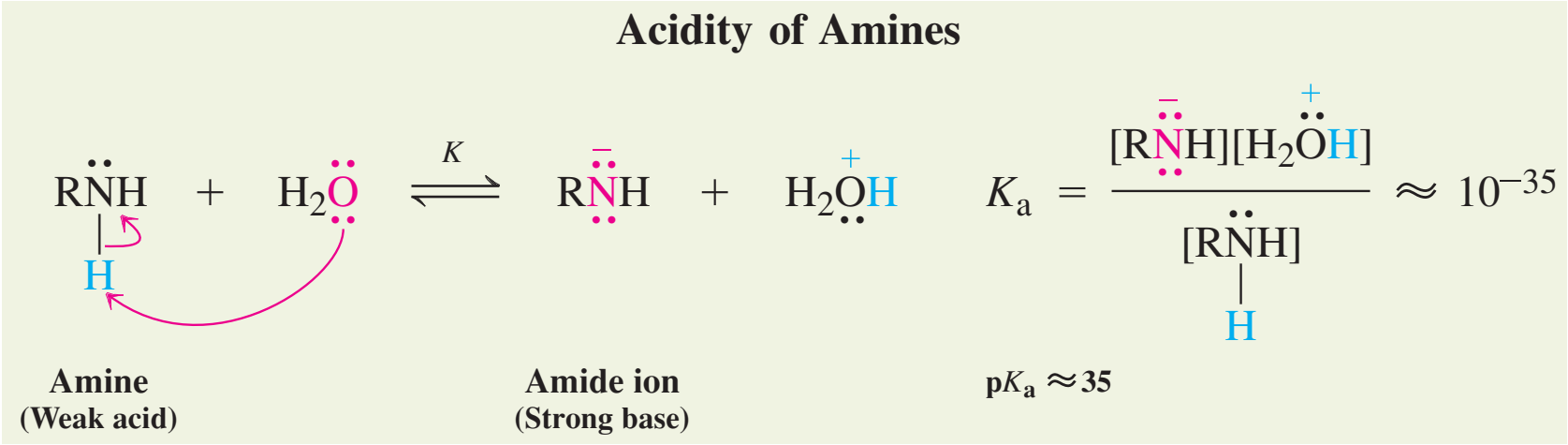
Acidity and Basicity of Amines



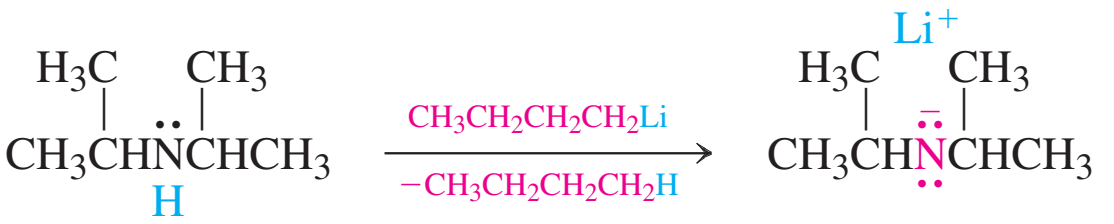
Amines are very weak acids

Amines are much less acidic than alcohols: Amide ions, R_2N^-, are used to deprotonate alcohols. The equilibrium of this proton transfer lies strongly to the side of the alkoxide ion.

The high value of the equilibrium constant, about 10^{20}, is due to the strong basicity of amide ions, which is consistent with the low acidity of amines. The pK_a of ammonia and alkanamines is of the order of 35.



The deprotonation of amines requires extremely strong bases, such as alkyllithium reagents. Lithium diisopropylamide (LDA), the sterically hindered base used in some bimolecular elimination reactions.



***N*-(1-Methylethyl)-2-propanamine (Diisopropylamine)**

Lithium diisopropylamide, LDA

An alternative synthesis of amide ions is the treatment of amines with alkali metals. Alkali metals dissolve in amines (albeit relatively slowly) with the evolution of hydrogen and the formation of amine salts (much as they dissolve in water and alcohol, furnishing H_2 and metal hydroxides or alkoxides).

Preparation of Sodium Amide

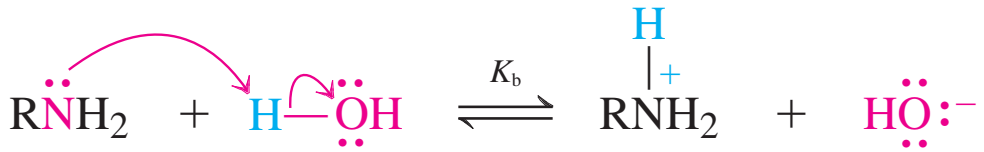
$$2\ Na + 2\ NH_3 \xrightarrow{\text{Catalytic } Fe^{3+}} 2\ NaNH_2 + H_2$$

Sodium amide can be made in liquid ammonia from sodium metal in the presence of catalytic amounts of Fe^{3+}, which facilitates electron transfer to the amine. In the absence of such a catalyst, sodium simply dissolves in ammonia (labeled "Na, liquid NH_3") to form a strongly reducing solution.

Amines are moderately basic, ammonium ions are weakly acidic

Amines deprotonate water to form ammonium and hydroxide ions. Thus, amines are more strongly basic than alcohols but not nearly as basic as alkoxides. Protonation occurs at the site of the free electron pair.

Basicity of Amines



Amine **Ammonium ion**

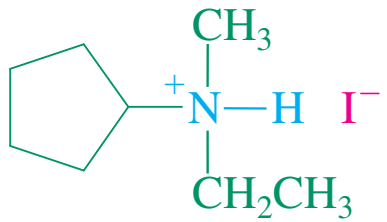
The resulting ammonium salts can be primary, secondary, or tertiary, depending on the number of substituents on nitrogen.

Primary ammonium chloride

Secondary ammonium bromide

Tertiary ammonium iodide

Methylammonium chloride



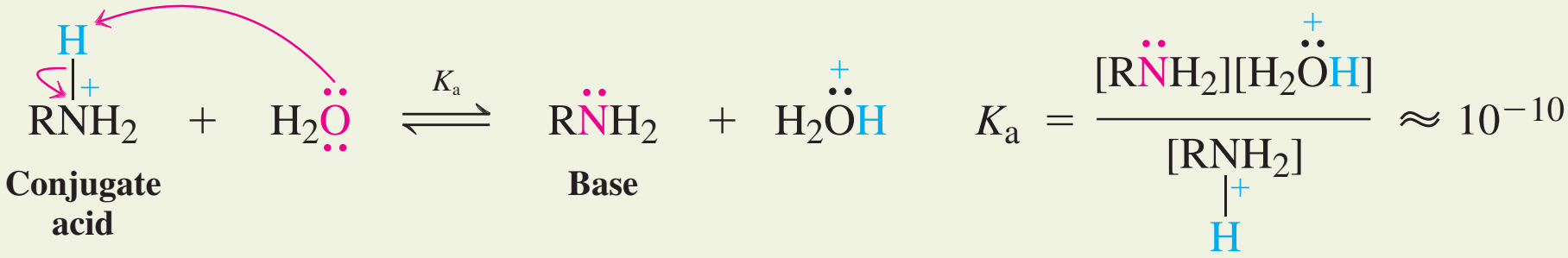
Cyclopentylethyl-methylammonium iodide

Ammonium salts are named by attaching the substituent names to the ending *-ammonium* followed by the name of the anion.

It is useful to view the basicity of the amines as a measure of the acidity of their conjugate acids, the ammonium ions.

These species are stronger acids than water (pK_a = 15.7) or alcohols but much weaker than carboxylic acids (pK_a = 4–5).

Acidity of Ammonium Ions



Reminder: The weaker the conjugate acid, the higher its pK_a and the stronger the corresponding base

Any factor, such as substituents or hybridization, that increases the electron density of the amine nitrogen increases the basicity of the amine and therefore the pK_a of the corresponding ammonium salt.

Conversely, decreasing the electron density of the amine nitrogen decreases its basicity and the pK_a of the corresponding ammonium salt.

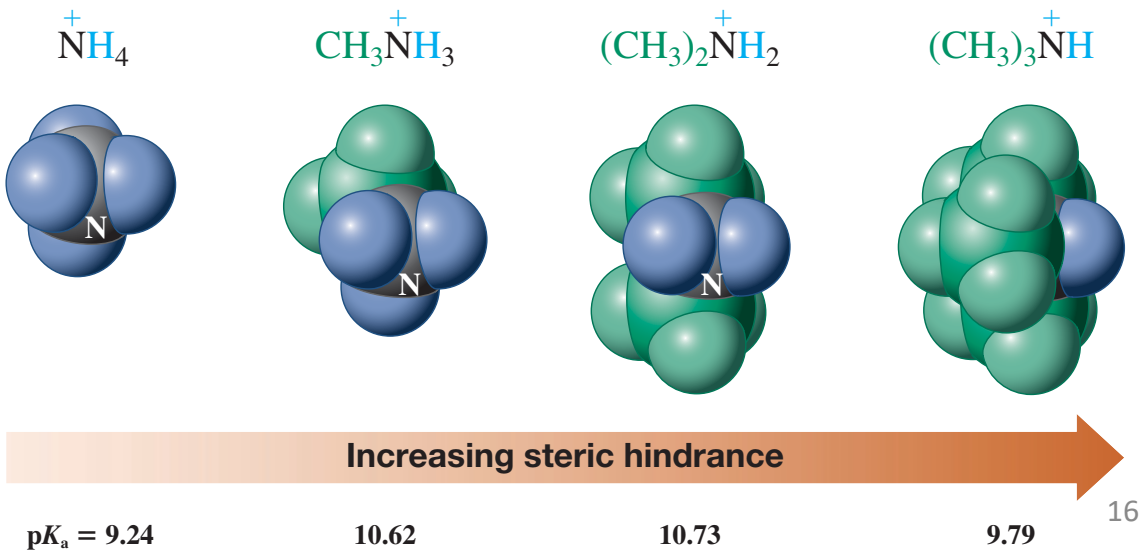
For example, alkylammonium salts are slightly less acidic than ammonium ion, $^{+}NH_4$, and therefore the corresponding amines are more basic. The reason is the electron-donating character of alkyl groups.

However, the pK_a values do not increase in a regular way with increasing alkyl substitution. In fact, tertiary amines are typically less basic than secondary systems.

Solvation is responsible for this observation. Thus, increasing the number of alkyl groups on the amine nitrogen increases unfavorable steric disruption of the solvent shell.

Moreover, it decreases the number of hydrogens attached to the nitrogen capable of entering into favorable hydrogen bonds.

pK_a Values of a Series of Simple Ammonium Ions*



Both phenomena counteract the inductive donor properties of the alkyl groups in solution.

Indeed, in the gas phase, in which there is no solvent, the trend is as expected:

pK_a: $^{+}NH_4 < CH_3NH_3^{+} < (CH_3)_2NH_2^{+} << (CH_3)_3NH^{+}$

The ready equilibration between free amine and ammonium salt is important for the formulation and activity of amine-based pharmaceuticals.

The neutral forms are typically insoluble in water, and therefore the medications are sold in their salt forms, to allow for ready oral or intravenous administration.

The pK_a of the amino function also affects the distribution, metabolism, excretion, and binding to receptor sites.

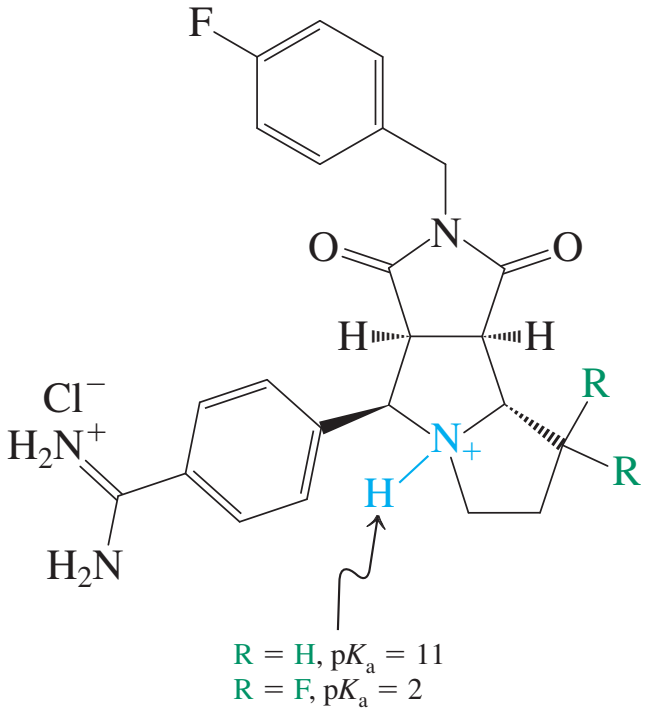
After ingestion, the acidic environment of the stomach (pH ~ 2–4) will keep the drug protonated, therefore minimizing absorption through the nonpolar gastric walls.

Once in the intestines (pH ~ 5–7), the acid-base equilibrium is shifted toward the amine, maximizing penetration.

This balancing act is continued until the molecule reaches the active site, where it may dock by hydrogen bonding (in the neutral form) or polar interactions (in the salt form).

Medicinal chemists often fine-tune lead structures for optimal pK_a profiles.

The blood anticoagulant scaffold has been modified extensively to tune its acidity over a pK_a range of 2–11.

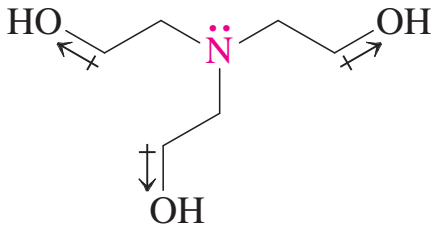


Blood anticoagulant

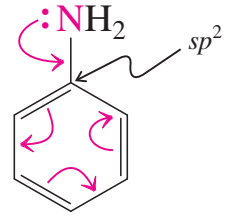
The nitrogen lone pairs in arenamines, carboxamides, and imines are less available for protonation

In contrast to the effect of alkyl groups, the basicity of amines is decreased by electron-withdrawing substituents on the nitrogen.

For example, the pK_a of triethanolamine is only 7.75, a consequence of the presence of three inductively electron-withdrawing oxygens.

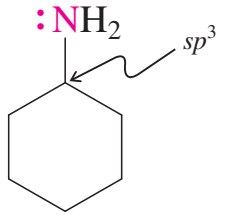


2-[Bis(2-hydroxyethyl)amino]ethanol (Triethanolamine)

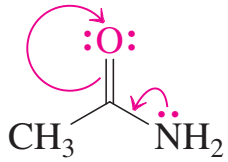


Benzenamine (Aniline)

Resonance diminishes the availability of the N lone pair

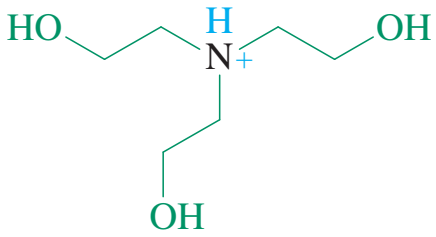


Cyclohexanamine

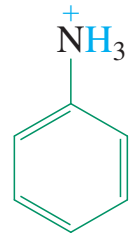


Acetamide

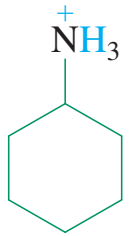
Resonance diminishes the availability of the N lone pair



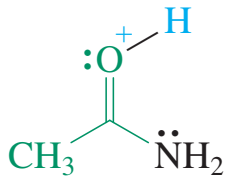
pK_a = 7.75



4.63



10.66



0.63

Protonation occurs on oxygen

Similarly, aniline is considerably less basic (pK_a = 4.63) than its saturated analog cyclohexanamine (pK_a = 10.66) and other primary amines. Two reason:

(1) the sp^2 hybridization of the aromatic carbon attached to the nitrogen in aniline, which renders that carbon relatively electron withdrawing, making the nitrogen lone pair less available for protonation,

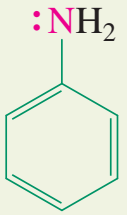
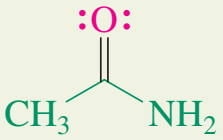
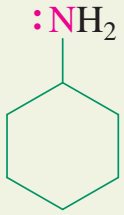
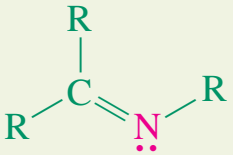
(2) the resonance stabilization of the system by delocalization of the electron pair into the aromatic **π** system. This resonance is lost upon protonation.

A similar example is acetamide, in which the appended acetyl group ties up the nitrogen lone pair by induction (the carbonyl carbon is positively polarized) and resonance.

As might be expected, the hybridization at nitrogen itself also drastically affects basicity, in the order **:**NH_3 > R_2C=NR' > RC≡N**:**, a phenomenon that we already encountered in the discussion of the relative acidity of alkanes, alkenes, and alkynes.

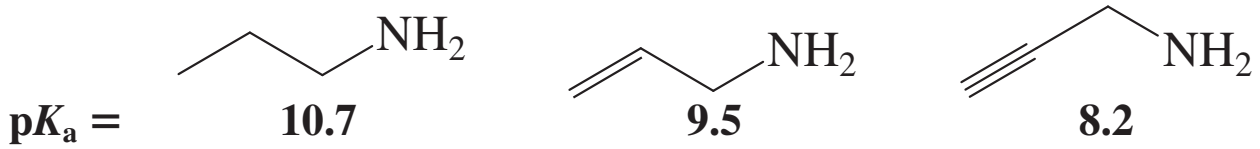
Thus, iminium ions have pK_a values estimated to be of the order of 7 to 9; *N*-protonated nitriles are even more acidic (pK_a < –5).

Table 21-2 pK_a Values of Various Amines

Compound	pK_a of conjugate acid	Compound	pK_a of conjugate acid
$:NH_3$	9.24		4.63
$CH_3\ddot{N}H_2$	10.62		
$(CH_3)_2\ddot{N}H$	10.73		
$(CH_3)_3N:$	9.79		
$(HOCH_2CH_2)_3N:$	7.75		0.63
	10.66		7–9
		$R-C\equiv N:$	< -5

Exercise 21-7

Explain the decreasing pK_a values of the following (protonated) amines:



21-5 SYNTHESIS OF AMINES BY ALKYLATION

(i) Amines can be synthesized by alkylating nitrogen atoms. Several such procedures take advantage of an important property of the nitrogen in many compounds: It is *nucleophilic*.

Amines can be derived from other amines

As nucleophiles, amines react with haloalkanes to give ammonium salts. Unfortunately, this reaction is not clean, because the resulting amine product usually undergoes further alkylation.

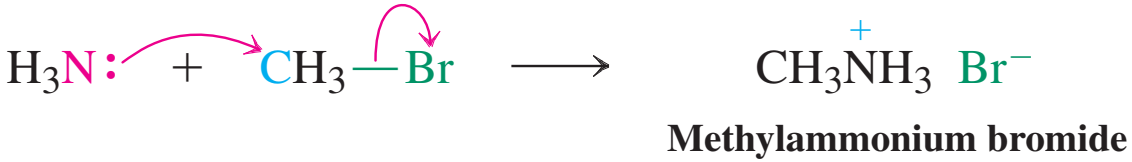
The mixture of products obtained upon treatment of haloalkanes with ammonia or amines is a serious drawback that limits the usefulness of direct alkylation in synthesis.

As a result, indirect alkylation methods are frequently applied, particularly in the preparation of primary amines.

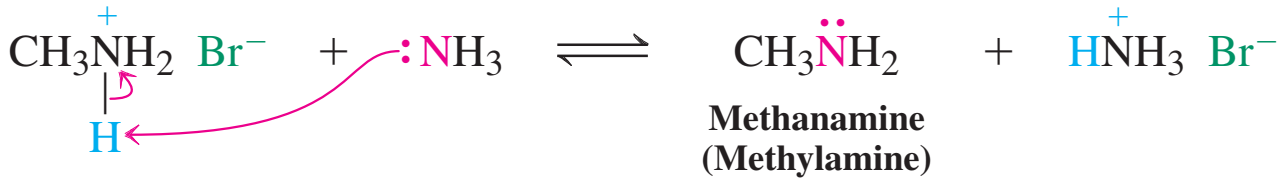
Methylation of Ammonia

First Alkylation. Two steps give primary amine

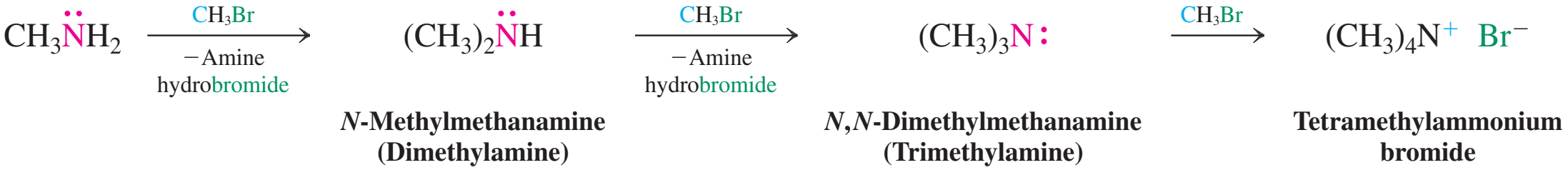
Step 1. Nucleophilic Substitution:



Step 2. Deprotonation:



Subsequent Alkylation. Gives secondary, tertiary, and quaternary amines or ammonium salts, respectively



Consider the alkylation of ammonia with bromomethane:

When this transformation is carried out with equimolar quantities of starting materials, the weakly acidic product (methylammonium bromide), as soon as it is formed, (reversibly) donates a proton to the starting, weakly basic ammonia.

The small quantities of methanamine generated in this way then compete effectively with the ammonia for the alkylating agent, and this further methylation generates a dimethylammonium salt.

The process does not stop there. This salt can donate a proton to either of the other two nitrogen bases present, furnishing *N*-methylmethanamine (dimethylamine).

This compound constitutes yet another nucleophile competing for bromomethane; its further reaction leads to *N*,*N*-dimethylmethanamine (trimethylamine) and, eventually, to tetramethylammonium bromide, a *quaternary* ammonium salt.

The final outcome is a mixture of alkylammonium salts and alkanamines.

Indirect alkylation leads to primary amines

(ii) The synthesis of primary amines requires a nitrogen-containing nucleophile that will undergo reaction *only once* and that can be converted subsequently into the amino group.

Cyanide ion, ^{-}CN, turns primary and secondary haloalkanes into nitriles, which are then reduced to the corresponding amines. This sequence allows the conversion:
$RX \rightarrow RCH_2NH_2$

Note that this method introduces an additional carbon into the haloalkane framework, because cyanide is alkylated at carbon and not nitrogen.

Conversion of a Haloalkane into the Homologous Amine by Cyanide Displacement–Reduction

$$RX + {}^{-}CN \longrightarrow RC{\equiv}N + X^{-}$$

$$RC{\equiv}N \xrightarrow{LiAlH_4 \text{ or } H_2, \text{ metal catalyst}} RCH_2NH_2$$

$$CH_3(CH_2)_8Br + NaCN \xrightarrow[-NaBr]{DMSO} CH_3(CH_2)_8CN \xrightarrow{H_2, \text{ Raney Ni, 100 atm}} CH_3(CH_2)_8CH_2NH_2$$

93% 92%

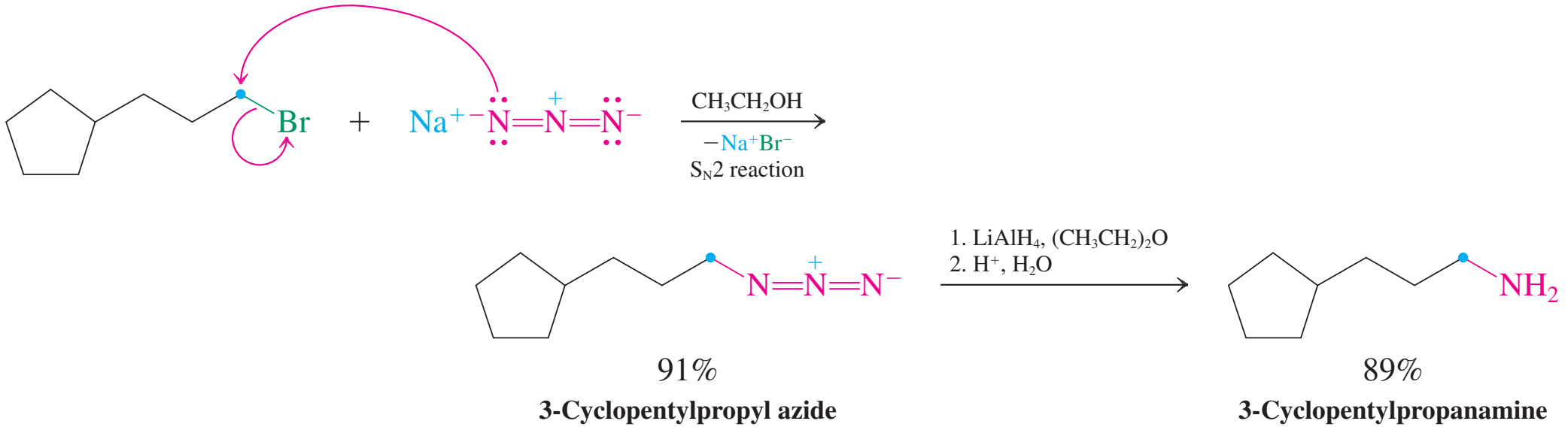
1-Bromononane **Decanenitrile** **1-Decanamine**

(iii) To transform a haloalkane selectively into the corresponding amine without additional carbons requires a modified nitrogen nucleophile that is unreactive after the first alkylation.

Such a nucleophile is the **azide ion,** N_3^-, which reacts with haloalkanes to furnish **alkyl azides (**R—N_3).

These azides in turn are reduced by catalytic hydrogenation (Pd–C) or by lithium aluminum hydride to the primary amines.

Azide Displacement–Reduction



(iv) A nonreductive approach to synthesizing primary amines uses the (commercially available) anion of 1,2-benzenedicarboximide (phthalimide), the ***imide*** of 1,2-benzenedicarboxylic (phthalic) acid.

This process is also known as the **Gabriel synthesis.**

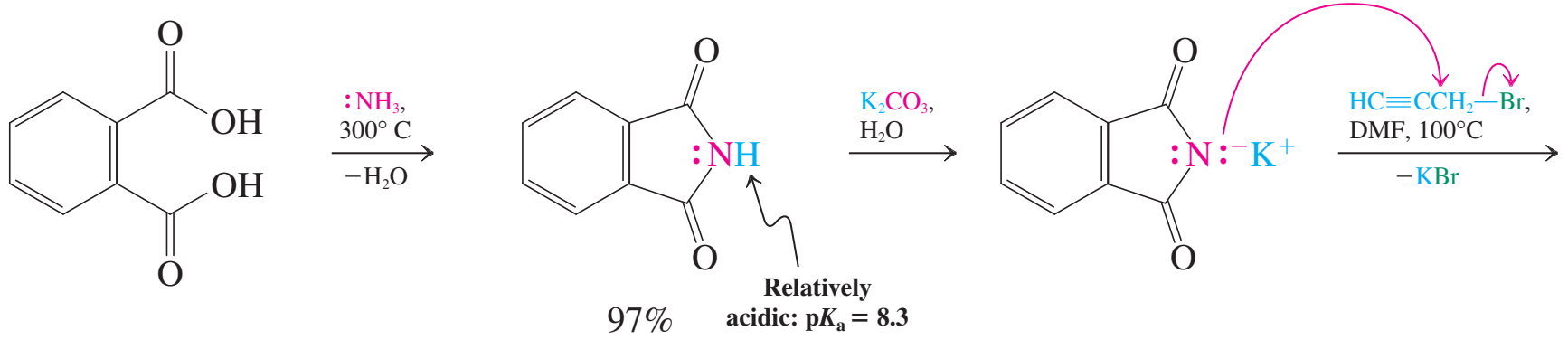
Because the nitrogen in the imide is adjacent to two carbonyl functions, the acidity of the NH group (pK_a = 8.3) is much greater than that of an ordinary amide (pK_a = 22).

Deprotonation can therefore be achieved with as mild a base as carbonate ion, the resulting anion being monoalkylated in good yield.

The amine can be liberated subsequently by acidic hydrolysis, initially as the ammonium salt.

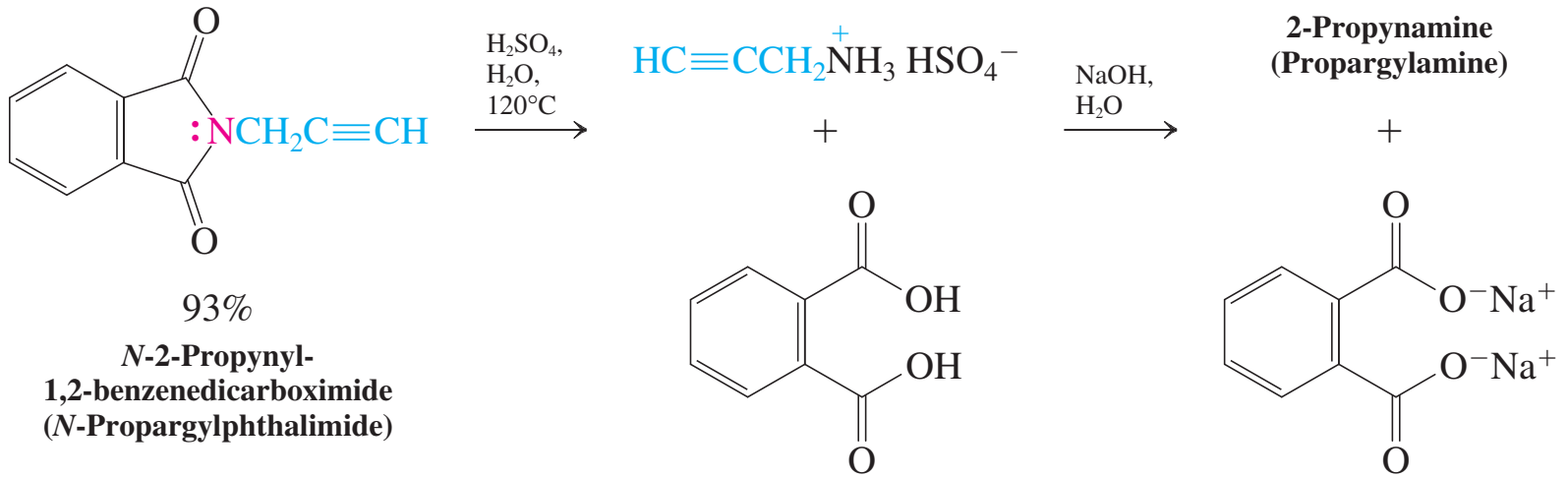
Base treatment of the salt then produces the free amine.

Gabriel Synthesis of a Primary Amine



1,2-Benzenedicarboxylic acid (Phthalic acid)

1,2-Benzenedicarboximide (Phthalimide)



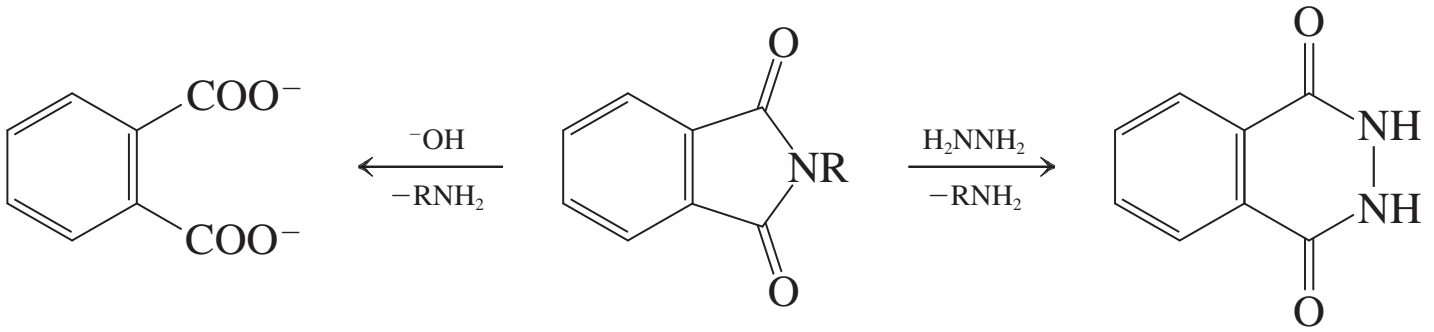
N-2-Propynyl-1,2-benzenedicarboximide (N-Propargylphthalimide)

2-Propynamine (Propargylamine)

Removed in aqueous work-up

Exercise 21-9

The cleavage of an *N*-alkyl-1,2-benzenedicarboximide (*N*-alkyl phthalimide) is frequently carried out with base or with hydrazine, H_2NNH_2. The respective products of these two treatments are the 1,2-benzenedicarboxylate A or the hydrazide B. Write mechanisms for these two transformations.



A **B**