

A Guide to Solvents and Reagents in Introductory Organic Chemistry for students in 2.222

Dr. P.G. Hultin, February 2002

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1. Solvents

Most organic reactions are carried out in solution, although in some cases it is possible to simply mix all reacting components together. Solvents facilitate mixing, help to regulate temperature, stabilize (or destabilize) reactive intermediates, and mediate proton transfers. The specific choice of solvent can make the difference between success and failure in a particular reaction, but for the purposes of an introductory course, only a few solvents and their properties need be considered.

1.2. Polar Protic Solvents

The term “protic” indicates that these solvents are all relatively Bronsted acidic – that is, they contain one or more hydrogen atoms that can be lost as a proton in a transfer reaction with water.

Water (H_2O): MW 18.015, density 1.00 g/mL, mp 0 °C, bp 100 °C.

Water is not really an organic solvent, and the majority of organics are insoluble or only slightly soluble in it. Even so, it can be mixed with a variety of polar organic “co-solvents” to provide solubility for organics while maintaining many of the properties of pure water. Typical “co-solvents are: Methanol, Ethanol, Acetone, Tetrahydrofuran, Dimethylsulfoxide, Dimethylformamide.

Water is an excellent solvent for many ions, because it is a highly polar substance. Likewise it stabilizes ionic intermediates. This behaviour is partly related to its properties as a Lewis base, since it interacts with electron-deficient atoms (Lewis acids) via the lone pair electrons on oxygen. These electrons make it fairly nucleophilic, and thus water sometimes competes with other nucleophiles for cations and strongly electrophilic centres.

It is a strong hydrogen-bond donor and acceptor. In the context of organic chemistry, water is considered a Bronsted acid, and thus is incompatible with most carbanions. When exposed to bases it forms the hydroxide ion (OH^-), which is a moderately strong Bronsted base and a much better nucleophile than water itself. Water can also behave as a Bronsted base, forming the hydronium ion H_3O^+ .

Methanol ($MeOH$, CH_3OH): MW 32.042, density 0.791 g/mL, mp -98 °C, bp 65 °C.

Ethanol ($EtOH$, CH_3CH_2OH): MW 46.069, density 0.789 g/mL, mp -114 °C, bp 78 °C.

Isopropanol ($i-PrOH$, $(CH_3)_2CHOH$): MW 60.096, density 0.786 g/mL, mp -90 °C, bp 82 °C.

Tert-Butanol ($t-BuOH$, $(CH_3)_3COH$): MW 74.123, density 0.786 g/mL, mp 26 °C, bp 82 °C.

Alcohols are frequently used as highly polar solvents, when water is not suitable. In most cases that will be encountered in introductory organic chemistry, the specific choice of alcohol is not very important. The main exceptions to this are reactions in

which the alcohol molecule is actually becoming incorporated into the organic product, where obviously only the appropriate alcohol will do.

The low molecular weight alcohols listed here are miscible with water in all proportions, and thus can be used as co-solvents with water. Note that while *t*-butanol is very miscible with water, *n*-butanol is not. The longer the alkyl chain in the alcohol, the better it solvates low-polarity organics, but the less soluble it is in water.

Like water, alcohols are Bronsted acids with similar strengths to water. They are also good hydrogen bond donors and accepters. Primary and secondary alcohols are good nucleophiles. On the other hand, they do not dissolve inorganic ions very well. Just try dissolving salt in rubbing alcohol (70% isopropanol/water) or vodka (ca. 50% Ethanol/water) sometime!

When treated with base, alcohols form alkoxide ions (RO^-). Alkoxides are similar to hydroxide in terms of their basicity and nucleophilicity.

In the presence of strong acids (HCl, HNO_3 , H_2SO_4 , *p*-toluenesulfonic acid), tertiary alcohols and some secondary alcohols may ionize, by loss of water, forming a carbocation. Usually if the alcohol is being used as a solvent this process is undesirable, but it can be an important source of electrophilic cation intermediates in certain specific situations. Generally, it is unwise to treat alcohols with concentrated nitric acid, because they are converted to alkyl nitrates in a rather violent reaction under these conditions.

Acetic Acid (AcOH, CH₃CO₂H): MW 60.052, density 1.049 g/mL, mp 17 °C, bp 118 °C.

Acetic acid is a very good solvent for many organic molecules, although it does not dissolve inorganic ions well. It is miscible with water in all proportions, and it dissolves in most common organic solvents too.

Like most simple carboxylic acids, it is a weak Bronsted acid (pKa 4.7). Acetic acid is not usually chosen as a solvent unless the reaction specifically calls for mildly acidic conditions. Acetic acid is too weak to protonate alkenes and other weak Lewis basic functional groups, but it can provide a good polar environment to stabilize ionic reactive intermediates generated by stronger acids.

Acetic acid is somewhat nucleophilic, and will attack strongly electrophilic atoms and cationic intermediates to form an *acetate ester* product.

1.3. Polar Aprotic Solvents

The term “aprotic” indicates that while these solvents are highly polar, they do not behave as Bronsted acids towards water.

Polar aprotic solvents provide a polar reaction environment and are frequently used for $\text{S}_{\text{N}}2$ displacement reactions, where they stabilize the charge-separation that occurs in the transition state. They are hydrogen-bond acceptors, but not hydrogen bond donors.

Acetone ($\text{CH}_3\text{C}(\text{O})\text{CH}_3$): MW 58.08, density 0.788 g/mL, mp $-95\text{ }^\circ\text{C}$, bp $56\text{ }^\circ\text{C}$.

Acetone is a good solvent for medium-to-high polarity organic molecules, and for some hydrocarbons as well. It is miscible with water in all proportions. Inorganic salts in which either (or both) the cation or anion is from the bottom of the periodic table are soluble in acetone (e.g. CsF, NaI), but many simple salts are not (e.g. NaCl). Acetone is often used for $\text{S}_{\text{N}}2$ displacement reactions where a soluble salt is the source of the nucleophile, but the leaving group forms an insoluble salt.

Because the ketone group is moderately electrophilic, acetone cannot be used in reactions involving very strong nucleophiles such as carbanions or Grignard reagents. These reagents are also very strong bases, and will deprotonate acetone to form an enolate ion.

Dimethylsulfoxide (DMSO, $\text{CH}_3\text{S}(\text{O})\text{CH}_3$): MW 78.089, density 1.096 g/mL, mp $19\text{ }^\circ\text{C}$, bp $189\text{ }^\circ\text{C}$.

DMSO is a very polar solvent that dissolves most organics and most inorganic salts very well. It is miscible with water in all proportions. Because it freezes at just below room temperature, it cannot be used for reactions involving low temperatures.

Like acetone, it is a good solvent for $\text{S}_{\text{N}}2$ displacements. Also like acetone it is incompatible with very strong nucleophiles or bases.

DMSO differs from acetone in that it is somewhat nucleophilic. If there is no better nucleophile around, DMSO will displace good leaving groups.

The main drawback of DMSO is its very high boiling point, which makes it difficult to remove by evaporation.

N,N-Dimethylformamide (DMF, $\text{HC}(\text{O})\text{N}(\text{CH}_3)_2$): MW 73.095, density 0.945 g/mL, mp $-60\text{ }^\circ\text{C}$, bp $152\text{ }^\circ\text{C}$.


DMF behaves in many ways like DMSO, but it is not significantly nucleophilic. It is also very high boiling, but since its freezing point is $-60\text{ }^\circ\text{C}$, it can be used at lower temperatures than can DMSO.

1.4. Ethers

There are two common ether solvents, THF and diethyl ether. Diethyl ether is usually simply called “ether”. Ethers are medium-polarity solvents, which dissolve the majority of organics but do not dissolve common salts to any significant extent. Ether solvents are typically used in Grignard reactions, reactions of organolithium reagents or LDA, or other reactions where the reagent involves a metallic cation. This is because the ethers are Lewis bases and can coordinate to Lewis acidic metal ions. It is also because they are not Bronsted acids and are thus impervious to the very strongly basic Grignard or organolithium reagents.

Diethyl ether (Ether, Et_2O , $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$): MW 74.123, density 0.713 g/mL, mp $-117\text{ }^\circ\text{C}$, bp $35\text{ }^\circ\text{C}$.

Ether is widely used as a general-purpose organic solvent. Its main drawbacks are its very low boiling point and high flammability. It dissolves many organic materials, but is only very slightly soluble in water. It is a weak Bronsted base, and can be protonated by anhydrous HCl or H₂SO₄. It is not protonated by weaker acids. It is a fairly good Lewis base as well, and thus can solvate some metallic reagents (although not ionic salts).

Tetrahydrofuran (THF, , C₄H₈O): MW 72.107, density 0.888 g/mL, mp -109 °C, bp 67 °C.

THF is one of the most frequently used organic solvents. It dissolves almost any organic molecule and a large number of inorganic reagents as well, although most ionic salts are not very soluble. It solvates Lewis acids much better than does diethyl ether. This is because the oxygen of THF is very exposed and thus the lone pairs can easily coordinate to the electron deficient centres. However, ethers are weak Bronsted bases and thus are only protonated by very strong Bronsted acids.

Unlike diethyl ether, THF is miscible with water and thus can be used as a co-solvent to help get organic molecules into aqueous media.

1.5. Chlorinated Solvents

Chlorinated solvents are, like ethers, moderate polarity media. They are all denser than water. Because of concerns over their potential toxicity, they are not used much in industry, but they are used in laboratory-scale work extensively. A major advantage of chlorinated solvents over ethers or hydrocarbons is that they are not flammable.

Dichloromethane (methylene chloride, CH₂Cl₂): MW 96.944, density 1.326 g/mL, mp -95 °C, bp 40 °C.

Dichloromethane is another “workhorse” organic solvent. It is almost totally immiscible with water, and it does not dissolve common salts at all, but it dissolves most mid- to low-polarity organics very well. It also dissolves common inorganic Lewis acids, and because it is neither acidic nor basic, it does not interfere with their chemistry. Dichloromethane is stable to weak and medium Bronsted bases (i.e. up to and including hydroxide ion), but it is incompatible with carbanions and other very strong organic bases.

Chloroform (CHCl₃): MW 118.37, density 1.489 g/mL, mp -64 °C, bp 61 °C.

Chloroform is only occasionally used as a solvent for organic reactions. It has properties quite similar to dichloromethane, but it is less volatile. It is suspected of causing cancer, and so has been largely relegated to niche uses. Its deuterated form, *chloroform-d* or CDCl₃, is the most widely used solvent for organic NMR spectrometry.

Chloroform cannot be exposed to bases even as strong as hydroxide, since it is easily converted to (*singlet*) dichlorocarbene by an α -elimination reaction.

1.6. Hydrocarbon Solvents

Hydrocarbon solvents are generally inert to reagents of all kinds. They are neither acidic nor basic, in either the Lewis or Bronsted senses. They will only dissolve low polarity organics, although the *aromatic solvents* are a bit more tolerant in this regard. Hydrocarbon solvents provide a reaction environment that is as close to the gas phase as a solution can get.

The main factor dictating the choice of one hydrocarbon over another is *boiling point*, if the reaction involves heating, or *melting point*, if the reaction is to be done at low temperature.

Common Aliphatic Solvents: Pentane (mostly isomers of C_5H_{12} , bp 35-36 °C), Hexanes (mostly isomers of C_6H_{14} , bp 69 °C), iso-Octane (2,2,4-trimethylpentane, C_8H_{18} , bp 98-99 °C), and decalin (perhydronaphthalene, $C_{10}H_{18}$, bp 189-191 °C).

Common Aromatic Solvents: Benzene (C_6H_6) bp 80 °C, Toluene ($C_6H_5CH_3$) bp 111 °C, and Xylenes (*o,m,p* isomers of $C_6H_4(CH_3)_2$) bp 140 °C.

Benzene is no longer used as a reaction solvent because of its carcinogenicity. Toluene and Xylenes are much safer and are usually equivalent substitutes.

One of the main uses of aromatic solvents is their ability to remove water by *azeotropic distillation*. For example, the toluene/water azeotrope, boiling at 84 °C, contains 14% water. Reactions that generate water, such as elimination of OH groups or ester formation, can be done in boiling toluene. When the vapour is condensed, the water is not miscible with the toluene and can be removed while the toluene is returned to the reaction vessel.

1.7. Amine Solvents

Several “special purpose” organic solvents are encountered from time to time. The most common of these are the *amines*, which are Bronsted and Lewis bases. Reactions that generate protons are frequently performed in the presence of amine bases, and occasionally the amine is the solvent for the process. The properties of common amines are also discussed under the “Reagents” heading.

Triethylamine (Et_3N , $(CH_3CH_2)_3N$): MW 101.19, density 0.726 g/mL, mp –115 °C, bp 90 °C.

Triethylamine is miscible with water and with most organics. Thus it has become one of the most common organic bases. It is often used as a reagent or a co-solvent, but it can be used as the solvent for several types of reactions as well. It is unfortunately rather smelly, as are most amines.

Pyridine (Pyr , *Error! Objects cannot be created from editing field codes.*, C_5H_5N): MW 79.102, density 0.983 g/mL, mp –42 °C, bp 115 °C.

Pyridine is an aromatic amine. It is less basic than is triethylamine, but it is quite nucleophilic because the nitrogen lone pair is very exposed. It is used as a solvent for many of the same reactions that triethylamine might be used for. Pyridine is also very soluble in water.

1.8. Miscellaneous Solvents

Ethyl Acetate (EtOAc, CH₃CO₂CH₂CH₃): MW 88.106, density 0.901 g/mL, mp -84 °C, bp 77 °C.

Ethyl acetate is not usually encountered as a reaction solvent, but it is frequently used in extractions and in chromatography. Because it is an ester, it cannot be exposed to aqueous acid or base for more than short periods without being hydrolysed.

Likewise, in the presence of strong organic bases it will be deprotonated to form an *enolate* or it will be alkylated by nucleophilic attack at the ester carbonyl.

Ethyl acetate is more polar than ether but less polar than THF. It is only slightly soluble in water.

Acetonitrile (Methyl cyanide, CH₃CN): MW 41.053, density 0.782 g/mL, mp -44 °C, bp 82 °C.

Acetonitrile is a highly polar solvent, similar to alcohols in its solvating ability.

Unlike alcohols it is not a hydrogen bond donor, but it is a good hydrogen bond acceptor. The nitrogen of acetonitrile is very weakly basic, but it can be quite nucleophilic, somewhat similar to pyridine in this regard. It is miscible with water in all proportions.

Acetonitrile is frequently used as a solvent for S_N2 reactions.

2. Reagents

The distinction between the terms “solvent”, “reactant” or “substrate” and “reagent” is largely one of emphasis. It is quite possible for a particular substance to be a solvent in one process, a reactant in another, and a reagent in yet another. However, for convenience organic chemists will treat “reagents” as those components added to effect change in an organic material (or set of materials) of interest, but whose own fates are unimportant.

2.2. Bronsted Acids

Inorganic acids (mineral acids): HCl, HBr, HNO₃, H₂SO₄, H₃PO₄. These are all very strong acids, essentially completely ionized in water. The hydrogen halides have nucleophilic anions, and can undergo addition reactions with alkenes (Chapter 10). Nitric, sulphuric and phosphoric acids have non-nucleophilic counter-ions, and are used to form cationic intermediates for trapping by other independent nucleophiles (e.g. acid-catalyzed addition of water to alkenes).

HCl and HBr are reasonably soluble in organic solvents as well, and thus can be used under non-aqueous (anhydrous) conditions.

Organic acids: Acetic acid (CH₃CO₂H), like most simple carboxylic acids, is a weak acid. It cannot protonate organic groups such as alkenes, although it will form salts with strong organic bases such as amines. It also can protonate carbonyl groups to a small extent. Its conjugate base, *acetate ion* (CH₃CO₂⁻) is moderately nucleophilic. Acetic acid is often used as a highly polar organic solvent, for reactions requiring mildly acidic conditions.

p-Toluenesulfonic acid (*p*-TsOH, tosic acid, *para*-CH₃C₆H₄SO₃H) is a strong acid, only somewhat less acidic than sulphuric acid. If an organic-soluble strong acid with a non-nucleophilic anion is required, tosic acid is the first choice. It can be used to protonate alkenes, for example, under anhydrous conditions where sulphuric acid is not appropriate.

2.3. Lewis Acids

Recall that Lewis acids are *electron acceptors*. This means that the concept of Lewis acidity is very broad and covers all electrophilic species. However, in organic chemistry, a “Lewis acid” reagent is usually a covalent or weakly ionic metal compound. Generally the metals are in their higher oxidation states, since neutral metal atoms are not Lewis acids.

Promoters for electrophilic aromatic substitutions: Lewis acids activate weak electrophiles for Friedel-Crafts type reactions.

BF₃•OEt₂ (Boron trifluoride etherate) is a complex between the highly electrophilic BF₃ (boron trifluoride) and the weak Lewis base *diethyl ether*. Do not confuse it with *borane* (BH₃), which is used in hydroboration reactions!

AlCl₃ (Aluminum trichloride) is also a very strong electrophile. Recall that both B and Al form trivalent compounds and thus are formally electron-deficient.

FeCl_3 , FeBr_3 (Iron trichloride, Iron tribromide). These are weaker Lewis acids, usually used to activate the appropriate *dihalogen* or *alkyl halide* for electrophilic addition.

Mercury (II) salts: $\text{Hg}(\text{OAc})_2$ is sufficiently electrophilic to activate alkenes towards nucleophilic attack (*oxymercuration*). It forms a bridged cation, a 3-centre, 2-electron structure in which positive charge is spread over two carbons and the mercuric ion. Note that the charge is *not* evenly distributed in such structures, so that addition obeys Markovnikov's rule.

2.4. Electrophiles

As noted above, in the broadest sense the terms *electrophile* and *Lewis acid* are synonymous. However, we will consider here only those organic structures that we have found to be electrophilic components in reactions.

Alkyl halides: Since halogens are more electronegative than carbon, the C-X bond is polarized with partial positive charge on carbon. Thus, alkyl halides are susceptible to *nucleophilic attack*. Primary and secondary halides may react by the concerted $\text{S}_{\text{N}}2$ pathway, while tertiary halides always react by the two-step $\text{S}_{\text{N}}1$ path.

In the presence of Lewis acids, alkyl halides *ionize* by loss of halide ion to form *carbocations*, which are obviously good electrophiles.

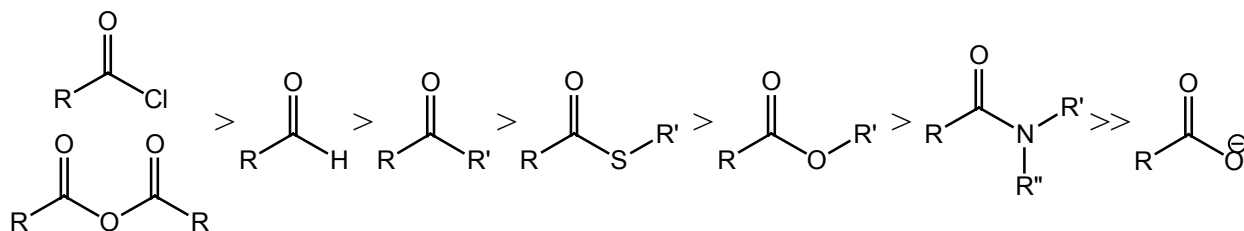
Epoxides: The strained 3-membered cyclic ether structure is quite electrophilic. This is due to two factors. First, the C-O bond is polarized such that the carbon has a partial positive charge. Second, attack by a nucleophile on this carbon leads to breakage of the strained C-O bond and release of strain energy, making the reaction quite thermodynamically favourable. Note that ethers in general are NOT susceptible to nucleophilic attack.

Aryl diazonium ions (ArN_2^+): Aryl diazonium ions are involved in two types of reactions in which they are formally behaving as electrophiles. In *Azo Coupling*, the ion is attacked by any electron-rich aryl nucleophile, via a mechanism similar to the Friedel-Crafts reaction. In the *Sandmeyer Reaction*, Cu(I) salts react with aryl diazonium ions to form products that appear to arise from nucleophilic displacement of N_2 from the ring. However, these reactions *do not proceed by nucleophilic mechanisms*, and probably involve radical intermediates.

Aryl diazonium ions are also reduced by *hypophosphorous acid* to arenes (i.e. the N_2 grouping is replaced by H).

When aryl diazonium ions are treated with *aqueous sulfuric acid* at 100 °C, they are converted to phenols, with loss of N_2 .

Carbonyl groups: All carbonyl groups are electrophilic to some extent, but their



susceptibility towards nucleophilic attack varies over a wide range.

Acid chlorides and anhydrides, the most electrophilic members of the family, can be activated by strong Lewis acids like AlCl_3 or $\text{BF}_3 \cdot \text{OEt}_2$ to form *acylium ions*, which will add to aromatic rings. The reaction of either of these groups with an alcohol forms an *ester*, while reaction with water forms the parent *carboxylic acid*. They form *amides* when treated with either a primary or a secondary amine – tertiary amines do not react in this way. All of these processes are generically labelled *acylation reactions*.

Aldehydes are somewhat more reactive than are ketones. Both readily undergo addition or substitution reactions with hydride donors, *O*- and *N*-nucleophiles, and with *C*-nucleophiles. Their electrophilicity can be enhanced by protonation at oxygen, or by interaction with Lewis acids.

Thioesters are marginally more reactive than esters. Both can be attacked by strong hydride donors like LiAlH_4 . On treatment with aqueous base or aqueous acid, they are *hydrolysed* to form the parent *carboxylic acid*.

Amides are quite resistant to nucleophilic attack. They can be reduced by LiAlH_4 to *amines* but they do not react with weaker nucleophiles. Amides are hydrolysed by strongly alkaline or strongly acidic aqueous solutions, particularly when heated.

Carboxylic acids and their conjugate bases are essentially inert to nucleophilic attack except under the most vigorous conditions. It is possible to reduce a carboxylic acid with LiAlH_4 in boiling THF.

Thionyl chloride (SOCl_2): Thionyl chloride is strongly electrophilic at sulfur. It reacts with OH groups of alcohols to form *alkyl chlorides* via an intermediate *chlorosulfite ester*. The chlorosulfite ester functional group is a very good leaving group, and $\text{S}_{\text{N}}2$ displacement at carbon leads to formation of the alkyl chloride, plus SO_2 (sulfur dioxide) and HCl . Thionyl chloride reacts with carboxylic acids to form *acid chlorides* by a similar mechanism.

***p*-Toluenesulfonyl chloride (TsCl , *tosyl chloride*, *para*- $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$):** Tosyl chloride is the acid chloride of tosic acid (see above). Like all acid chlorides it will react with alcohols to form an ester. The resulting *tosylate esters* are also electrophiles and undergo $\text{S}_{\text{N}}2$ displacement reactions at carbon with a variety of nucleophiles.

Phosphorus tribromide (PBr_3): Although the phosphorus atom in PBr_3 has a lone pair of electrons, it is quite electrophilic. Attack by three equivalents of an

alcohol displaces all three bromines, forming a *phosphite ester* ((RO)₃P). This phosphite ester is also electrophilic at carbon, and is attacked by the bromide ions released at the first stage to form the corresponding *alkyl bromide*.

2.5. Bronsted Bases

Bronsted bases are defined as *proton acceptors*. Therefore, they will be either anions, which form a stable neutral species on protonation, or they will be structures that possess lone pair electrons and which can form relatively stable cationic species. On reflection, you can see that these definitions come close to the Lewis definition of a base, which will be discussed in more detail below.

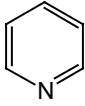
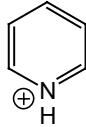

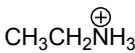
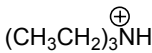
The strength of a Bronsted base is usually measured indirectly by the pKa of its conjugate acid. Thus, a strong Bronsted base will correspond with a weak Bronsted acid, and a *high* pKa value. A weak Bronsted base has a strong conjugate acid, with a very low or even negative pKa.

Hydroxide ion (OH⁻): This is the classic Bronsted Base. In water, its pKa is 14. Most simple hydroxide salts are insoluble in any but the most polar organic solvents. Thus, NaOH or KOH may be used in methanol, ethanol, DMSO or DMF, but are essentially insoluble in ethers, halocarbons or hydrocarbons.

Tetrabutylammonium hydroxide ((C₄H₉)₄N⁺OH⁻): This is an organic-soluble hydroxide reagent. It can be used on its own as a stoichiometric source of hydroxide in organic media, or it may be used as a *phase transfer agent* to shuttle OH⁻ between an alkaline aqueous phase and an immiscible organic layer. This method is used, for example, to make *dichlorocarbene* from *chloroform*.

Amide ions (R₂N⁻): The conjugate bases of amines are strongly basic reagents that can deprotonate many organic species. They are sufficiently strong bases to remove acetylenic protons, for example, in the formation of *acetylide ions*. A typical amide base is *sodium amide* (NaNH₂).

Amines (RNH₂, RR'NH, RR'R''N): All amines are Bronsted bases, and form salts in which the nitrogen has four ligands and thus bears a formal positive charge. The strength of amine bases varies considerably depending on structure, but generally the more highly substituted the nitrogen is, the stronger its basicity. This can be rationalized in terms of the electron-donating character of alkyl substituent groups. A few common amine reagents and the approximate pKa values of their conjugate acids are tabulated at right.

Amine	Conjugate Acid	pKa
		5.21
NH ₃		9.2
CH ₃ CH ₂ NH ₂		10.6
(CH ₃ CH ₂) ₃ N		10.75

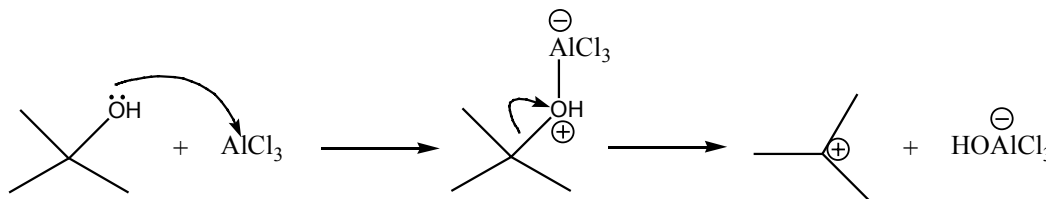
Although low molecular weight amines are water-soluble, amine bases are usually used in organic media to “soak up protons” generated in other reactions. As you can

see from the table, amine bases are not strong enough to deprotonate even an alcohol ($pK_a \approx 17$) to a significant extent.

2.6. Lewis Bases

A Lewis base is defined as an *electron donor*. Thus, in the broadest sense, any nucleophilic substance, as well as all Bronsted bases, are also Lewis bases. The term is primarily useful to reinforce the mechanistic concept of an electron donor or source.

Alcohols: In Friedel-Crafts chemistry, the active electrophilic agent (a *carbocation*) can be generated from an alcohol on treatment with a Lewis acid such as $AlCl_3$. In



this process, the alcohol oxygen is behaving as a Lewis base.

Alkenes: Alkenes can be protonated by strong Bronsted acids to form cationic intermediates. They can also interact with strong Lewis acids in the same way. In this kind of reaction, the alkene would be described as a Lewis base.

Carbonyl groups: The carbonyl lone pairs can interact with Lewis acidic reagents. This enhances the positive character of the carbonyl carbon, making it more susceptible to nucleophilic attack. A similar effect is observed when carbonyl groups are protonated by Bronsted acids as well.

2.7. Nucleophiles

As noted above, all nucleophiles may be regarded as a special case of the Lewis base. Listed here are typical nucleophilic species that are encountered in introductory organic courses. Nucleophilicity and basicity are closely correlated but not identical concepts. Roughly speaking, nucleophilicity is a kinetic concept, while basicity refers to equilibrium thermodynamics.

In general, anions are stronger nucleophiles than are neutral species of similar structure. Thus, notice that water will not hydrolyse esters, but aqueous sodium hydroxide will. However, the “strength” of the nucleophile is not sufficient to determine whether a given reaction will occur. The relative thermodynamic stabilities of starting and product states must also be considered. If the product is much higher in energy than the starting state, the reaction will not occur.

Grignard reagents: When alkyl halides are exposed to magnesium metal in ether solvents, they react to form organometallic reagents conventionally represented as “R-Mg-X”. These so-called *Grignard reagents* are nucleophilic carbanion equivalents. They do not add to weak electrophiles like alkyl halides, but in they react readily with *epoxides* and *carbonyl compounds*. This behavior is similar to that of organolithium reagents (see below).

Organolithium reagents (R-Li): Organolithium reagents are prepared in a similar way to Grignard reagents, by treating an alkyl halide with 2 equivalents of lithium metal in an ether solvent. They are strongly basic, but are poor nucleophiles towards alkyl halides and tosylates. Organolithium reagents will undergo *addition* reactions with epoxides, however, by an S_N2 mechanism. They are similar to Grignard reagents in their general reactivity.

Acetylide ions (RC≡C⁻): The conjugate bases of terminal alkynes are formed by deprotonating the alkyne with a strong base such as *sodium amide* (NaNH₂). They are highly nucleophilic carbanions that can attack alkyl halides, tosylate esters, epoxides and other electrophilic species that can undergo S_N2 displacements.

Lithium dialkyl cuprates (R₂CuLi): These carbanion compounds will react with alkyl halides to form C–C bonds. The reaction is formally a nucleophilic displacement, although it does not actually proceed by that mechanism. This is evident from the fact that even *aryl halides* will be alkylated by lithium dialkyl cuprates.

Lithium dialkyl cuprates are formed from the reaction of 2 equivalents of an *alkyl lithium compound* with CuI. Note that the parent alkyl lithium compounds are strong bases but poor nucleophiles towards alkyl halides.

Cyanide ion: Cyanide (CN⁻) is a strongly nucleophilic anion. It is highly potent in S_N2 reactions.

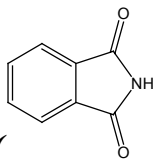
The mixture of KCN and Cu₂(CN)₂ will react with aryl diazonium ions in a *Sandmeyer reaction* to form aryl cyanides. This is not a nucleophilic process, but instead appears to proceed via radical pathways.

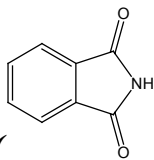
Azide ion: Azide ion (N₃⁻) is similar to cyanide in nucleophilic reactivity.

Hydroxide, alkoxide and thiolate ions: The conjugate bases of water, common alcohols and thiols are good nucleophiles in S_N2 reactions as well as in addition to carbonyl compounds. Alkoxide ions may be formed by the reaction of alcohols with *sodium metal*, or by reaction with *sodium hydride* or *potassium hydride*. Thiolates are usually formed by treating thiols with these hydride bases as well.

Halide ions: The nucleophilicity of the halides increases with decreasing electronegativity. Thus, iodide is more nucleophilic than chloride. Fluoride is a very poor nucleophile in most cases.

Cu(I) chloride and bromide will undergo *Sandmeyer reactions* with aryl diazonium ions, to form aryl chlorides and bromides. Aryl iodides may be formed from a similar reaction using *potassium iodide* (KI).



Phthalimide (): The nitrogen of phthalimide is only weakly nucleophilic since its lone pair is delocalized with two adjacent carbonyl groupings.

However, the N–H bond is quite acidic for a similar reason, and the conjugate base of phthalimide is a good nucleophile towards alkyl halides. The reaction of phthalimide with an alkyl halide in the presence of *potassium hydroxide* (KOH) is referred to as the *Gabriel synthesis*. Primary amines can be obtained from the alkyl phthalimide derivatives prepared in this way on treatment with *hydrazine* (N_2H_4).

Phosphines (R_3P): Phosphines such as *triphenyl phosphine* have nucleophilic lone pair electrons. They will attack primary and secondary alkyl halides and similar electrophilic species that can undergo S_N2 displacement, to form *phosphonium salts*.

Hydrazine (N_2H_4): Hydrazine is a very good neutral nitrogen nucleophile, because the presence of two lone pairs on adjacent atoms leads to repulsion that enhances their reactivity. It is commonly used as a component in the *Wolff-Kishner reduction of ketones*, and to cleave phthalimide derivatives in the *Gabriel Synthesis of amines*.

Amines: Primary and secondary amines are good nucleophiles, that can react with alkyl halides to form more highly substituted amines. In the reaction of alkyl halides with *ammonia*, it is difficult to form primary amines because the alkyl halide can react with the primary amine to form a secondary, and ultimately a tertiary amine. For this reason, the *Gabriel Synthesis* is preferred when primary amines are desired products.

Ammonia, primary and secondary amines also react with carboxylic acid derivatives such as acid chlorides, anhydrides, and esters to form amides.

The conjugate bases of amines are called *amide ions* and are not generally used as nucleophiles. They are extremely basic (the pKa of a typical amine is around 35) and will behave as Bronsted bases instead. A typical example is *sodium amide*.

Water and alcohols: Water and alcohols are weak nucleophiles under neutral conditions. They will react rapidly with highly electrophilic carbonyl compounds such as acid chlorides and anhydrides, forming carboxylic acids or esters.

Under moderately acidic conditions water and alcohols will attack carbonyl compounds to form hydrates, acetals, hemiacetals, ketals or hemiketals (from aldehydes or ketones respectively). Likewise, water will hydrolyse esters and amides, while alcohols will *transesterify* these species. Under strongly acidic conditions they may be protonated themselves to become essentially non-nucleophilic.

2.8. Oxidizing Agents

Oxidation refers to the removal of electrons from a substance. However, in organic chemistry the actual formation of ionic species by direct removal of electrons is rare. A compound is said to be oxidized at a particular carbon centre if that centre either *gains electronegative substituents* or *loses hydrogen substituents*. These operations will increase the formal oxidation number of the carbon atom.

Potassium permanganate ($KMnO_4$): A very strong oxidizing agent. Under cold alkaline conditions it will *add hydroxyl groups to alkenes*, forming diols. This reaction is difficult to control, however. Under acidic conditions it will *oxidatively*

cleave alkenes, forming carbonyl compounds. It also rapidly oxidizes aldehydes to carboxylic acids.

Permanganate will oxidize benzylic positions with cleavage of the benzylic C–C bond to form benzoic acid derivatives.

Osmium tetroxide (OsO_4): Osmium tetroxide is also a very potent oxidizing agent, but it is better behaved than is potassium permanganate. It is the preferred reagent for the oxidative addition of hydroxyl groups to alkenes, to form *vicinal diols*.

Elemental halogens: All of the dihalogens are oxidizing agents. F_2 is too powerful to be of any use in organic chemistry. Cl_2 and Br_2 will add to alkenes by an electrophilic mechanism, forming vicinal dihalides. I_2 will not add in this way because the addition is thermodynamically unfavourable.

Cl_2 and Br_2 can be induced to add electrophilically to aromatic systems as well, when activated by strong Lewis acids. This reaction is also a formal oxidation, although the textbook does not discuss it in this context.

Br_2 will fragment into *bromine atoms* on exposure to strong light. Bromine atoms are *radicals*, and will react with benzylic CH_2 groups by a chain reaction mechanism to form benzylic bromide derivatives.

Hydrogen peroxide (HO_2H): Basic solutions of hydrogen peroxide are used in the oxidative workup of the *hydroboration/oxidation* process, to convert a C–B bond to a C–OH grouping.

Peroxyacid reagents (RCO_3H): Peroxyacids such as *m-chloroperoxybenzoic acid (m-CPBA)* will form epoxides from alkenes by the oxidative addition of an atom of oxygen. The addition is concerted and stereospecific – thus the relative stereochemistry of the substituents in the alkene is preserved in the epoxide product.

Ozone (O_3): Ozone is a very powerful oxidant that will cleave alkenes and alkynes to the corresponding carbonyl compounds after a reductive workup with $Zn/AcOH$. It reacts by a cycloaddition mechanism.

Nitrous acid (HNO_2): Nitrous acid is formed *in situ* when *sodium nitrite* is mixed with aqueous HCl. Under these acidic conditions, nitrous acid in turn loses water to form the very reactive *nitrosonium ion* (NO^+), which can oxidize aryl amines to *aryldiazonium ions*.

Chromate reagents (Cr^{6+} compounds): Chromium trioxide (CrO_3) in acidic aqueous solutions forms complex mixtures that contain *chromic acid*. The specific combination of CrO_3 with H_2SO_4 is called the *Jones Reagent*. These reagent mixtures will oxidize primary and secondary alcohols to carbonyl compounds. Secondary alcohols are converted to ketones, while primary alcohols form carboxylic acids via an intermediate aldehyde that is rapidly oxidized.

If the chromate reagent is made basic by the addition of *pyridine*, a new reagent called *pyridinium dichromate (PDC)* is formed. This reagent will oxidize primary alcohols to aldehydes but cannot proceed further.

2.9. Reducing Agents

Reduction is formally the addition of electrons, but in organic chemistry it is usually regarded as an increase in the number of hydrogen substituents, or a decrease in the number of electronegative substituents.

Hydrogen (H_2): Hydrogen in the presence of a *platinum or palladium catalyst* will add to alkenes or alkynes to form alkanes. The addition is always *syn* – that is, both hydrogen atoms are added to the same face of the alkene.

Under more forcing conditions (i.e. higher pressure of H_2 , higher temperature or presence of an acid) aryl ketones may be hydrogenated all the way down to CH_2 groups. Since a benzylic alcohol is an intermediate in the process, by implication any benzylic C–O bond can be reduced under these conditions.

Adding a catalyst poison such as pyridine or quinoline deactivates the transition metal catalyst. Hydrogenation of alkenes becomes very slow, and as a result alkynes can be reduced to form *cis alkenes* by this poisoned catalyst system.

Alkali metals: Reduction by *dissolving metal systems* is one of the few reductions that actually proceed by direct addition of an electron to an organic acceptor.

Although we have not discussed mechanisms for most of these reactions, they all proceed via *radical anions* that are protonated, accept a second electron to form anions, and are again protonated.

Sodium metal in ether or liquid ammonia will reduce alkynes to *trans alkenes*, via a vicinal dianion intermediate. The observed *trans* selectivity can be understood in terms of repulsion between the two anionic orbitals.

Reducing metal/acid reagents: Zinc, tin and iron are referred to as *reducing metals* because they readily lose electrons to form metal ions, under acidic conditions. They are less reactive than the alkali metals in this regard, however, and will not react without the presence of acids.

In *Clemmensen reduction*, an aryl ketone is reduced by a Zn(Hg) couple in aqueous HCl, losing oxygen to form a CH_2 group. This reaction will *not* reduce a saturated ketone.

Nitro groups can be reduced to amines by Zn/HCl, Sn/HCl or Fe/HCl, conditions very similar to those of the Clemmensen reduction. Nitro groups are also reduced to amines by $LiAlH_4$ (see below).

The Wolff-Kishner reduction: Treatment of a ketone with *hydrazine* (N_2H_4) and KOH in hot DMSO will reduce just about any ketone to a CH_2 group.

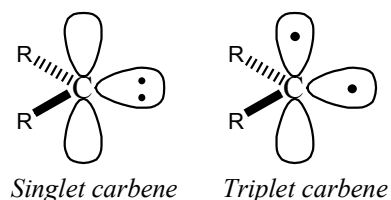
Hydride donor reagents: Sodium borohydride, $NaBH_4$, and lithium aluminum hydride ($LiAlH_4$) will reduce carbonyl compounds to hydroxyl compounds by addition of hydride via a nucleophilic mechanism. $LiAlH_4$ will reduce all carbonyl species in this way, but the less-reactive $NaBH_4$ is generally used only with aldehydes and ketones.

LiAlH_4 is a very powerful reducing agent, and among other things it will also reduce nitro groups to amines.

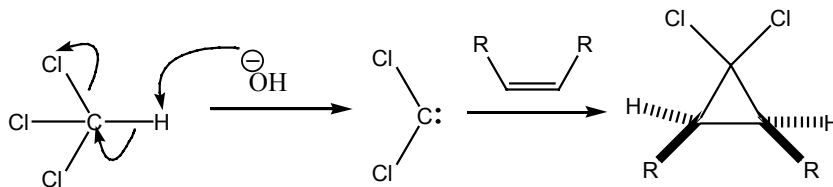
2.10. Miscellaneous

Carbenes and carbenoids: Carbenes are divalent neutral carbon compounds (R_2C). Structures of this type have 2 *nonbonding electrons* that can either be paired in a single orbital (*singlet carbenes*) or separated (*triplet carbenes*). Carbenes are highly reactive species that must be generated and reacted *in situ*.

Singlet carbenes behave as hybrid nucleophile/electrophile combinations. This is because they have a filled sp^2 orbital and a vacant p-orbital, which behave as donor and acceptor respectively. Singlet carbenes add to alkenes by a *concerted cycloaddition mechanism*, forming *cyclopropanes*. Because the addition is concerted, the substituents in the product cyclopropane retain the relative configuration they had in the starting alkene.



Dichlorocarbene ($\text{Cl}_2\text{C}:$) is a readily formed example of a singlet carbene that can form dichlorocyclopropane rings from alkenes. In a typical preparation, *chloroform* is exposed to *aqueous NaOH* in the presence of a *phase transfer agent* such as *tetrabutylammonium hydroxide*. The base abstracts the proton from chloroform, leading to a rapid *alpha elimination reaction* to form dichlorocarbene. If an alkene is also present, the carbene will add to form a cyclopropane.

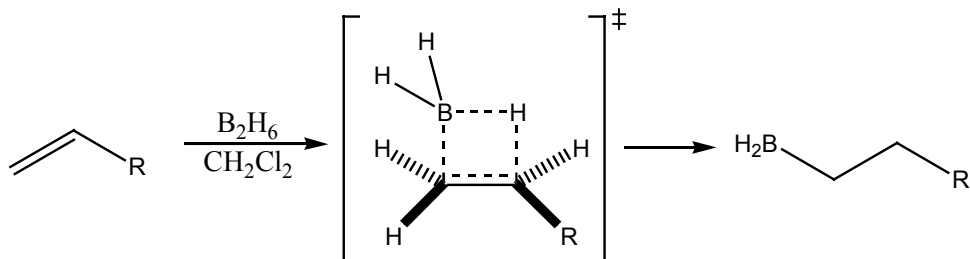


Triplet carbenes are more difficult to generate, and have not been discussed in detail in this course. Unlike singlet carbenes, their addition reactions with alkenes are not concerted and proceed via a biradical intermediate. Because this intermediate has a significant lifetime, bond rotation can occur before the cyclopropane ring is formed. Thus, the products of these reactions are mixtures of stereoisomers.

Carbenoids are organometallic species that behave as if they were singlet carbenes. The *Simmons-Smith Reaction* employs a zinc amalgam (Zn/Cu) in combination with CH_2I_2 to form the carbenoid $\text{I-CH}_2\text{-Zn-I}$. This will add to alkenes to give a cyclopropyl ring with no substituents on one carbon. If additional substituents are needed, a modification of the Simmons-Smith procedure permits conversion of RCHI_2 or ArCHI_2 to the corresponding carbenoids using *diethylzinc* (Et_2Zn).

Borane (BH_3) and diborane (B_2H_6): Borane is a highly electrophilic molecule, due to the formally electron-deficient character of trivalent boron. Because of this, it tends to be used as its dimer, *diborane*, or as a complex with Lewis bases such as THF. Borane interacts strongly with alkenes, and undergoes addition of B-H across the double bond via a concerted cycloaddition mechanism. As a consequence, the

added boron and hydrogen are always *syn* – that is, they are added to the same face of the starting alkene. The resulting *organoborane* (RBH₂) can add to additional alkene



groups until all the B-H bonds have been utilized. At this point, the reaction halts. Notice that the boron is attached to the *less-substituted end* of the alkene, in order to minimize steric repulsion between the B-H bonds and the alkene substituents.

Addition of *aqueous alkaline hydrogen peroxide* (i.e. NaOH (aq.) + H₂O₂) to the organoborane oxidizes the C-B bond to a C-OH group, with complete retention of the stereochemistry at carbon. The mechanism of this process is complex and will be left to a later course. The

hydroboration/oxidation sequence is one of the few ways of converting an alkene to the *anti-Markovnikov alcohol* product.

