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COMMON ACIDS AND BASES FOR ORGANIC SYNTHESIS

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ABSTRACT

A proper selection of acid and base plays pivotal role in organic synthesis. The rate of reaction, desired product, yield, handling easiness, stability, solubility, and many more factors depends on acids and bases what we are using. Both the acid and base can be categorized in two classes; organic (eg. Acid- Acetic acid, Formic acid, Ascorbic acid etc., Base- DMAP, DBU, Triethylamine, *n*-Butyllithium etc.) and inorganic (Acid- Boric acid, Sulfuric acid, Hydrochloric acid, Phosphoric acid etc., Base- Sodium hydroxide, Ammonium hydroxide, Calcium carbonate, Sodium amide etc.). Furthermore, the Lewis acid (eg. Aluminium bromide, Boron trifluoride, Tin (IV) chloride etc.), and Phosphazene base (eg. P_1-t-Bu, P_2-t-Bu, P_4-t-Bu, P_1-t-Oct, P_2-F, BTPP, BEMP etc.) are also more popular classes. Based on the molecular structure we may need weak, mild, strong or strongest acid and base. This concise review provides updated information about acids and bases commonly used in organic synthesis.

KEYWORDS: *Acid, base, organic synthesis, Phosphazene, Lewis acid, reaction.*

1. INTRODUCTION

The role of acid and base is immense in organic synthesis.[1] We can use organic as well as inorganic acid and base in organic synthesis according to the nature of chemical reaction we are doing, desired product, stability, stereochemistry etc. The hard and soft acids and bases are of great choice for proper reactions.[2] The acids can be broadly categorized into Inorganic, Organic and Lewis acid. Similarly, the bases can be categorized as Organic, Inorganic and Phosphazene Base.[3] Regarding the great importance of these acids and bases in organic synthesis, we cannot even imagine the synthesis if we do not have knowledge about it. The major examples of each category are presented here from commercially available sites.[4-6] This review will illustrate the updated information about the common acids and bases used in organic synthesis with detail structure of each, proper handling, and recent advancement in acid base chemistry.

1.1 Acids

Acids are any molecules or ions that are capable of donating proton (H+) (Bronsted acids)[7] or capable of making a covalent bond with an available electron pair (a Lewis acid).[8] The aqueous solution of an acid has pH value less than 7. The lower pH means more acidic, which will have higher amount of hydrogen ion concentration in a solution. Commonly, any substance having property of acid are called as acidic. Acids dissolved quickly in aqueous solution giving sour taste and can turn blue litmus to red. It reacts with base to form salt and water violently according to its strength, so usually acid base reaction are carried out in a lowered temperature with proper safety because acids are corrosive in nature. The common aqueous acid in our body is hydrochloric acid which has great role in digestion and activation of digestive enzymes.[9] Some other common aqueous acids are acetic acid, sulfuric acid, and citric acid. It can be further divided into three categories; Organic, Inorganic and Lewis acid as below.

1.1.1 Inorganic acids

The most popular acids in the synthetic chemistry are inorganic acids. Most of these are highly corrosive.[10] Below shows the common category of inorganic acids.[4] The **Chart 2** shows detail examples of Inorganic acids.

- ✔ Boric Acid (pKa ~ 9.23)
- ✔ Hydrogen Halides (pKa ~ 3.17, -8.0, -9.0 for HF, HCl, HBr)
- ✔ Nitric Acid (pKa ~ -1.3)
- ✔ Phosphoric Acid (pKa ~ 2.12, 7.21, 12.32)
- ✔ Sulfuric Acid (pKa ~ -3.0, 1.99)

1.1.2 Organic acids

The organic acids has diverse role in all synthetic chemistry. It could be either used as a solvent, a catalyst, a strong acid, or as a substrate. The production of many kinds of deuterated organic acids are increasing for kinetic reactions as well as deuterium exchange reactions.[11] The **Chart 1** shows the detail examples of common organic acids.

1.1.3 Lewis acids

The Lewis acids are commonly known as electron pair acceptor, they have good ability to coordinate[12] with the carbonyl groups, nitrogen and oxygen containing other functional groups. Many of them, sometimes used in catalytic amounts for various chemical transformations. The common category of Lewis acids are Aluminum, Boron, Iron, Montmorillonite, Tin and Titanium. The **Chart 3** shows the detail examples of Lewis acids.

1.2 Bases

The base are capable of releasing hydroxide ion in aqueous solution (OH-), bitter in taste (if an alkali), turns red litmus paper to blue, on reaction with acids forms salt, can be used as a base catalyst in a reaction. The water soluble base is called as alkali (release OH- ions). The neutralization is a common term used in acid base reaction. When acid and base react, it will give salt that will separate into its each component’s corresponding ions.

1.2.1 Organic Bases

The organic bases are organic compounds which work as a base, having multifunctional roles in organic synthesis. With opposed to inorganic base, these are readily soluble in the organic solvents which makes them suitable to form a homogeneous reaction mixture. The common organic bases used in synthesis are pyridine, alkanamine (such as methylamine, ethylamine, isopropyl amine etc.), imidazole, benzimidazole, histidine, guanidine, phosphazene bases, and hydroxides of quaternary ammonium cations. Below is some major category of organic bases. The **Chart 4-a and 4-b s**hows detail examples of organic bases.

- ✔ Organolithiums
- ✔ Grignard Reagents
- ✔ Amines
- ✔ N-Heterocyclic Compounds
- ✔ Tetraalkylammonium and phosphonium hydroxides
- ✔ Metal Alkoxides and Amides
- ✔ Metal Silanoates

1.2.2 Inorganic Bases

These are opposed to the organic bases which do not contain carbon on their skeleton. In all organic as well as inorganic synthesis, these bases are common. The **Chart 5** shows detail examples of inorganic bases.

1.2.3 Phosphazene Bases

Phosphazene bases are a family of extremely strong, a non-ionic and a non-charged nitrogen-base having diverse advantages. In phosphazene class bases, the phosphorus atom is linked to a nitrogen atom covalently with double bond and to other three atoms with a single bond. In a synthetic chemistry, the activation of acidic C-H bond by using strong base becomes key step in organic synthesis. The selection of proper base is extremely important in base catalyzed common organic reactions like alkylation, elimination, silylation, Michael addition, and aldol condensation. With comparison to the conventional base catalyzed reaction, the phosphazene base produce naked enolates (highly reactive) are far more stable towards undesired reactions. The highly reactive anions produced by phosphazene bases have low nucleophilicity and inertness towards electrophilic part which enables the reaction of a very weak C-H acidic region through deprotonation in good to excellent yields. Moreover, its enhanced solubility in nonpolar to moderately polar organic solvents benefits solubility function and it solubilizes hydrophilic substrate that allows base catalyzed reaction in organic media. The **Chart 6** shows detail examples of Phosphazene bases.

2. Proper handling of Acids and Bases

Acids and bases can easily damage our body surface wherever it gets into contact. The intensity of affection and overall severity depends on how strong it is, duration of exposure, and the nature of action taken after contact happened. The acids or bases could be liquid, solid, granular, powdered, vapor or in gaseous form. We use acids and bases not only for reaction purpose but also cleansing so the exposure is higher. To handle it properly, following points are needed to be considered:

- Always wear full protecting clothes, lab coat, gloves, mask etc., and work in well-ventilated area with proper risk handling devices.
- If possible work with small quantities and always try to work on fume hood.
- Always check MSDS for the chemical what you are going to use and be aware about how to handle with risk.
- Washing hands properly after use, other general safety measures and search information as much as possible etc.
- Select proper category gloves like, **latex or natural rubber** for most general purposes and working with mild acid and bases, **butyl** gloves for protection from strong acid and bases, **nitriles** gloves for most acid and base, and the **neoprene** gloves to protect from organic acids that are more tear resistant than the general latex gloves.

- First aid: in case of contact to body, skin or eye, rinse with cool water for 15 minutes, if more exposed remove contaminated clothes.

3. Neutralization of acid base reaction

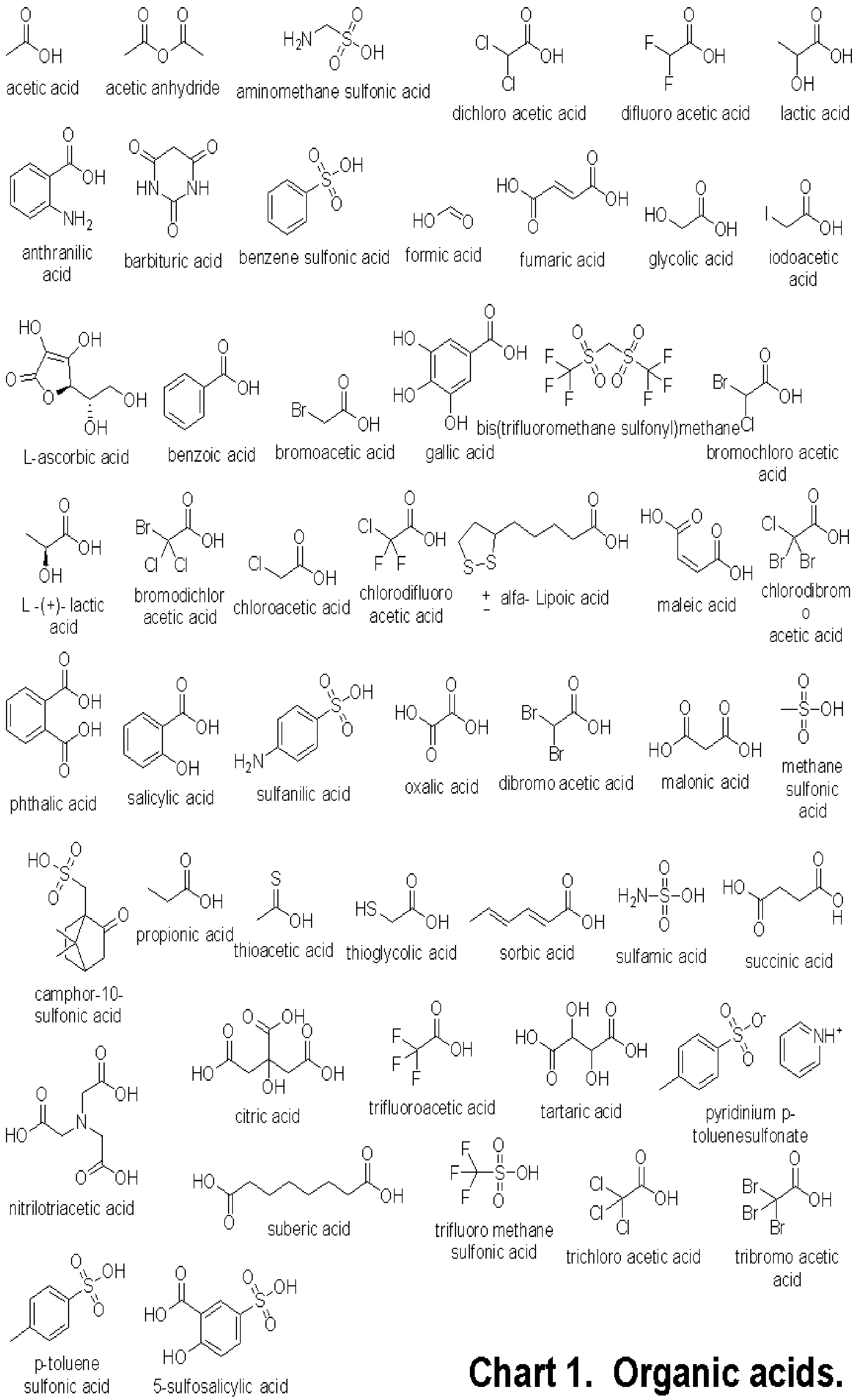
The neutralization of acid base reaction should be done at low temperature and slowly. Due to the exothermic nature of acid base reaction, it could be sometime more explosive based on how strong is the acid or base.[13]

4. Deuterated Acids and Bases

As presented the examples of acids and bases in **chart 1 to 6**, some of them are commercially available as a deuterated form. These kinds of deuterated acids and bases are used in various organic synthesis like deuterium exchange reactions[11], NMR solvents[14], and other enzymatic reactions.

5. Recent advancements in acid-base chemistry

With time there are many theory approached about acid-base chemistry. Sometime it is straightforward and sometime relative to one another. The concept about hard and soft acid-base is also more diversified.[15,16] Moreover, the role of Lewis acid and bases are elaborating in many reaction conditions for the desired facile transformation.[17-20] In organic synthesis the relative strength of an acid-base, its selectivity and orientation diversely affect our desired one. So many of the todays reactions are optimized with various kinds of acids and bases to increase yield, product structure, to shorten reaction time, easiness in workup and purification, to decrease side reactions and many more.[21]



acetic acid
acetic anhydride
aminomethane sulfonic acid
dichloro acetic acid
difluoro acetic acid
lactic acid
anthranilic acid
barbituric acid
benzene sulfonic acid
formic acid
fumaric acid
glycolic acid
iodoacetic acid
L-ascorbic acid
benzoic acid
bromoacetic acid
gallic acid
bis(trifluoromethane sulfonyl)methane
bromochloro acetic acid
L -(+)- lactic acid
bromodichlor acetic acid
chloroacetic acid
chlorodifluoro acetic acid
± alfa- Lipoic acid
maleic acid
chlorodibromo acetic acid
phthalic acid
salicylic acid
sulfanilic acid
oxalic acid
dibromo acetic acid
malonic acid
methane sulfonic acid
camphor-10-sulfonic acid
propionic acid
thioacetic acid
thioglycolic acid
sorbic acid
sulfamic acid
succinic acid
citric acid
trifluoroacetic acid
tartaric acid
pyridinium p-toluenesulfonate
nitrilotriacetic acid
suberic acid
trifluoro methane sulfonic acid
trichloro acetic acid
tribromo acetic acid
p-toluene sulfonic acid
5-sulfosalicylic acid

Chart 1. Organic acids.

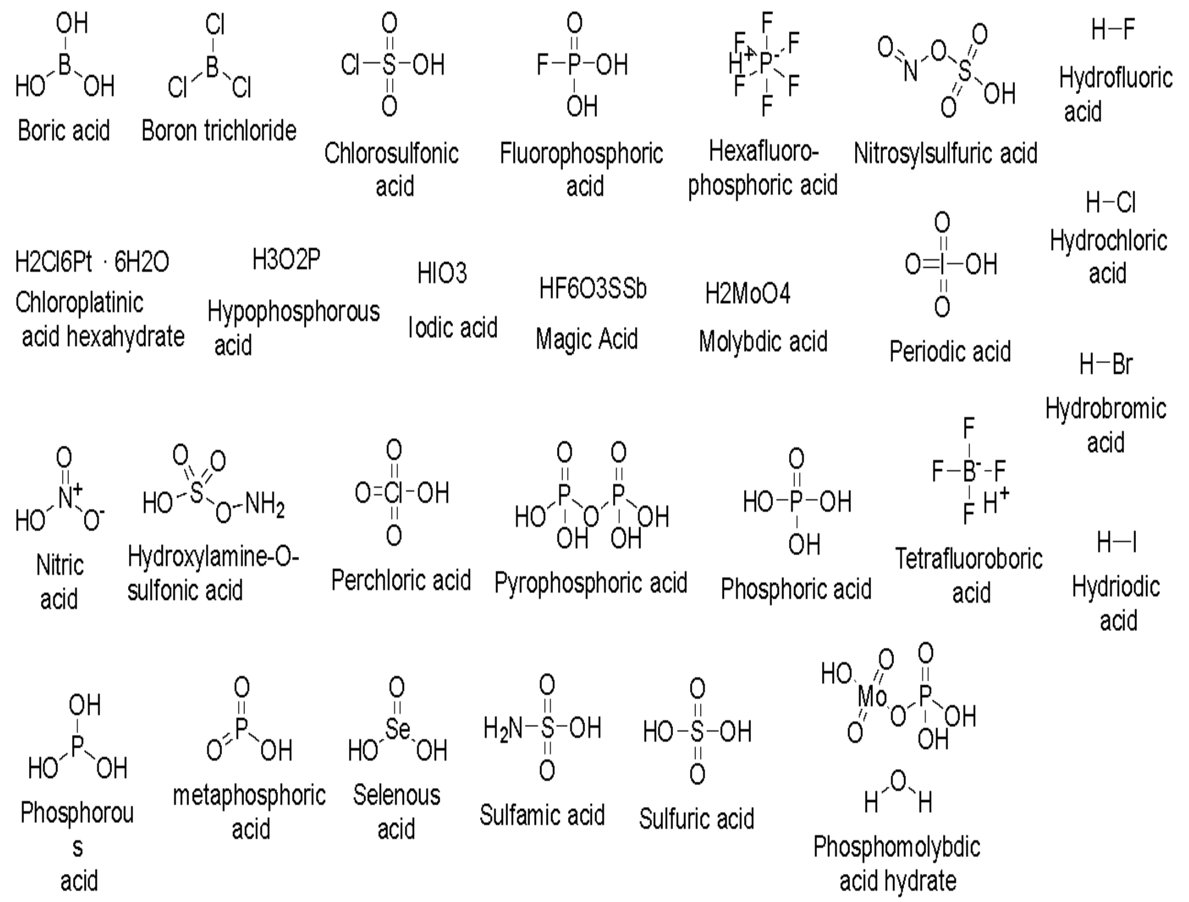


Chart 2. Inorganic acids.

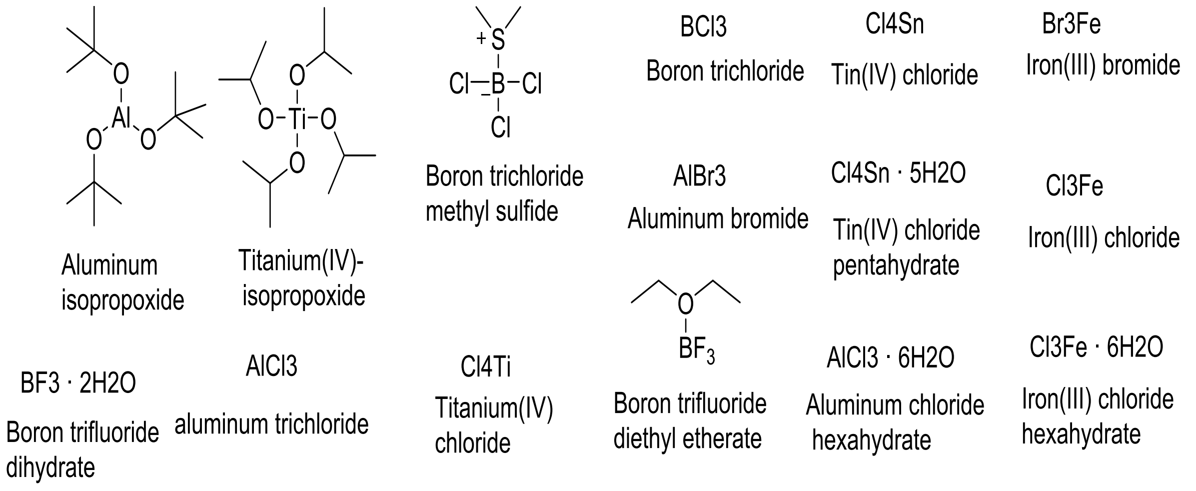


Chart 3. Lewis acids.

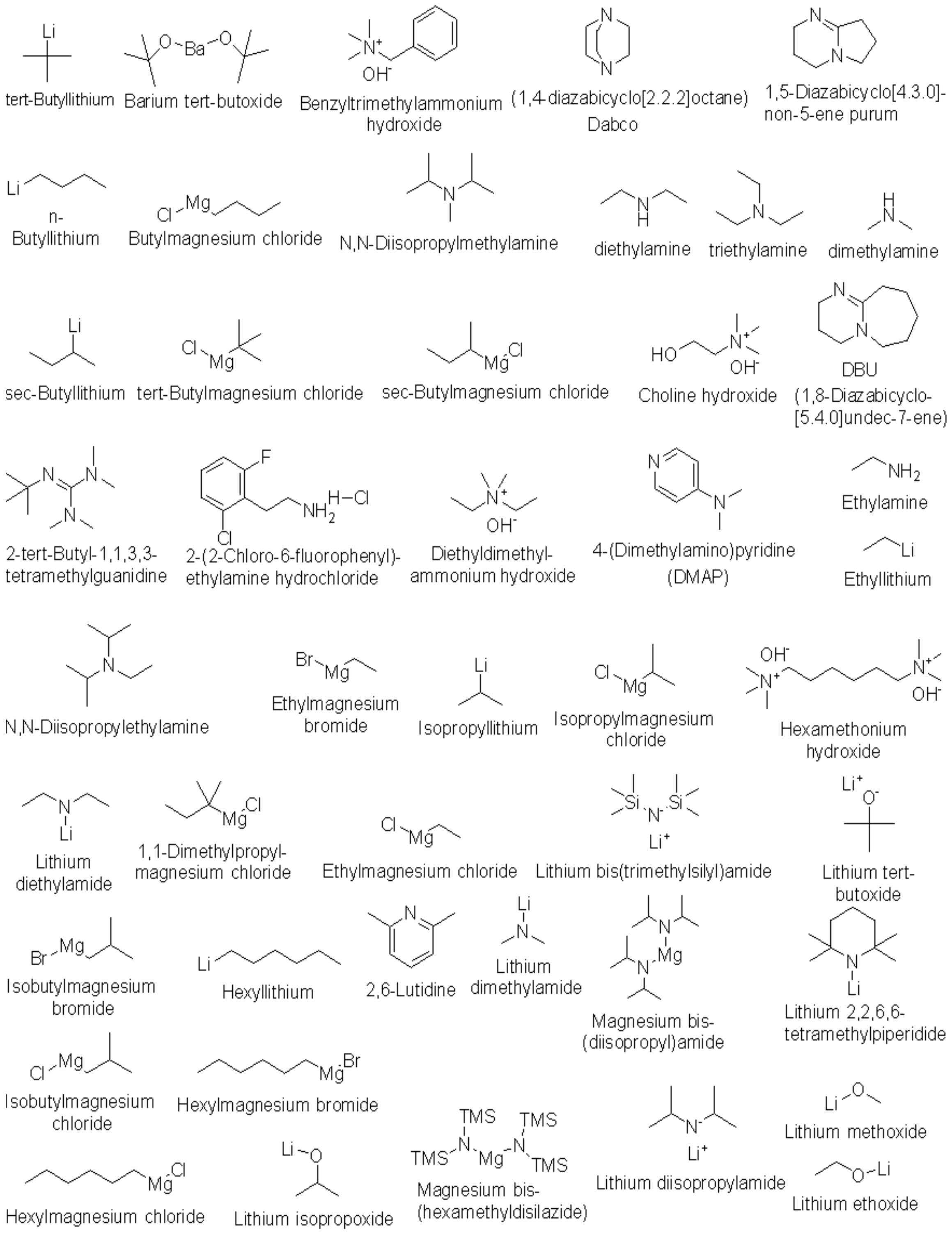


Chart 4-a. Organic bases.

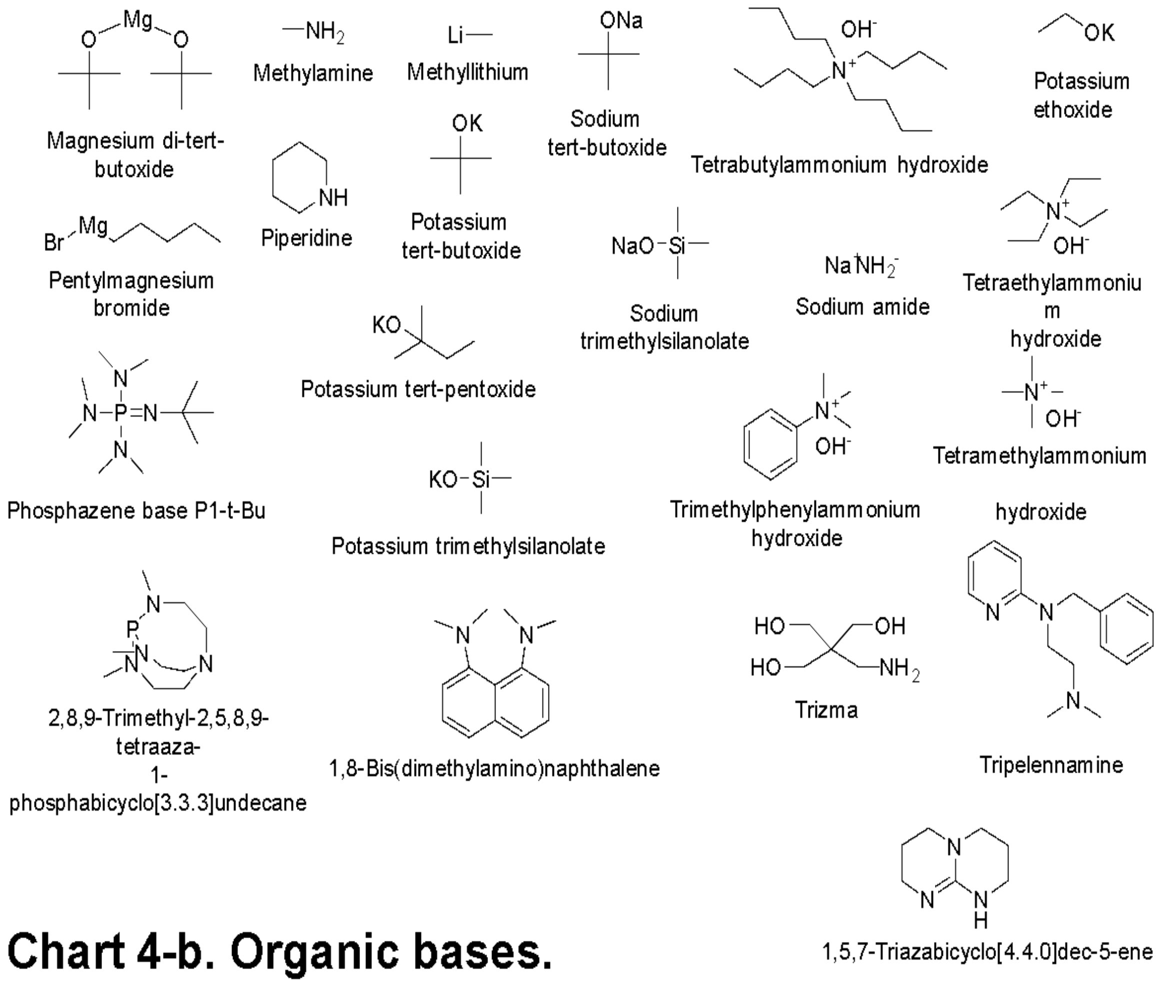


Chart 4-b. Organic bases.

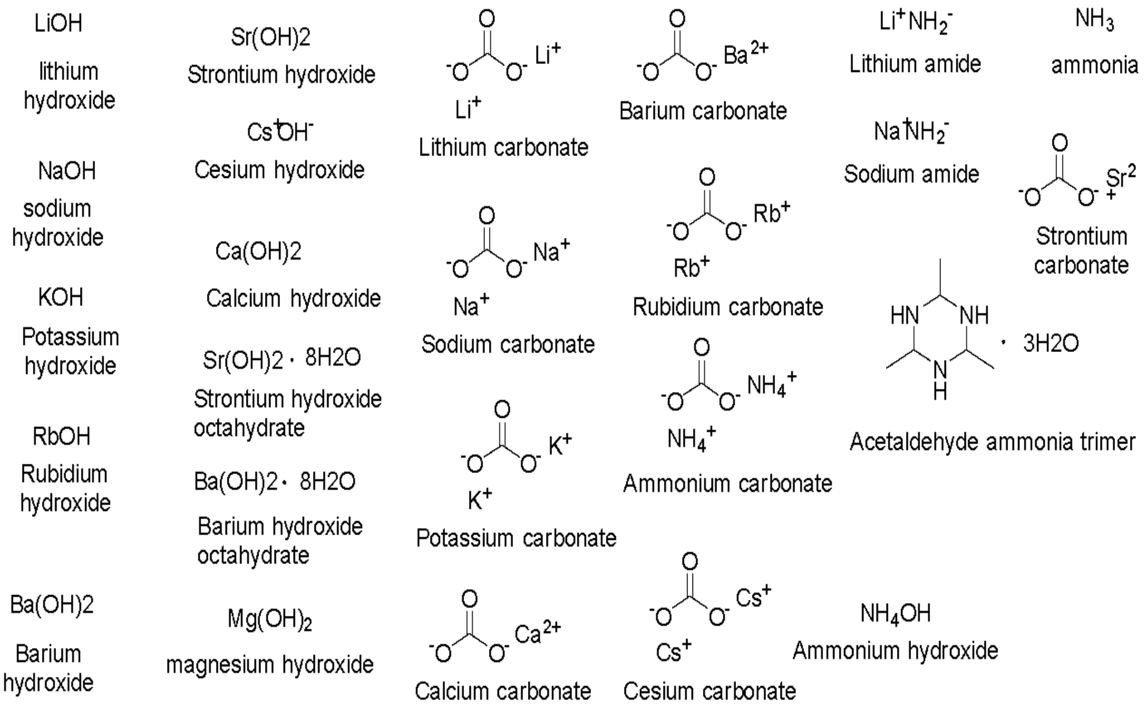
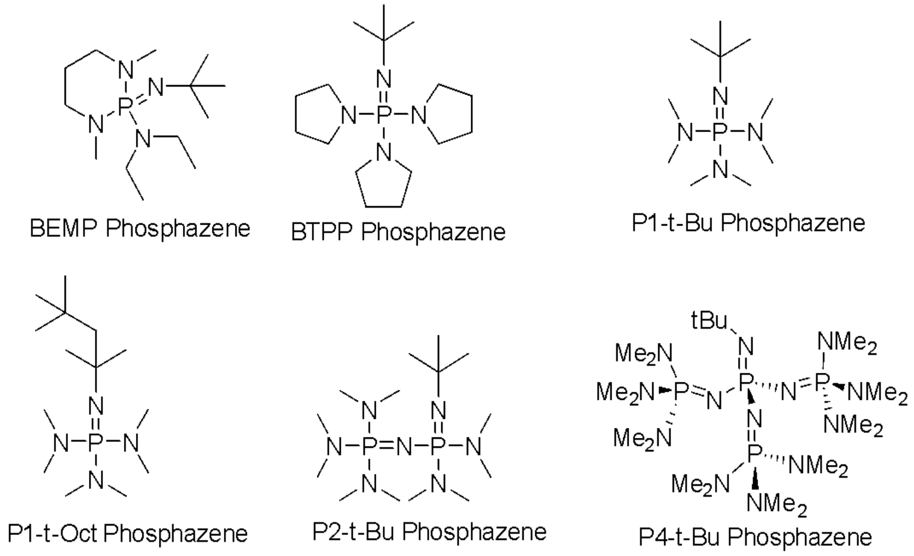


Chart 5. Inorganic bases.



BEMP Phosphazene BTPP Phosphazene P1-t-Bu Phosphazene P2-F Phosphazene

P1-t-Oct Phosphazene P2-t-Bu Phosphazene P4-t-Bu Phosphazene

Chart 6. Phosphazene bases.

6. CONCLUSION

From the beginning of child age of synthetic chemistry to today's great revolutionary discovery in the field of synthetic chemistry; acids and bases have always remained core corner to begin, proceed and end many process in synthesis. We hope this compiled information about the common acids and bases will provide detail, broad mindset in short period of time in a smart way.

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