Lewis Acids and Bases

Hard and Soft Acid/Base Theory

Definitions of Lewis Acid-Base Theory. Lewis acid/base theory (sometimes called donor-acceptor theory) is a broad, widely applicable approach to the classification of chemical substances and the analysis of chemical reactions. According to this theory, a base is defined as an electron pair donor, and an acid as an electron pair acceptor. Donation of an electron pair from base to acid results in the joining of the acid and base via a covalent bond. The bonded acid-base species is called an adduct (short for addition product), a coordination compound, or a complex. Lewis theory puts the emphasis on the donation and acceptance of electrons; this is appropriate, because it is the give and take of electrons (+ seeks – and avoids +) that drives all of chemistry. As we will see, there is often a change in stereochemistry at the acceptor atom when the adduct forms.

Recognition of Acids and Bases. Lewis Acids. Generally speaking, Lewis acids are not as easily recognized as are the bases, but there are certain "hallmarks" of Lewis acids to be alert for. In general, a species that contains a fully or partially positive atom with an empty or underused valence orbital is very likely to function as a Lewis acid--an electron pair acceptor. According to this idea, species such as H⁺, (CH₃)₃C⁺ (a carbocation), and Fe³⁺ are expected to function as Lewis acids, accepting one or more electron pairs into empty valence orbitals. The positive charge of the acid serves to attract the lone electron pair of the base into the vicinity of the acid so that orbital overlap and bonding may take place. The first two of these acids have a single open valence orbital (1s in the case of H⁺, 2pₓ in the case of (CH₃)₃C⁺), so are capable of interacting with only one Lewis base. Fe³⁺, on the other hand, readily accepts up to 6 lone pairs into empty 4s, 4p, and 4d valence orbitals. For example, dissolution of a salt of Fe³⁺ in water results in the following process:

$$\text{Fe}^{3+} (\text{acid}) + 6\text{H}_2\text{O} (\text{base}) \rightarrow \text{Fe(H}_2\text{O)}_6^{3+} (\text{adduct})$$

The adduct, Fe(H₂O)₆³⁺, involves bonding of 6 Lewis base species to one Lewis acid center. Lewis bases bonded to a transition metal center are often called ligands. We will take this word as a synonym for Lewis base.

Less obvious examples of Lewis acids are CO₂, SnCl₂, and SO₃. None of these species is positively charged. However, in all cases the central atom is attached to electronegative terminal atoms and therefore carries a partial positive charge. In addition, in each case the central atom is involved in at least one pi bond with the terminal atoms. Because pi bonds are substantially weaker than sigma bonds, we regard the carbon p orbitals used in these bonds to be underused. All of these species are subject to attack by a Lewis base at the pi-bonding p orbital of the central atom. This results in disruption of the pi bond and its replacement by a stronger sigma bond between the attacking base and the central atom of the acid, as shown below:

$$\text{CO}_2 + \text{OH}^- \rightarrow \text{HCO}_3^-$$
$$\text{SnCl}_2 + \text{Cl}^- \rightarrow \text{SnCl}_3^-$$
$$\text{SO}_3 + \text{O}^2- \rightarrow \text{SO}_4^{2-}$$

Generally speaking, species in which the central atom is involved in multiple bonds to (electronegative) terminal
atoms are potential Lewis acids.

Finally, species such as BF$_3$, AlCl$_3$, and PF$_5$ are Lewis acids because in all cases the central atom bears a partial positive charge, and there is at least one unused valence orbital on the central atom. In the first 2 species, the unused orbital is the valence pz orbital of B or Al. In PF$_5$, there are 4 unused valence 3d orbitals that may be used to accept electron pairs.

**Lewis Bases.** Lewis bases (ligands) are quite easy to recognize; they are species that contain atoms with lone pairs. Such atoms are called donor atoms. Thus H$_2$O (donor atom, O), NH$_3$ (donor atom, N), Cl-, and CH$_3$CH$_2$OH (donor atoms, O) are immediately recognized as Lewis bases. Because the number of Lewis bases is almost unlimited, it is useful to categorize them based on the number of donatable nonbonding electron pairs that they contain.

1) Monodentate (1-toothed) bases (ligands). These are ligands that donate one electron pair to one acid ion or molecule. Examples of monodentate ligands include anions such as OH-, O$_2$-, NH$_2$-, S$_2$-, HS-, CH$_3$-, H-, X-; neutral molecules such as H$_2$O, NH$_3$, CO, CH$_3$CH$_2$OH, (CH$_3$)$_2$C=O, (CH$_3$CH$_2$)$_2$O (and many more); and species with relatively high energy $\pi$ electrons, such as olefins.

2) Polydentate (many-toothed) ligands. A polydentate ligand, sometimes called a chelating ligand, has 2 or more donor atoms spaced so that they can attach to the same Lewis acid. Normally the donor atoms must be "spaced" by 2 or 3 intervening atoms. Polydentate ligands are subdivided more precisely as follows.

a) Bidentate (2-toothed) ligands. The prototype for bidentate ligands is ethylenediamine, H$_2$NCH$_2$CH$_2$NH$_2$. This molecule donates both N atoms to the same Lewis acid to give a 5-membered ring, as shown. A second example is the dianion of aspartic acid, H$_2$NCH(CH$_2$COO-)COO-, which can conceivably be bidentate in a couple of ways. Draw a careful structure of the molecule, identify the potential donor atoms, and determine the ways in which aspartate can be bidentate. A third example of a bidentate ligand is 1,10-phenanthroline. Because many metal ions use 6 (of 9 possible) coordination positions, they can accommodate up to 3 bidentate ligands. Thus adducts such as Ni(en)$_3^{2+}$ and Ni(phen)$_3^{2+}$ are common.

b) Tridentate ligands. Examples of potentially tridentate ligands include diethylenetriamine (abbreviated dien) and 2,6-pyridinedicarboxylate. The structures are shown.

c) Tetradebate ligands have four appropriately spaced donor atoms. Such ligands can be linear, branched, or cyclic. A linear tetradebate ligand is one in which all 4 donor atoms occur in a single chain of ligand atoms. The prototype for the linear tetradebate ligand is triethylenetetramine, H$_2$N-CH$_2$-CH$_2$-NH-CH$_2$-CH$_2$-NH$_2$. A second and interesting example is the anion, bis(salicylaldehyde)ethylenediimine (abbreviated salen). Coordination of the salen anion to a transition metal ion results in adducts with interesting physical and chemical properties. Tetradebate ligands can also have a branched structure, meaning that donor atoms are located in 2 or more atom chains in the molecule. An example is tris-(2-aminoethyl)amine, which has the tripod-like shape shown. This ligand tends to retain its tripod-like arrangement even when bound to a metal ion. It can therefore be used to force a specific coordination geometry on the metal ion. Finally, many tetradebate ligands are (macro)
cyclic in structure. A macrocyclic ligand is a chelate ligand with the donor atoms in a ring. The most famous example is the porphyrin, a naturally occurring macrocyclic ligand of great importance. In addition, a large variety of synthetic macrocyclic ligands has been designed and studied as models for the porphyrin ligand. Interesting chemistry has been discovered with Lewis adducts of these macrocycles, some of which are shown.

d) Hexadentate ligands offer six donor atoms to an acid center. The best known of these is ethylenediaminetetraacetate (abbrev. EDTA). This ligand is used as a sequestering (gathering) agent in water treatment, food preservation, analysis, and heavy metal poisoning. It functions by tying up metal ions that might otherwise precipitate with CO_3^{2-} (water treatment), catalyze undesirable reactions (food preservation), or interfere with enzyme and protein function (heavy metal poisoning).

It is very generally true that for a specified type of donor atom in the ligand (for example, N), stabilities of adducts with a particular metal ion acid tend to increase as follows:

monodentate < chelate < macrocyclic

Thus Ni(14aneN_4)^{2+} is more stable than Ni(trien)^{2+}, which is in turn more stable than Ni(en)_2^{2+} which is finally more stable than Ni(NH_3)_4^{2+}.

Exercise. Classify as Lewis acids and/or bases: pyridine; DMSO, COCl_2, benzene, SCN-.

Interpretation of Reactions in Terms of Lewis Theory. To illustrate the applicability of Lewis acid/base theory, we will analyze several simple and familiar reactions in terms of Lewis ideas.

Example: C_6H_6 + CH_3Cl \rightarrow C_6H_5CH_3 + HCl, carried out in the presence of AlCl_3 as a catalyst. The generally accepted mechanism for this process involves several steps, each step involving a Lewis acid-base interaction.

Step 1: CH_3Cl + AlCl_3 \rightarrow CH_3^+ + AlCl_4^- . In this step, the Lewis acid, AlCl_3, extracts the Lewis base, Cl-, from its adduct with the Lewis acid, CH_3+. The products are the acid CH_3+ and a new adduct, AlCl_4-.

Step 2: C_6H_6 + CH_3^+ \rightarrow C_5H_5C(H)(CH_3)^+, in which the methyl carbocation has formed a sigma bond with one carbon atom of the benzene ring by accepting one of the 3 pairs of pi electrons of the ring in a Lewis acid-base reaction.

Step 3: C_5H_5C(H)(CH_3)^+ \rightarrow C_6H_4(CH_3) + H+. In this process, the adduct of H+ with toluene dissociates.

Step 4: H+ + AlCl_4^- \rightarrow HCl + AlCl_3. H+ strips the Lewis base, Cl-, from the adduct AlCl_4- to form a new adduct, HCl, and regenerate the catalyst, AlCl_3.

Example: GaCl_3 + Cl- \rightarrow GaCl_4-. We recognize GaCl_3 as a potential Lewis acid because Ga has an unused p valence orbital. Attack of the Lewis base, Cl-, on this vacant p orbital may be thought of as pictured.
Example: $\text{CH}_3\text{CO}^+ + \text{F}^- \rightarrow \text{CH}_3\text{COF}$. We perceive that $\text{CH}_3\text{CO}^+$ has 2 underused valence p orbitals on the positively charged carbon atom. Attack by the Lewis base may take place at either of these orbitals, as shown.

The Hard/Soft Acid/Base (HSAB) Principle. HSAB is an extremely useful qualitative theory that enables predictions of what adducts will form in a complex mixture of potential Lewis acids and bases. Although there have been numerous attempts to make the theory quantitative by assigning numbers representing "hardness" and "softness" to acids and bases, these have not been particularly successful. Even if only qualitative, the theory is so useful that it is essential to know something about it.

Fundamentals. The basic premise of Hard/Soft Acid/Base Theory is very simple: Hard acids prefer hard bases; soft acids prefer soft bases. We must now define these terms.

Hard acids (in context, HA) are characterized by (s,f blocks, left side of d block in higher OS's)

- Low electronegativity ($\chi$) of the acidic atom. A value in the range 0.7-1.6 is typical of hard acids;
- Relatively small size;
- Relatively high charge ($\geq 3+$).

High charge often results in small size, because the remaining electrons are contracted toward the nucleus by the substantial excess positive charge. Specific examples of hard acids are the metal cations from the s and f blocks,
and the higher-charged ions from the left side of the d block. \( \text{Na}^+, \text{Mg}^{2+}, \text{Fe}^{3+}, \) and \( \text{Al}^{3+} \) are examples of hard acids.

**Hard bases** (in context, HB) are characterized by

- Very high \( \chi \) of the donor atom (in the range 3.4-4);
- Relatively small size of the donor atom.

The combination of high electronegativity and small size results in a nonpolarizable electron cloud surrounding the donor atom. The only 2 donor atoms with electronegativities in the specified range are oxygen and fluorine. So the hard bases are those in which the donor atom is either O or F. Specific examples are \( \text{O}^2-, \text{F}^-, \text{OH}_2^-, \text{CO}_3^{2-}, \) and \( \text{PO}_4^{3-}. \)

**Soft acids** (in context, SA) are characterized by an acceptor atom of

- Intermediate to high \( \chi \) (1.9-2.5);
- Large size;
- Low charge (1+, 2+)

Species of large size generally have many electrons, some of which can be quite far from the nucleus. The low charge of the species results in a polarizable (distortable) electron cloud. Specific examples of soft acids include \( \text{Cu}^+, \text{Hg}^{2+}, \text{Au}^+, \text{Ag}^+, \) and \( \text{Pb}^{2+}. \) Note that these metals are all clustered in the same region of the periodic table.

**Soft bases** (in context, SB) are characterized by donor atom of

- Intermediate to high \( \chi \) (2.1-3.0)
- Large size, leading to polarizability

Specific examples of soft bases are \( \text{S}^2-, \text{PEt}_3-, \text{RSe}^-, \text{I}^-, \) and \( \text{Br}^-_. \) Note that these fall in groups 15-17 in periods with \( n \geq 3. \)

In addition to the fundamental "hard" and "soft" categories, two additional categories are useful. **Borderline acids** (in context, BA) are intermediate between hard and soft acids. Thus they tend to have lower charge and somewhat larger size than hard acids, and higher charge and somewhat smaller size than soft acids. The 2+ ions of the d block, such as \( \text{Fe}^{2+}, \text{Cu}^{2+}, \text{Ni}^{2+}, \) and \( \text{Zn}^{2+}, \) are borderline acids. **Borderline bases** (in context, BB) are intermediate between hard and soft bases. They tend to be larger and less electronegative than hard bases, smaller and more electronegative than soft bases. Bases in which the donor atom is N or Cl fall in this category. Thus \( \text{NH}_3, \text{Cl}^-, \text{RCI}, \) and pyridine are borderline bases.

Example: Classify each species as Lewis acid or base; as hard, soft, or borderline. Which of the Lewis bases would prefer to form adducts with each of the acids?
Fe\(^{3+}\): this has high positive charge, so is expected to be a hard acid.

I\(^-\): This is a large anion with low electronegativity and low charge; it is expected to be a soft base.

CH\(_3\)\(^-\): This is an anion, so is probably a base. The donor atom has low electronegativity and relatively low charge. Even though the donor atom is fairly small, this behaves as a soft base.

CO\(_3\)^{2-}\: This is an anion with oxygen atoms as potential donors. It is a hard base.

Cu\(^+\): This is a transition metal cation with a low charge. It is expected to be a soft acid.

Cl\(^-\): This is an anion with a chlorine donor atom. It should be a borderline base.

Se(CH\(_3\))\(_2\)F\(^-\): This is an anion with two potential donor atoms: F, which is a hard donor; and Se, with two electron pairs, which is expected to be a soft base. This species is definitely a base, but can be soft or hard depending on circumstances.

We predict that Fe\(^{3+}\) should prefer to form adducts with the carbonate anion and the F donor of Se(CH\(_3\))\(_2\)F\(^-\). Cu\(^+\) should prefer adducts with the soft bases, I\(^-\) and CH\(_3\)\(^-\). Cl\(^-\) will probably bind to either the hard or soft acid, but would prefer a borderline acid such as Fe\(^{2+}\).

Because hard acids and bases tend to be highly charged and nonpolarizable, the interaction between them is largely ionic. Their small sizes allow the acid and base to get close enough together so that the ionic interaction is quite strong (remember Coulomb's Law: force of attraction increases as the attracting species get closer together). A good image to keep in mind when thinking of a hard acid/hard base adduct is the juxtaposition of a golf ball (the "acid") with a baseball (the base). Both of these items are small, hard, and undistortable (try pushing the golf ball and baseball together--what happens?). In contrast, soft acids and soft bases have covalent interactions because their electron clouds are polarizable. A good image for soft-soft interactions is the juxtaposition of a large nerf ball (the base) with a smaller nerf ball (the acid). Here the electron clouds are squishy, and can be easily distorted during the interaction (try pushing the 2 nerf balls together--what happens?).

Refinements to HSAB Theory: Factors Influencing Hardness/Softness. Before considering some broad applications of the HSAB ideas, we will add some refinements to the major principle that "hard acids prefer hard bases; soft acids prefer soft bases".

1) There are degrees of hardness and softness. Hardness/softness of acids is affected by several factors. First, the nature of the acceptor atom. Thus Au\(^+\) > Hg\(^{2+}\) > Pb\(^{2+}\) in softness. Hardness increases with distance from gold. Second, the charge: hardness increases with increasing charge (oxidation state). For example, Tl\(^3+\) is harder than Tl\(^+\). Third, the attached groups: Attaching soft substituents (bases) to an acceptor atom increases the softness of the acceptor atom; attaching hard bases increases the hardness of the acceptor atom. Thus, for example, AlF\(_3\) is harder than Al(CH\(_3\))\(_3\).
Exercise: Order the following acids according to softness:

- Fe\(^{2+}\)(aq)
- Fe\(^{3+}\)(aq)
- Ni(H\(_2\)O)\(_6\)\(^{2+}\)
- Ni(CN)\(_4\)\(^{2-}\)

Hardness/softness of bases is affected by, first, the nature of the donor atom. For example, softness decreases (hardness increases) in each of the following series:

- I > Br > Cl > F
- Te,Se > S > O
- Sb < As > P > N

Second, charge affects the hardness/softness of bases. Increased negative charge increases the polarizability, hence the softness, of the base. Third, the attached groups affect the hard/soft character of a base. Hard substituents increase hardness; soft substituents increase softness. For example, NF\(_3\) is a harder base than N(CH\(_3\))\(_3\).

Exercise: Order the following bases according to softness:

- SCl\(_2\)
- SO\(_2\)
- SH\(_2\)

In summary, the HSAB Principle can now be refined as follows: **harder acids prefer harder bases; softer acids prefer softer bases.**

2) Stronger acids prefer stronger bases. This often complicates application of the HSAB guidelines. Strengths of acids and bases can take precedence over hard/soft rules, particularly in cases where only one soft species is present. For example, Bronsted-Lowry acid-base reactions always involve a hard acid (H\(^+\)) and mostly hard bases (e.g., H\(_2\)O, OH\(^-\)) so are not predictable using HSAB. The following reaction illustrates the point.

Example: HCl (HA-BB) + HOH:OH\(_2\) (HA-HB) → H\(_3\)O\(^+\) (HA-HB) + HOH-Cl\(^-\) (HA-BB)

where HA = hard acid, etc. Although HSAB ideas are not applicable here, the direction of reaction can easily be predicted using relative acid and base strengths.

**Applicability of HSAB Theory.** The HSAB principle applies to exchange (double displacement) reactions, represented generally as follows:

\[ A_1-B_1 + A_2-B_2 → A_1-B_2 + A_2-B_1 \]
The position of equilibrium for an exchange reaction can be predicted from HSAB ideas, provided that acids and bases can be "ranked" for hardness/softness. For example, in the reaction

\[
\text{ZnI}_2(\text{aq}) + \text{HgCl}_2(\text{aq}) \rightarrow \text{ZnCl}_2(\text{aq}) + \text{HgI}_2(\text{s})
\]

the reactants are, respectively, adducts of a borderline acid with a soft base, and a soft acid with a borderline base. The products are adducts of a borderline acid and base, and a soft acid and base, so products are clearly favored here. Exchange reactions may be dissected via Hess's Law into adduct dissociation or formation processes, as shown below.

\[
\begin{align*}
A_1\cdot B_1 & \rightarrow A_1 + :B_1 \\
A_2\cdot B_2 & \rightarrow A_2 + :B_2 \\
A_1 + :B_2 & \rightarrow A_1\cdot B_2 \\
A_2 + :B_1 & \rightarrow A_2\cdot B_1
\end{align*}
\]

Reaction is driven according to which adducts are more stable. In solution, many reactions can be viewed as exchange processes if solvation is explicitly allowed for. Thus the Lewis acid-base reaction \(A(\text{sol}) + B(\text{sol}) \rightarrow AB(\text{sol})\) can be made to look like an exchange process by writing it as follows.

\[
A(S)_n + B(S)_m \rightarrow A-B + \left[(n+m)/2\right]S-S
\]

The second product here is an adduct of solvent with solvent.

Example: \(\text{Ni(H}_2\text{O})_6^{2+} (\text{BA-HB}) + \text{H}_3\text{N-HOH} (\text{HA-BB}) \rightarrow \text{Ni(NH}_3)_6^{2+} (\text{BA-BB}) + \text{HOH-OH}_2 (\text{HA-HB})\)

With solvation explicitly represented, this reaction can be seen to favor products. HOWEVER, the principal is not applicable when there is only one soft species (acid or base) involved. In terms of HSAB ideas, we can say nothing about whether reactants or products are favored in the following reaction.

\[
\text{Hg}^{2+}(\text{aq}) + F^-(\text{aq}) \rightarrow \text{HgF}_2 + \text{aq-aq}
\]

**Applications of the HSAB Principle.** Here we will address the applications primarily by example.

1) Predicting favorable equilibria.

Example: In the following situation, which product will form, LiI or LiF?

\[
\text{LiCl}(\text{aq}) + (\text{KF, KI})\text{aq} \rightarrow
\]

We recognize that here we have a soft base but no soft acid; the principle is not applicable.
Example: In the following situation, which product will form?

\[
\text{HgCl}_2(aq) + (KF, KI)aq \rightarrow
\]

Here we recognize a soft acid and a soft base, so the principle applies. We predict that \( \text{HgI}_2 \) will be found in the products.

Example: In the following situation, what if anything can we predict will happen?

\[
\text{SrCl}_2(aq) + (\text{Na}_2S, \text{NaOH})(aq) \rightarrow
\]

Reactants involve a soft base but no soft acid; the principle is not applicable.

Exercise: Is the HSAB principle applicable to the following situation?

\[
\text{Ag}^+(aq) + [(\text{NH}_2)C=O, (\text{NH}_2)C=S](aq) \rightarrow ?
\]

Example: An aqueous solution contains \( \text{Hg}^{2+}, \text{Cl}^-, \text{Na}^+, \) and \( \text{I}^- \). What adducts (complexes) will form? We can attack this by preparing a table of the species present, sorted into acid or base categories. We can then attempt to apply HSAB ideas to predict predominant adducts in the mixture. We recognize that \( \text{Hg}^{2+} \) and \( \text{Na}^+ \) are likely to be acids; and that \( \text{Cl}^- \) and \( \text{I}^- \), anions, are bases. Further, we must recognize that the solution contains a large concentration of water, which can be both an acid and a base. Now we can place the species in acid and base columns in a table as follows. Likely adducts can then be predicted by matching soft acids with soft bases, and hard acids with hard bases. \( \text{Cl}^- \), a borderline base, is matched by default with water, by far the most abundant acid in the mixture.

<table>
<thead>
<tr>
<th>Acids</th>
<th>Bases</th>
<th>Adducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Hg}^{2+} ) (SA)</td>
<td>( \text{Cl}^- ) (BB)</td>
<td>( \text{HgI}_2 )</td>
</tr>
<tr>
<td>( \text{Na}^+ ) (HA)</td>
<td>( \text{I}^- ) (SB)</td>
<td>( \text{Na(H}_2\text{O})_6^+ )</td>
</tr>
<tr>
<td>( \text{H}_2\text{O} ) (HA)</td>
<td>( \text{H}_2\text{O} ) (HB)</td>
<td>( (\text{H}_2\text{O})_n \text{Cl}^- )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \text{HOH-OH}_2 )</td>
</tr>
</tbody>
</table>

Example: An aqueous solution contains \( \text{NO}_3^- \), \( \text{Ag}^+ \), \( \text{Cl}^- \), and \( \text{K}^+ \). What adducts will form?
Lewis Acids/Bases; HSAB Theory

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<th>Bases</th>
<th>Adducts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag⁺ (SA)</td>
<td>NO₃⁻ (HB)</td>
<td>AgCl</td>
</tr>
<tr>
<td>K⁺ (HA)</td>
<td>Cl⁻ (BB)</td>
<td>K(H₂O)₆⁺</td>
</tr>
<tr>
<td>H₂O (HA)</td>
<td>H₂O (HB)</td>
<td>(H₂O)ₙ NO₃⁻</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOH-OH₂</td>
</tr>
</tbody>
</table>

**Exercise:** An aqueous solution contains Au⁺, Cl⁻, Ru²⁺, HS-CH₂-CH(NH₂)-C(=O)OH, La³⁺. What adducts will form?

2) Geochemistry of the elements. In nature, hard acids are found associated with hard bases, and soft acids are found associated with soft bases. Thus hard acids tend to occur as oxides, silicates, carbonates, and fluorides, whereas soft acids occur as sulfides, selenides, and tellurides, or as free elements (in which case they can be viewed as cations associated with electrons, which are very soft bases). Borderline acids often occur as sulfides. Metals found in nature in combination with the group 16 elements S, Se, and Te are sometimes called chalcophiles.

Exercise: Predict the type of ore in which each metal ion is likely to be found: Fe³⁺, Fe²⁺, Hg²⁺, Zn²⁺, Na⁺, Ca²⁺, Si⁴⁺.

3) Toxicology, Medicinal Chemistry. Ions of many so-called heavy metals, such as Hg²⁺ and Pb²⁺, are highly toxic. Why? Heavy metal ions are soft acids, and therefore have high affinity for S²⁻, a soft base. S occurs in the side chains of two amino acids, methionine and cystine, and is important in maintaining tertiary structure of proteins and enzymes upon which life depends. Ingested heavy metal ion seeks out and coordinates with amino acid sulfur, disrupting protein structure and deactivating the protein. Eventual death is the usual result of prolonged exposure to heavy metal ions. As an illustration of the affinity of heavy metal ions for sulfur, we consider the Hg²⁺ cation. The solubility product for HgS in aqueous solution is about 10⁻⁵⁰ M², meaning that HgS has a solubility of 1 x 10⁻²⁵ M in water. Think about this number. It means that in one liter of such a solution, there will be less than 1 Hg²⁺ ion! Based on this solubility, we can calculate that to dissolve 1.0 g HgS would require 4 x 10²² L H₂O. But there are only 1 x 10²¹ L of water on earth!!!

Exercise: Why are HCN, CO, H₂S, H₂Se, and PH₃ poisons?

4) Ligand selections in metalloproteins and enzymes. Ions of many of the 3d transition metals are essential for life in trace amounts. A number of proteins and enzymes incorporate these metal ions specifically into their structures, forming adducts with the metal ion using donor atoms on the side chains of their amino acids. Side chains containing oxygen, nitrogen, and sulfur donors are usually involved in adduct formation. It is interesting
to apply HSAB ideas to attempt to understand why certain amino acids are frequently found with their side chain donors bound to particular metal ions. As a particular example, consider the \( \text{Fe}^{2+} \) ion, perhaps the most-used metal ion in life processes. This ion is found in species such as myoglobin and hemoglobin, in which its function is to accept an electron pair from an \( \text{O}_2 \) molecule to form an adduct, carry the \( \text{O}_2 \) to the muscle tissues of the body, and release the \( \text{O}_2 \) unaltered where it is needed. It is found in electron transfer proteins such as cytochrome \( \text{c} \), where its function is to mediate the movement of an electron between other proteins. It is found in the iron-sulfur proteins, where its function is again redox related. In all of these varied proteins, with their different functions, the \( \text{Fe}^{2+} \) ion is invariably associated with N and S donor atoms. This is sensible in terms of HSAB theory, because \( \text{Fe}^{2+} \) is a borderline acid. Its association with the borderline donor, N, and the soft donor, S, is therefore understandable. Similarly, the \( \text{Zn}^{2+} \) and \( \text{Cu}^{2+} \) ions are attached to proteins and enzymes via N and O donors. \( \text{Fe}^{3+} \), on the other hand, is a hard acid and is invariably found bound by O donors.

Exercise: What donor atoms might be appropriate for binding \( \text{Cu}^+ \) in an enzyme or protein? \( \text{Na}^+ \)? \( \text{K}^+ \)? \( \text{Ca}^{2+} \)?

Interestingly, \( \text{Cu}^{2+} \) is found in the so-called blue copper proteins coordinated by N and S donors, and it is natural to wonder why a soft donor atom is involved? The purpose of the blue copper proteins is electron transfer, requiring that the copper ion cycle back and forth between the 1+ and 2+ oxidation states. The coordination sphere of the ion is thus optimally designed to accommodate both oxidation states: S donors are there to stabilize \( \text{Cu}^+ \), and N donors are there to stabilize \( \text{Cu}^{2+} \).

5) Reduction Potentials. The electron has been termed the "ultimate soft base". Viewing the electron in these terms, standard reduction potential can be understood in terms of HSAB theory. Several standard reduction potentials are given below.

\[
\begin{align*}
\text{Fe}^{3+}(aq) + 3e^- & \rightarrow \text{Fe}(s), \varepsilon^o = -0.036 \\
\text{Cu}^+(aq) + e^- & \rightarrow \text{Cu}(s), \varepsilon^o = 0.522 \\
\text{Na}^+(aq) + e^- & \rightarrow \text{Na}(s), \varepsilon^o = -2.711 \\
\text{La}^{3+}(aq) + 3e^- & \rightarrow \text{La}(s), \varepsilon^o = -2.37
\end{align*}
\]

Recall that the more positive the value of \( \varepsilon^o \), the more spontaneous the reduction. The data reveal that the \( \varepsilon^o \) values parallel the hardness/softness of the metal cation (acid). Thus the soft acid, \( \text{Cu}^+ \), interacts quite spontaneously with the soft electron. The hard acids, \( \text{Fe}^{3+} \), \( \text{Na}^+ \), and \( \text{La}^{3+} \) are very difficult to reduce because their interaction with the soft electron is not favorable.

Ex: Arrange the following half reactions in order of decreasing standard reduction potential. "Decrease" means "to become less positive". After you have predicted an order, look up the SRPs to see if you were correct!

\[
\begin{align*}
\text{Cr}^{2+} + 2e^- & \rightarrow \text{Cr}(s) \\
\text{Pt}^{2+} + 2e^- & \rightarrow \text{Pt}(s) \\
\text{Hg}^{2+} + 2e^- & \rightarrow \text{Hg}(s) \\
\text{Co}^{3+} + 3e^- & \rightarrow \text{Co}(s)
\end{align*}
\]