Abstract

The concept of hard and soft acids and bases (HSAB) proved to be useful for rationalizing stability constants of metal complexes. Its application to organic reactions, particularly ambident reactivity, has led to exotic blossoms. By attempting to rationalize all the observed regioselectivities by favorable soft–soft and hard–hard as well as unfavorable hard–soft interactions, older treatments of ambident reactivity, which correctly differentiated between thermodynamic and kinetic control as well as between different coordination states of ionic substrates, have been replaced. By ignoring conflicting experimental data and even referring to untraceable experimental data, the HSAB treatment of ambident reactivity has gained undeserved popularity. In this Review we demonstrate that the HSAB as well as the related Klopman–Salem model do not even correctly predict the behavior of the prototypes of ambident nucleophiles and, therefore, are rather misleading instead of useful guides. An alternative treatment of ambident reactivity based on Marcus theory will be presented.

Historical background

Kornblum : Alkylations of ambident anions (1950’s)

“The greater the $S_{N1}$ character of the transition state the greater is the preference for covalency formation with the atom of higher electronegativity and, conversely, the greater the $S_{N2}$ contribution to the transition state the greater the preference for bond formation to the atom of lower electronegativity”.

\[ \text{Preferred by } S_{N1} \quad \text{Preferred by } S_{N2} \]

\[ \text{Scheme 1. Preferred reaction pathways of ambident nucleophiles according to Marcus’s Advanced Organic Chemistry textbook.}\]
“The principle of hard and soft acids and bases states that hard acids prefer hard bases and soft acids prefer soft bases (...). In an S_N1 mechanism, the nucleophile attacks a carbocation, which is a hard acid. In an S_N2 mechanism, the nucleophile attacks the carbon atom of a molecule, which is a softer acid. The more electronegative atom of an ambident nucleophile is a harder base than the less electronegative atom. We may thus make the statement: As the character of a given reaction changes from S_N1- to S_N2-like, an ambident nucleophile becomes more likely to attack with its less electronegative atom. Therefore, changing from S_N1 to S_N2 conditions should favor C attack by CN, N attack by NO_2, C attack by enolate or phenoxide ions, etc.”

March’s textbook

The Klopman–Salem concept of charge and orbital control of organic reactions uses similar ideas: Hard–hard interactions are charge-controlled and soft–soft interactions are orbital-controlled.

Fleming (2009)

Criticism
The HSAB concept does not differentiate between kinetic and thermodynamic control, although in many cases different conditions give rise to different products.

The decision as to whether a certain reaction is dominated by charge or orbital control is often made a posteriori, that is, after knowing the experimental facts, with the consequence that it has little predictive value.

Gompper & Wagner (1976)

We have analyzed literature reports on the regioselectivities of these and other ambident nucleophiles and electrophiles, and we have realized that the number of cases where the HSAB principle and the concept of charge- and orbital-controlled reactions give correct predictions approximate the number of cases where they fail. For that reason, we suggest abandoning these concepts as guides for predicting ambident reactivity.

Mayer (2011)

“This can’t miss approach sweeps a lot of interesting chemistry under the rug and leads one to believe he has understanding when in reality he may not”.

Drago (1974)

Systematic Analysis of Ambident Reactivity

\[ \log k = s_0 [N + E] \quad (1) \]

Scheme 2. A systematic approach to ambident reactivity.
Differentiation between Activation- and Diffusion-Controlled Reactions

The rates of bimolecular reactions in solution are limited by diffusion, in other words, the time needed for two molecules to meet in an encounter complex:

Diffusion limit
cation–anion combinations: \( k < 2 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1} \) (acetonitrile)
\( k < 5 \times 10^{9} \text{ M}^{-1} \text{ s}^{-1} \) (water)

Database: http://www.cup.lmu.de/oc/mayr/DBintro.html

620 nucleophiles
182 electrophiles
Marcus Theory of Electron Transfer

\[ \Delta G^\pm = \frac{\lambda}{4} \left( 1 + \frac{(\Delta G^0)^2}{\lambda} \right) \]

\[ \lambda = \lambda_1 + \lambda_\alpha \]

reorganization energy

The energy that needs to be put into distorting either the reactant-solvent or product-solvent ensemble to make the energy of the donor and acceptor orbitals the same.

Marcus Inverted Region

In this picture \( \Delta G \) is the free energy change between the reactants on the left and the products on the right and \( AE \) is the activation energy. \( \lambda \) is the reorganization energy. This is the energy it would take to force the reactants (on the left) to have the same nuclear configuration as the products (on the right) without letting the electron transfer.

All Marcus did was realize that he could solve for the point of crossing between the two parabolas and derive the activation energy (and thus the rate constant) from the thermodynamic parameters of the system. So let’s do this. You don’t need to actually do this derivation on the test, but you need to understand what is being done and why.

Let’s assume that the bottom of the left parabola is \( a = 0 \) and its equation is \( y = x^2 \). This is completely general because we have not assigned any scale to the axes. If this is true, and if we assume that the shape of the second parabola is the same as the first and it is just displaced, then the equation of the second parabola is just \( y = (z-x)^2 \). In other words, the bottom of the second parabola is at the point \((a,b)\) All we have to do is solve for \( y \) that the two are equal and we will know the activation energy.
The excellent agreement of directly calculated activation energies with those obtained by the Marcus approach (Figure 3) already implies that there are no variable hard–hard or soft–soft interactions between the different groups X and Y in Equations (4)–(6). Thus, the intrinsic barrier for the reaction of HS+H3CF equals the average of the barriers for F+CH3F and HS+H3CSH.

Application of the Marcus equation [Eq. (3)] to ambident reactivity thus requires knowledge of relative product stabilities (ΔΔG°) and relative magnitudes of the intrinsic barriers (ΔΔG°). Relative product stabilities (ΔΔG°) are usually known or can be derived experimentally or computationally by standard methods.

**How Can Relative Magnitudes of Intrinsic Barriers Be Predicted?**

**Hoz Approach**

<table>
<thead>
<tr>
<th>C-X bond length</th>
<th>X＋H3C-Y → X-CH3 + Y—</th>
<th>X＋H3C-X → X-CH3 + X—</th>
<th>Y＋H3C-Y → Y-CH3 + Y—</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCH2—</td>
<td>MeNH2—</td>
<td>MeO—</td>
<td>F—</td>
</tr>
<tr>
<td>44.7</td>
<td>29.3</td>
<td>19.5</td>
<td>11.4</td>
</tr>
<tr>
<td>MeSH2—</td>
<td>MePH2—</td>
<td>MeS—</td>
<td>Cl—</td>
</tr>
<tr>
<td>45.8</td>
<td>29.8</td>
<td>21.9</td>
<td>13.2</td>
</tr>
<tr>
<td>MeGeH2—</td>
<td>MeAsH2—</td>
<td>MeSe—</td>
<td>Br—</td>
</tr>
<tr>
<td>38.1</td>
<td>24.5</td>
<td>17.8</td>
<td>10.8</td>
</tr>
<tr>
<td>MeSnH2—</td>
<td>MeSbH2—</td>
<td>MeTe—</td>
<td>I—</td>
</tr>
<tr>
<td>30.6</td>
<td>19.7</td>
<td>15.3</td>
<td>9.6</td>
</tr>
</tbody>
</table>

**Figure 2.** Intersecting parabolas in a) non-identity reactions and b) identity reactions. q refers to the nuclear configuration.
Principle of Least Nuclear Motion (PLNM)

\[ \Delta Q^0 = \lambda / 4 \quad \lambda = \text{reorganization energy} \]

“those elementary reactions will be favored that involve the least change inatomic position and electronic configuration”

(Hine 1977)

Calculated Barriers for Identity Reactions of Ambident Nucleophiles

\[
\begin{align*}
\Delta \Delta G^0 &= 181 \text{ kJ mol}^{-1} \\
\text{NC}^+ + \text{H}_2\text{C} = \text{ON} &\rightarrow \text{NC} = \text{CH}_3 + ^3\text{CN} \quad (8\text{C})
\end{align*}
\]

\[
\begin{align*}
\Delta \Delta G^0 &= 10.4 \text{ kJ mol}^{-1} \\
\text{CN} = \text{H}_2\text{C} = \text{NC} &\rightarrow \text{CN} = \text{CH}_3 + ^3\text{CN} \quad (8\text{N})
\end{align*}
\]

\[
\begin{align*}
\Delta \Delta G^0 &= 87.3 \text{ kJ mol}^{-1} \\
^3\text{CO} + \text{H}_2\text{C} = \text{CO} &\rightarrow ^3\text{CO} + \text{CH}_3 + \text{CO} \quad (9\text{K})
\end{align*}
\]

\[
\begin{align*}
\Delta \Delta G^0 &= 178 \text{ kJ mol}^{-1} \\
^3\text{CO} + \text{H}_2\text{C} = \text{CO} &\rightarrow ^3\text{CO} + \text{CH}_3 + ^3\text{CO} \quad (9\text{C})
\end{align*}
\]

C > N \quad C > O

smaller intrinsic barriers for attack at the atom which is further right inthe periodic table

Qualitative Marcus Approach to Ambident Reactivity

Whenever a thermodynamically less stable product is formed preferentially under conditions of kinetic control, it must begenerated via the lower intrinsic barrier. On the other hand,kinetically controlled reaction products are not necessarilyformed via the lower intrinsic barrier.
3. Ambident Nucleophiles
3.1. Carbon versus Nitrogen Attack (C vs N)
3.1.1. Cyanide Anion (CN)

Scheme 5. Common description of the ambident reactivity of cyanide, which should be revisited.

Contradictory results

![Image](image1.png)

Scheme 6. Reactions of propio- and bromo-3-(methylthio)butanes 1 and 2 with metal cyanides.\(^{[19]}\)

The reactions with NaCN and AgCN follow the same mechanism and that “the observed regioselectivity with both metal cyanides (...) cannot be explained as variations in the hardness of the electrophilic carbon induced by the interactions between the metal cation and the halogen” found little attention. In agreement with “older hypotheses”, the formation of isonitriles with AgCN (Scheme 6) was explained by the “participation of a species (non-free CN) in which the Ag+ ion is bonded to the carbon atom.” Carretero (1985)

![Image](image2.png)

Scheme 8. Exclusive formation of acetonitrile in the reactions of Bu$_3$N"CN" with the hard methylation agents methyl triflate and trimethylsilyl tetrafluoroborate.\(^{[20]}\)

Free cyanide ions generally react at the carbon atom with “hard” and “soft” electrophiles and that nitrogen attack only occurs when the attack at carbon is blocked by another group (e.g. by Ag+ or Me$_3$Si+).
When the more electrophilic m-chloro-substituted tritylium ions 3b and 3c were employed, the nitrile/isonitrile ratio decreased because the rate of attack at the carbon atom remained constant while the rate of attack at the nitrogen atom increased.

In summary, all the experimental investigations indicate that free cyanide ions are attacked at the carbon atom by C electrophiles.

Attack at the C atom accompanied by attack at the N atom is observed in diffusion-controlled reactions, and predominant attack at the nitrogen atom was only found when the carbon terminus was blocked by coordination with silver ions or other Lewis acids. The large thermodynamic preference for C-alkylation (Table 1, entry 1), which is also reflected by Richardt's work on the isocyanide–cyanide rearrangement, overrules the intrinsically favored attack at the nitrogen atom, which is quantified in Scheme 4.

Anilines

soft alkyl halides as well as hard dialkyl sulfates react selectively at the nitrogen atom of aniline

The reversible attack at the nitrogen atom is generally 20–25 times faster than the attack at the carbon atom

Azo

Scheme 16. Ambident reactivity of aniline in reactions with aryl diazonium ions. The reversible attack at the nitrogen atom is generally 20–25 times faster than the attack at the carbon atom.
3. The further right the nucleophilic reaction center in the periodic table, the lower the intrinsic barrier.

4. Whereas the influence of $\Delta G_0$ on $\Delta G$ is well known much less is currently known about intrinsic barriers ($\Delta G_0$)—the second term which controls the rates of chemical reactions [Eq. (3)].

Conclusion

1. The rationalization of ambident reactivity by the HSAB or the Klopman–Salem concept has to be abandoned.

2. Marcus theory has been shown to be suitable for predicting the regioselectivities of kinetically controlled reactions, which proceed over an energy barrier.

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1) What is the physical meaning of the reorganization energy?

2) What is the relationship between the free energy change and the reorganization energy when the rate constant is maximal?

3) Does rate always increase as the free energy change becomes more negative?

4) If I increase the distance between the electron donor and acceptor by 5 angstroms, I find that the rate constant for a particular electron transfer reaction decreases by 10-fold. What is $\beta$?

5) I find that at 37 C the rate constant for a particular electron transfer reaction is twice what it is at 0 C. Assuming that the equilibrium constant for the reaction is about 100 (favoring the product) and roughly independent of temperature over this range, what is the reorganization energy for this reaction (assume $\Delta G = \Delta G^*$ for this reaction)?