The Nature of the Hydrogen Bond and its Application Towards Enantioselective Catalytic Reactions

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Lead Material:
A brief introduction to various hydrogen bond applications

- Examples of hydrogen bonding are incredibly common
  - Mineralogy, material science, organometallics, biochemistry, organic chemistry, supramolecular chemistry
  - Molecular medicine and pharmacy

- Many important structural functions
  - Stabilizes protein folding, organizes DNA, organizes water and carbohydrates

- Being discovered and elaborated on in bioorganic, organic and inorganic chemistries

Hydrogen bonds and reactivity

- The proposed interaction
  - Charge transfer occurs from an electron lone pair from an acceptor (A) to the antibonding orbital of a donor (D) hydrogen bond

\[
\text{A} \sigma^* \xrightarrow{\text{H}^+} \text{D}\]

- Lewis acid activator

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\hline
\text{H} \\
\text{H}
\end{array}
\]

- LUMO lowering catalysis

- Transition state organizer
  - Initially seen in enzymes and is now be utilized in current synthesis
  - Provide a route for asymmetric catalysis
  - Dual reactivity

- Reaction lubricant
  - Can provide a source of energy to facilitate a reaction
  - Completes a "circuit" to allow for reaction to occur
The three major types of H bonds and important parameters

**General Characteristics**

<table>
<thead>
<tr>
<th>Interaction Type</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>H- - -A</td>
<td>strongly covalent</td>
<td>mostly electrostatic</td>
<td>electrostatic/dispersed</td>
</tr>
<tr>
<td>Bond Lengths (Å)</td>
<td>1.2–1.5</td>
<td>1.5–2.2</td>
<td>2.2–3.3</td>
</tr>
<tr>
<td>Lengthening of X–H (Å)</td>
<td>0.08–0.25</td>
<td>0.02–2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>X–H vs. H- - -A</td>
<td>X–H ≈ H- - -A</td>
<td>X–H&lt; H- - -A</td>
<td>X–H &lt;&lt; H- - -A</td>
</tr>
<tr>
<td>X- - -A (Å)</td>
<td>2.2–2.5</td>
<td>2.5–3.2</td>
<td>&gt;3.2</td>
</tr>
<tr>
<td>Directionality</td>
<td>Strong</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>Bond Angles (°)</td>
<td>170–180</td>
<td>&gt;130</td>
<td>&gt;90</td>
</tr>
<tr>
<td>H-1 downfield shift</td>
<td>14–22</td>
<td>&lt;14</td>
<td></td>
</tr>
<tr>
<td>Bond Energy (kcal/mol)</td>
<td>15–40</td>
<td>4–15</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

- The "normal" hydrogen could also be termed as the "weak strong" or "strong weak" H bond
Qualitative properties H bond lengths

- **Strong hydrogen bonds**

  \[ \begin{align*}
  & X \quad d_1 \quad d_1 \quad \text{H}^- \quad \text{d} \quad -A \\
  & d_1 \simeq d_2
  \end{align*} \]


- **Moderate hydrogen bonds**

  \[ \begin{align*}
  & X \quad d_1 \quad d_1 \quad \text{H}^- \quad \text{d} \quad -A \\
  & d_1 < d_2, \text{X–H is long compared to weak bonds}
  \end{align*} \]

  - moderate bonds have both weak and strong characteristics and tends to be blurred depending upon the experimental treatment
  - generally regarded as electrostatic

- **Weak hydrogen bonds**

  - C–H donor groups are most widely studied, includes the H-bond pi interaction
  - generally regarded as electrostatic/dispersed
  - ability to form bifurcated and trifurcated structures

  \[ \begin{align*}
  & \delta^- \quad d_1 \quad d_1 \quad \delta^+ \\
  & X \quad \text{H}^- \quad \text{d} \quad -A
  \end{align*} \]

  \[ d_1 < d_2, \text{X–H is shorter than in moderate H bonds} \]

  - A reasonable way of thinking about the H-Bond is as a frozen proton transfer event
  - Currently no widely accepted theoretical method for predicting H bonds exists

The types of hydrogen bond geometries

- Two centered hydrogen bonds
  - most understood and researched
  \[ \begin{align*}
  & \quad \text{X} - \text{H} - \text{A} \\
  & \quad \text{NH}_3\text{H} - \text{Bn} \\
  & \quad \text{HOH} - \text{OH}
  \end{align*} \]

- Three centered hydrogen bonds or bifurcated H bond
  - most examples are found in biology, especially carbohydrates (~25%) and amino acids (over 25%)

- Four centered hydrogen bonds or trifurcated H bond
  - Rare, found in molecules that have a high density of donors and acceptors
  - Also found in biology

\[ \text{NH(CH_2CH_2OH)_3} = \begin{align*}
  & \quad \text{H} - -\text{O}, 2.14-2.35 \text{ A} \\
  & \quad \text{N} - -\text{O}, 2.71-2.86 \text{A}
  \end{align*} \]
### Hydrogen bond energies

#### Energies for some gas phase dimers

<table>
<thead>
<tr>
<th>Dimer</th>
<th>Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[F–H–F]−</td>
<td>39</td>
</tr>
<tr>
<td>[H₂O–H–OH₂]⁺</td>
<td>33</td>
</tr>
<tr>
<td>[H₃N–H–NH₃]⁺</td>
<td>24</td>
</tr>
<tr>
<td>[OH–H–OH]−</td>
<td>23</td>
</tr>
<tr>
<td>H₄N– − -OH₂</td>
<td>19</td>
</tr>
<tr>
<td>H₄N– − -Bn</td>
<td>17</td>
</tr>
<tr>
<td>HOH– − -Cl</td>
<td>13.5</td>
</tr>
</tbody>
</table>

- strong H bonds, HOH− - -Cl is borderline

#### Comparing to other covalent BDE

<table>
<thead>
<tr>
<th>Bond</th>
<th>BDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂C≡CH₂</td>
<td>171</td>
</tr>
<tr>
<td>Me−H</td>
<td>105</td>
</tr>
<tr>
<td>Ph−I</td>
<td>65</td>
</tr>
<tr>
<td>Et−I</td>
<td>53</td>
</tr>
<tr>
<td>HO−OH</td>
<td>51</td>
</tr>
<tr>
<td>t-BuO−Ot-Bu</td>
<td>38</td>
</tr>
<tr>
<td>I−I</td>
<td>36</td>
</tr>
</tbody>
</table>

- the strongest H bonds start to take on a covalent nature!

Donor/Acceptor Strengths

- Relative donor strengths
  
  - General rule: donor strength is increased by neighboring electron-withdrawing groups and decreased by electron donating groups

\[
\text{O--H > N--H > S--H > C--H}
\]

- Oxygen subclass

\[
\text{H}_3\text{O}^+ > \text{O} = \text{C}--\text{OH} > \text{Ph}--\text{OH} > \text{C}_{\text{sp}3}--\text{OH} > \text{H}_2\text{O} > \text{OH}^-
\]

- Nitrogen subclass

\[
\text{Im}^+\text{N--H} > \text{R}_3\text{N}^+--\text{H} > \text{R}_2\text{NH}^+--\text{H} > \text{C}_{\text{sp}2}\text{N--H} > \text{C}_{\text{sp}3}\text{NH} > \text{N--NH}_2
\]

- Carbon subclass

\[
\text{Cl}_3\text{CH} > \text{C} \equiv \equiv \text{H} > (\text{RN}_2)_2\text{C}_{\text{sp}2}--\text{H} > (\text{Cl}, \text{C})\text{C}--\text{sp}_3--\text{H} > \text{R}_2\text{C}--\text{H} > \text{R}_3\text{C}--\text{H} > \text{O}--\text{CH}_3 > \text{CH}_3\text{CH}_2--\text{H}
\]

- Relative acceptor strengths

  - General rule: acceptor strength is increased by neighboring electron-donating groups and decreased by electron withdrawing groups

- Oxygen subclass

\[
\text{OH}^- > \text{COO}^- > \text{H}_2\text{O} > \text{C}_{\text{sp}3}--\text{OH} > \text{Ph}--\text{OH} > \text{C}--\text{NO}_2 > \text{M}--\text{CO}
\]

- Nitrogen subclass

\[
\text{C}_{\text{sp}3}--\text{NH}_2 > \text{R}_2\text{N}--\text{H} > \text{R}_3\text{N}--\text{H} > \text{CN} > \text{C}_{\text{sp}2}\text{NH}_2 > \text{C}--\text{N}--\text{S}
\]

- Halogen subclass

\[
\text{F}^- > \text{C}--\text{F} > \text{Cl}^- > \text{Br}^- > \text{I}^-
\]

- These trends are highly dependent on acceptor/donor pairings

Other interesting characteristics

■ Cooperativity

\[
\begin{align*}
\delta^- \delta^+ & \quad \rightarrow \quad \delta^- \delta^+ \delta^- \\
X-H & \quad \rightarrow \quad X-H-\delta^- A \quad \rightarrow \quad Y-H-\delta^- X-H
\end{align*}
\]

- Charges flow through the X–H sigma bonds. The net result is an overall strengthening of both sigma bonds by \( \sim 20\% \)
- This effect drives the clustering of polar groups (e.g. carbohydrates)
- Anticooperativity

■ Donor directionality

- the main feature distinguishing a H bond from van der Waals interaction is its preference for linearity
- degree of directionality depends on polarity of donor, \( O-H>C=H>C=CCH_2>CH_3 \)

■ Acceptor directionality

- for strong hydrogen bonds, the direction is the same as if a hypothetical proton transfer reaction occurred

- rule of thumb: the electron density on oxygen and nitrogen are diffuse enough that linear geometries are favored

■ Mixed strong/weak interactions

- difficult to assess structural importance

**The CH – II interaction – a weak hydrogen bond**

- **Intermolecular properties**

  Stabilized 2–4 kcal/mol

  acceptor substituent effects: Cl < D < CD₃ < p’(CD₃)₂ < o’(CD₃)₂ < (CD₃)₆ for C₆H₆-nXn/CHCl₃

  donor substituent effects: NO₂ < Br < Cl < H < Me < NH₂ for C₆H₆/CH₃C₆H₄Y

- **Intramolecular properties**

  n = 1,2 in most cases

  acceptor substituent effects: NO₂ < Br < Cl < H ~ Et < Me < NH₂

  donor substituent effects: CO, NMe, O, for C₆H₅CH₂XCHMe₂

- **Reactivity effects**


  - Remote functionalization reactions, diastereofacial and enantiofacial selectivity are all possible

The low barrier hydrogen bond in enzymes

■ General characteristics
  - basically the same as a strong hydrogen bond
  - enzymes modulate the pKa of a substrate to match that of the amino acid residue to which it is bonded

■ Chymotrypsin, a serine protease, and its weak hydrogen/LBHB catalytic cycle

"Long before round bottom flasks, enzymes roamed the earth"

- Hydrogen bonded scaffold acts as catalytic site for protease activity

- compounds 1–3 each contain low barrier hydrogen bond.
- electron flow model theory
- LBHB theory
- Alzheimer β-secretase/HIV

An example of enzyme mimicry—chemists are learning how to use H bonds

- A porphyrin-esque approach towards H₂O₂ activation

![Chemical reaction diagram]

H bonded intermediate
proton coupled electron transfer

- Control experiments indicate complex greatly increases rate of epoxidation
- Did not completely rule out any free radical degradation pathways

A non-heme example of \( O_2 \) activation

- The first reported example of an iron complex activation of molecular oxygen

1) KH (4 eq.)
   DMA, Ar, RT
2) KH (3 eq.)
   DMA, Ar, RT
3) Fe(OAc)\(_2\)
   DMA, Ar, RT
4) \( O_2 \) (0.5 eq.)
5) \( H_2O \), RT

- Homolysis of the \( O_2 \) bond creates the high spin Fe-oxo species
- Produces a crystallizable-stable oxygen radical species, stabilized by hydrogen bonding
- Compare this to similar cytochrome p450 species that oxidize C-H bonds via similar intermediates

Hine and co-workers develop the first hydrogen bond activated reaction

The initial idea was based on stable hydrogen bonded crystal structures

- The aryl groups of both donor and acceptor are planar.
- A comparison of 1,8 biphenylenediol (pKa = 8.01) to m-nitrophenol (pKa = 8.36) indicated the diol bound 50 x's stronger.

Rate studies provide convincing proof of a stable hydrogen bond catalyst

- The only yield reaction was set-up using 57 mol% catalyst and provided the product, after 15 days at 35 °C, in 86% yield.

<table>
<thead>
<tr>
<th>catalyst</th>
<th>10^5k, M^-2s^-1</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenol</td>
<td>6.0</td>
<td>9.99</td>
</tr>
<tr>
<td>p-Cl-phenol</td>
<td>7.7</td>
<td>9.41</td>
</tr>
<tr>
<td>m-Cl-phenol</td>
<td>8.2</td>
<td>9.12</td>
</tr>
<tr>
<td>m-nitrophenol</td>
<td>14.3</td>
<td>8.36</td>
</tr>
<tr>
<td>p-cyanophenol</td>
<td>15.3</td>
<td>7.97</td>
</tr>
<tr>
<td>p-nitrophenol</td>
<td>17.0</td>
<td>7.15</td>
</tr>
<tr>
<td>catechol</td>
<td>11.9</td>
<td>9.36</td>
</tr>
<tr>
<td>1-biphenylenol</td>
<td>11.5</td>
<td>8.64</td>
</tr>
<tr>
<td>8-methoxy-1-biphenylenol</td>
<td>7.3</td>
<td>9.15</td>
</tr>
<tr>
<td>1,8-biphenylenediol</td>
<td>75</td>
<td>8.01</td>
</tr>
</tbody>
</table>

- used 3.75 eq. catalyst

Application of Hine's discovery

- Kelly catalyzes the Diels Alder reaction

- Other dienes: 2,3-dimethylbutadiene, 1-methoxybutadiene
- Other dienophiles: acrolein, 2-methylacrolein, 3-methylacrolein, 3-phenyl acrolein, methylacrylate
- Esters and methoxydienes work poorly.

- The methoxy substituent competes with aldehydes for H bonding

**Another conceptual step leads to a hydrogen bonding framework**

- A purely crystallographic analysis of urea scaffold/carbonyl structures

![Chemical structure](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>NO₂</td>
<td>H</td>
</tr>
<tr>
<td>CF₃</td>
<td>CF₃</td>
<td>H</td>
</tr>
<tr>
<td>NO₂</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>NO₂</td>
<td>H</td>
<td>NO₂</td>
</tr>
</tbody>
</table>

- Finds that ortho EWG's have most prominent effect and may induce aryl–H/CO bonding.


- A set of rules for predicting H-bond in various molecules is proposed

  Some more interesting facets:
  - Six membered intramolecular H bond structures are preferred over intermolecular bonding.
  - After six membered ring bonding, the remaining H donating/accepting groups interact.
  - 2-aminopyrimidine as an illustrative example.

![Diagram](image)

**Proton accepting ability**

N1 > N2 > acid carbonyl > N3 = N4

**Proton donating ability**

OH (acid) > Ha > Hb > Hc

Two mechanistically different reactions, same H bond manifold

- Free radical allylation

\[ \text{Free radical allylation} \]

\[ \text{AIBN, benzene, 55 °C, 24 h} \]

\[ \text{top face shielded} \]

\[ \text{eq. 1 trans/cis yield} \]
\[ 0.25 \ 7.1:1 \ 70 \]
\[ 0.5 \ 11.3:1 \ 72 \]
\[ 1.0 \ 14.1:1 \ 72 \]


- Kinetic studies indicate H bonding accelerates the Claisen rearrangement

\[ \text{Kinetic studies indicate H bonding accelerates the Claisen rearrangement} \]

\[ \text{benzene, 80 °C} \]

\[ \text{E:Z = 2.6:1} \]

\[ \text{catalyst eq. k_{rel}} \]
\[ 1 \ 0 \ 1 \]
\[ 1 \ 0.1 \ 2.7 \]
\[ 1 \ 0.4 \ 5.0 \]
\[ 1 \ 1.0 \ 22.4 \]
\[ \text{thiourea} \ 1.0 \ 3.4 \]
\[ \text{DMSO} \ 5 \text{ eq.} \ 1.9 \]
\[ \text{DMSO + 1} \ 5 \text{eq, 1eq} \ 1.3 \]

Curran, D. P.; Kuo, L. H. *Tet. Lett.* 1995, 36, 6647
Jacobsen develops the most efficient and broadly used scaffold to date

Parallel library generated catalysts to effect the Strecker reaction were screened to provide the thiourea scaffold.

- Jacobsen, "a sequence of nonobvious modifications in the catalyst structure."

The original goal of the catalyst screen was to incorporate metal binding sites on the scaffold.

- Jacobsen, "a sequence of nonobvious modifications in the catalyst structure."

<table>
<thead>
<tr>
<th>R</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>78</td>
<td>91</td>
</tr>
<tr>
<td>p-OCH₃C₆H₄</td>
<td>92</td>
<td>70</td>
</tr>
<tr>
<td>p-BrC₆H₄</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>t-butyl</td>
<td>70</td>
<td>85</td>
</tr>
<tr>
<td>c-hexyl</td>
<td>77</td>
<td>83</td>
</tr>
</tbody>
</table>

Origins of selectivity in the catalyzed Strecker reaction

- NMR solution structure and MOLMOL modelling lead to a set of selection rules

- Determined that only the Z-isomer binds the catalyst and is bridged by the urea nitrogens.
- Large groups are directed into solvent.
- The small group is placed directly into the catalyst.
- The N-substituent is directed away from the catalyst.

Jacobsen extends this technology towards other transformations

- Synthesis of B-aryl, B-amino acids via asymmetric Mannich reactions

1) 

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{N} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{N} & \quad \text{S} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
t-\text{Bu} & \\
\end{align*}
\]

(5 mol%)

- Tolerates a wide range of aryl groups, no aliphatic examples.
- Currently the mechanism is not well understood


- Nitro-Mannich reaction

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
\text{R}^1 & \quad \text{NO}_2 \\
\end{align*}
\]

1 eq. 5 eq.

- Only aryl aldimines are used for the transformation
- Suspect the catalysts may activate BOTH reactants.

Other carbon-carbon bond forming reactions catalyzed by the thiourea scaffold

- Takemoto develops the Michael reaction of malonates and nitroolefins

\[
\text{F}_3\text{C}-\text{N} = \text{S}-\text{NMe}_2 (0.1 \text{ eq})
\]

\[
\text{EtO}_2\text{C} - \text{CO}_2\text{Et} (2 \text{ eq.})
\]

toluene, rt, 24 h

- aromatic olefins give the best yields and ee in most cases.
- aliphatic olefins give decent yields but lower ee. (81% ee in both examples)


- Another variant of the Mannich reaction

\[
\text{Ar} = \text{P(0)Ph}_2 (0.1 \text{ eq.}) \text{ catalyst above RCH}_2\text{NO}_2 (10 \text{ eq.)}
\]

\[
\text{CH}_2\text{Cl}_2, \text{ rt}
\]

yields ranged from 57–87% ee's ranged 63–76% ee

**One well known and one not-so-well-known H bond reaction**

- Rawal's TADDOL catalyzed Diels Alder cycloaddition

- Preparation of imines


- Only rate of catalyst acceleration was probed.

Chiral Bronsted Acid Catalysis

Mannich type reaction

- Only aromatic aldimes are used
- All the yields were high, as was syn/anti selectivity.
- ee's ranged from 81% – 96%

Morita-Baylis-Hillman reaction

R = aliphatic, 82 – 96% ee
R = conjugated, 67, 81% ee
low yields


Schaus, S. E.; McDougal, N. T. J. Am. Chem. Soc. 2003, 125, 12094.
Chiral Bronsted Acid Catalysis

- Aza Henry reaction

Conclusions

- The hydrogen bond is a fascinating molecule whose theory of interaction needs further development

- A well of chemical reactivity is filled with possibilities

- Theory is not as important as practice

- May be able to exploit a wide range of interactions to develop an asymmetric, catalytic system