Hydrogen-Bond Donor: Urea/Thiourea

Who discovered hydrogen bond??

Literature Seminar
Haruka Ida
2012.12.17 (Mon.)
Contents

1. Introduction
   Hydrogen bond
   Organocatalyst
   Urea/Thiourea

2. Organocatalysis
   Pioneering Studies
   Recognizing Carbonyl
       Nitro Group
       Sulfonate
       Hydrogen Cyanide

3. Material
4. Bioactive compound
5. Summary
1. **Introduction**
   - Hydrogen bond
   - Organocatalyst
   - Urea/Thiourea

2. **Organocatalysis**
   - Pioneering Studies
   - Recognizing Carbonyl
     - Nitro Group
     - Sulfonate
     - Hydrogen Cyanide

3. **Material**
4. **Bioactive compound**
5. **Summary**
About Hydrogen bond (H-bond)

Who discovered H-bond??
-- T. S. Moore and T. F. Winmill
‘The state of amines in aqueous solution’
H-bond has the 100-year history.

The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule in which there is evidence of bond formation.


Properties of H-bond.

<table>
<thead>
<tr>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
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<tbody>
<tr>
<td>type of bonding</td>
<td>mostly covalent</td>
<td>mostly electrostatic</td>
</tr>
<tr>
<td>length of H-bond [Å]</td>
<td>1.2–1.5</td>
<td>1.5–2.2</td>
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<tr>
<td>bond angles [°]</td>
<td>175–180</td>
<td>130–180</td>
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<td>bond energy [kcal mol⁻¹]</td>
<td>14–40</td>
<td>4–15</td>
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<td>typical example</td>
<td>intramolecular NH–N bond in conjugate acid of proton sponge</td>
<td>NH⋯O=O bonds in peptide helices and sheets</td>
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</table>

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**H-bond in Nature**

**1. Introduction**

**CIC chloride channel**

- Chloride ion
  - regulates membrane potentials.
  - is stabilized by electrostatic interactions with $\alpha$-helix dipoles and by chemical coordination with amino and hydroxyl groups.

**serine protease**

- A class of enzymes characterized by a uniquely reactive serine side chain cleaving peptide bonds in proteins.
- Stabilizing the oxyanion.

Organocatalyst

- Consist of elements like carbon, hydrogen, oxygen, nitrogen, sulfur and so on, not including any metal.
- Have low molecular weight.
- Possess the function catalyst.

Advantages:
- The reactions can be performed under an aerobic atmosphere with wet solvents. (Organocatalysts are often more stable than enzymes or metal catalysts.)
- The catalysts are inexpensive.
- They can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry.
Representative H-bond donor catalysts.

1. Introduction

About Urea/Thiourea 1

pKa

Electronegativity: O > S
Tendency to dimerize: Urea > Thiourea

pK_a: Urea > Thiourea

Turnover frequency (TOF): Urea < Thiourea


cf. Phenol: 9.95

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<tr>
<td>S</td>
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</table>

(in DMSO)
1. Introduction

About Urea/Thiourea 2
Conformational Preference of \(N,N'-\text{diarylurea}\)

\[
N,N'-\text{diphenyl urea}
\]

\[
N,N'-\text{diaryl-}N,N'-\text{dimethyl urea}
\]

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**Pioneering Study of Activation of Electrophile Using H-Bond --Hine**

Biphenylenediol-Promoted Epoxide-Opening Reaction

Fig. ORTEP drawing displaying the labeling scheme and bond distances (Å) for the 1,8-biphenylenediol-1,2,6-trimethyl-4-pyridone complex with non-hydrogen atoms drawn at the 50% probability level and hydrogen atoms drawn with an artificial radius. The estimated standard deviations on the bond distances are 0.003-0.004 Å.


1,8-biphenylenediol has two H-bond donor and make oxygen atom negative effectively.

Early Example of the Reaction with Recognition of Carbonyl group --Kelly
Diels-Alder Reaction: Rate Acceleration Promoted By A Biphenylenediol

\[
\text{Diene} + \text{Dieneophile} \xrightarrow{\text{S (4 mol\%)} \text{ CD}_2\text{Cl}_2 (0.11 \text{ or } 0.14 \text{ M})} \text{Adduct}
\]

Roles of acids in Diels-Alder Reaction
• Lower LUMO of dienophile and improve the regioselectivity.

Characteristics of 8
• Superior to acidic monodentate H-bond donor (such as p-nitrophenol, 4-nitro-3-(trifluoromethyl)phenol).

The energy barrier with 4 was smaller than that without 4 by 2 kcal/mol.


**Fig.** The Diels–Alder reaction of 1 and 2 uncatalyzed and catalyzed by 4. The energies at the B3LYP/6-31+G**//AM1 level relative to the starting materials are given in kcal/mol (the SCRF-energies are in parentheses, NBO-charges in italics). Some of the hydrogens were removed for clarity.
Activation and Cyanation of Carbonyl 1

Optimized Catalyst and Equilibrium

Equilibrium in ketone cyanosilylation.

Activation and Cyanation of Carbonyl 2

Relationship between Reaction Rate and Concentration of HCN

Fig. Rate dependence on [HCN].
Plot of the rate of cyanosilylation of 6b ([6b]i = 0.33 M) with TMSCN ([TMSCN]i = 0.50 M) catalyzed by HCN and 1a (0.025 M) at different [HCN] and at different conversions of 6b.

- Without HCN → No reaction.
- 15 mol% HCN → Sufficient to effect >90% substrate conversion.
- High [HCN] → Rate inhibition.

The reaction rate displays a less than first-order dependence on [1a] at elevated catalyst concentrations.

*(First-order dependence on [6])*

**Activation and Cyanation of Carbonyl 4**

**Possible Transition States**

Mechanism A was more favorable than B (4.7 kcal/mol).

**Mechanism B:**
- Lower nucleophilicity of cyanide anion.
- Smaller activation of carbonyl with mono H-bond.

(Thiourea recognize carbonyl.)

(Thiourea recognize cyanide.)

Conclusive factor of the enantioselectivity:
Repulsive interactions between the amide π-system and the substrate π-system.

Sharp decreases in enantioselectivity were observed when using electrondeficient acetophenone derivatives.

Recognition of Nitro Group 1
Biomimetic Reduction of Conjugated Nitroalkenes

They were inspired by NADH system. Nicotinamide adenine dinucleotide (NADH) is a coenzyme to reduce unsaturated functionalities under very mild conditions.

Hantzsch esters

Recognition of Nitro Group – Michael Reaction 2-1

Substrate Scope

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<tr>
<th>entry</th>
<th>3</th>
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<th>R²</th>
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<th>yield (%)</th>
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<td>Ph</td>
<td>48</td>
<td>trace</td>
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</table>

Large R¹ decreased reactivity.

Low ee.

These cannot form the six-membered TS.

Construct quaternary carbon center.

Recognition of Nitro Group – Michael Reaction 2-2

Mechanistic Studies

1H-NMR investigation:

H\textsubscript{a}: 6.63 to 6.67 ppm
H\textsubscript{b}: 7.31 to 7.35 ppm

Kinetic study:
The reaction is first-order in catalyst (1e), nitrostyrene (2a) and maronate (3a).

Transition-state models of Michael reactions of malonate.

B is favorable to C due to the steric hinderance.

Recognition of Sulfonate–Povarov Reaction 1

Structure-Reactivity/Enantioselectivity Studies

- Urea derivative showed better enantio- and diastereoselectivity than thiourea (catalyst 1a vs. 1b).
- The position of sulfonic amide O was important (1a vs. 1c).
- Phosphininc amide urea, pivalamide urea and amino urea induced both low reactivity and selectivity (1a vs. 1d, 1e and 1f).

Recognition of Sulfonate–Povarov Reaction 2

Geometry and energy-minimized structures

B: All four intermediates (I to IV) were expected to be energetically accessible. But nucleophile added, I’ was predicted to have over 1.3 kcal/mol lower energy than the other complexes. (Because of the π-π interaction (I’ vs. II’) and the room around the reactive sites (I’ vs. III’, IV’)).


Activation of Hydrogen Cyanide -- Strecker Reaction 1-1

Catalyst Optimization and Comparison Substrates

α-Amino acids are the building blocks of proteins and are widely used as components of medicinally active molecules and chiral catalysts.

\[
\begin{align*}
\text{R}^1 & = \text{Bn}, \text{R}^2 = \text{H}, \text{R}^3 = \text{Me}, \text{X} = \text{O} \\
\text{2: } \text{R}^1 & = \text{Bn}, \text{R}^2 = \text{Me}, \text{R}^3 = \text{Me}, \text{X} = \text{O} \\
\text{3: } \text{R}^1 & = \text{Bn}, \text{R}^2 = \text{Bn}, \text{R}^3 = \text{Me}, \text{X} = \text{O} \\
\text{4: } \text{R}^1 & = \text{Me}, \text{R}^2 = \text{Me}, \text{R}^3 = \text{Me}, \text{X} = \text{O} \\
\text{5: } \text{R}^1 & = \text{Me}, \text{R}^2 = \text{Me}, \text{R}^3 = \text{Ph}, \text{X} = \text{O} \\
\text{6: } \text{R}^1 & = \text{Me}, \text{R}^2 = \text{Me}, \text{R}^3 = \text{Me}, \text{X} = \text{S}
\end{align*}
\]

1 mol% catalyst, HCN, toluene, −78°C

<table>
<thead>
<tr>
<th>entry</th>
<th>(\text{R}^1)</th>
<th>(\text{R}^2)</th>
<th>(\text{R}^3)</th>
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<td>Ph</td>
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<td>97</td>
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<tr>
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<td>(n)-Pent</td>
<td>H</td>
<td>Ph</td>
<td>79</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(t)-Bu</td>
<td>Me</td>
<td>Ph</td>
<td>70</td>
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<td>Ph</td>
<td>Me</td>
<td>(p)-BrC₆H₄</td>
<td>92</td>
<td>96</td>
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<tr>
<td>5</td>
<td>(t)-Bu</td>
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<td>Ph</td>
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<td>Ph</td>
<td>H</td>
<td>Ph</td>
<td>96</td>
<td>99.3</td>
</tr>
</tbody>
</table>

The large group on the imine carbon is directed away from the catalyst and into solvent.

The $N$-substituent is also directed away from the catalyst.

!!!
HCN was absent from this condition.

Fig. Solution structure of catalyst 1 (B, C) two views of the complex generated upon binding of a Z-imine, as determined

Activation of Hydrogen Cyanide -- Strecker Reaction 2-1

Improvement in 2009 Nature

Report in 2002:
- High yield and ee
- Cryogenic temperatures
- Hazardous cyanide source
- Synthesis of the catalyst requires eight steps.

2009:
- 0 °C
- KCN/AcOH
- Three steps

**Fig.** Potassium cyanidemediated Strecker synthesis. a, Catalyst 4e (0.5 mol.%), KCN (2 equiv.), acetic acid (AcOH, 1.2 equiv.), H₂O (4 equiv.), toluene, 0 °C, 44-68 h. b, Aqueous H₂SO₄ and HCl, 120 °C, 44-68 h. c, NaOH, NaHCO₃. d, Di-tert-butyl dicarbonate (Boc₂O, 2.5-3 equiv.), dioxane, 16 h. e, Recrystallize directly from hexanes/diethyl ether or as the tert-butylamine (t-BuNH₂) salt from tetrahydrofuran/ethanol.

Activation of Hydrogen Cyanide -- Strecker Reaction 2-2
(Mechanistic Study) Via Cation or Anion ??

Figure 4. Rate dependence of imine hydrocyanation catalyzed by 4a or 4b on substrate electronic properties. Plot of the logarithm of pseudofirst-order rate constant (log(k_{obsd})) versus $\sigma_p$ for the hydrocyanation of p-substituted imines 2b-2g ([2] = 0.040 M) by TMSCN/MeOH (0.50 M) mediated by thiourea catalyst 4a ([cat]_{tot} = 0.0020 M, ●) or urea catalyst 4b ([cat]_{tot} = 0.0020 M, ▲) versus $\sigma_p$.

Hydrocyanation proceeded via cation species.

Activation of Hydrogen Cyanide -- Strecker Reaction 2-3
(Mechanistic Study) What Protonated Imine??

Activation of Hydrogen Cyanide -- Strecker Reaction 2-4
(Mechanistic Study) What Protonated Imine??

NH on urea was not exchanged to D. D was observed on nitrogen in TM.

Urea didn't protonate imine, i.e., to give TM, the interaction between the urea and the substrate was not necessary.

DCN, catalyst 7b and imine 2h

Figure Partial \(^1\)H NMR spectra of reactions depicted in eq 3 after 25 min. Data were collected at 32 °C. Under these conditions, the catalyst exists as a 5:1 mixture of amide rotamers. HCN and DCN were generated from TMSCN and MeOH or MeOD. The enantiomeric excess of the \(\alpha\)-aminonitrile isolated from these reactions is 84-85%.

Activation of Hydrogen Cyanide -- Strecker Reaction 2-5
(Mechanistic Study) Enantioselectivity-Determining Step


Scheme 8. Catalyst-Controlled, HNC-Mediated Imine Hydrocyanation
**Activation of Hydrogen Cyanide -- Strecker Reaction 2-6**

(Mechanistic Study) *Enanthioselectivity*

*Figure 13.* Calculated transition structures for HNC addition to imine 2a catalyzed by 6a. Transition structures leading to the (A) major and (B) minor enantiomer are shown.

There are no apparent “steric clashes” that might explain why some transition structures are significantly higher in energy than the one leading to *(R)*-TM with catalyst.

Why A is more stable than B??

Activation of Hydrogen Cyanide -- Strecker Reaction 2-7
(Mechanistic Study) Focus on the Distance between Catalysts and Cyanide Anion

**Figure 15.** H-bond distances between thiourea (X = S) or urea (X = O) and cyanide anion.

**Figure 16.** Correlation of transition structure bond length with enantioselectivity for HNC addition to imine 2a. Plot of the sum of the cyanide-(thio)urea H-bond lengths in B3LYP/6-31G(d) transition structures versus experimental energy difference between (R)- and (S)-transition states.

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<th>Expt. $\Delta \Delta G^\ddagger$ (kcal/mol)</th>
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</table>

**Smaller $d_1+d_2$ = More stable complex**

There was few difference of the sums ($=d_1+d_2$) between (S)-TS and (R)-TS.

$\Delta \Delta G^\ddagger = -RT \ln ([R]/[S])$

Activation of Hydrogen Cyanide -- Strecker Reaction 2-8

Structures of 6a - h
Activation of Hydrogen Cyanide -- Strecker Reaction 2-9
(Mechanistic Study) Focus on the Distance of Another Part of the Complex

Figure 17. H-bond distances between catalyst and iminium and between cyanide anion and iminium.

Figure 18. Correlation of transition structure bond length with enantioselectivity for HNC addition to imine 2a. Plot of the sum of the cyanide N-iminium H + amide O-iminium H bond lengths in B3LYP/6-31G(d) transition structures versus experimental energy difference between (R)- and (S)-transition structures.

\[ \Delta \Delta G^\ddagger = -RT \ln ([R]/[S]) \]

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**Gelation using H-bond 1**

**Structures and Gel/sol images**

Compound(s) in MCH at elevated temperature.

Cooling to rt → Gel or sol ??

**Fig. 1** Structure of the ESDA and the NDI derivatives.

**Fig. 2** Gel/sol images. Total concentration in each case = 0.3 wt%.

ESDA-1 + NDI-Py  
ESDA-2 + NDI-Py  
ESDA-1  
NDI-Py

ESDA : external structure directing agent  
NDI: naphthalene-diimide  
MCH: methylcyclohexane

Only ESDA-1 and NDI-Py mixture lead to gelation.

For gelation, both the urea core and the π-conjugated chromophore were needed.

General characteristics of fibrillar gel:
Superior abilities to transport of charge carriers.
Highly unpredictable photophysical properties.

ESDA: external structure directing agent
NDI: naphthalene-diimide
MCH: methylcyclohexane

**Gelation using H-bond 3**  
Experiment for Checking H-bond

![Image of chemical structures and FT-IR spectra](image)

Fig. Selected region of the FT-IR spectrum of (a) ESDA-1 (0.5 wt %), (b) ESDA-1 + NDI-Py gel in MCH (1 wt%).

**Frequency shift of NH and N-C=O to low energy** (right) showed H-bond.

**Gelation using H-bond 4**

**Physical Properties – Morphology**

**ESDA-1 + NDI-Py**: 
H-bonding among the urea groups and π-stacking among NDI-Py
→ the 1D assembly is too rigid to fold
→ fibrillar morphology

**ESDA-2 + NDI-Py**: 
π-stacking among NDI-Py alone
→ spherical assemblies

**Micrometer long fibers**
→ Gel

**discontinuous spheres**
→ no Gel

Fig. AFM images.


**Gelation using H-bond 5**

Physical Properties -- Photoluminescence

![Chemical structure with H-bond interactions](image)

**Fig.** Intensity normalized absorption (dashed line) and emission (solid line) spectra of gel (blue) and sol (black). Concentration of each component in gel (MCH) and sol (CHCl3) state=2.0 mM and 0.025 mM, respectively for UV/vis and PL experiments.

Gelation using H-bond 6

Physical Properties -- Electrical Conductivity ($\sigma$)

ESDA-1 + NDI-Py
\[ \sigma = 0.19 \times 10^{-4} \text{ S cm}^{-1} \]

ESDA-2 + NDI-Py
\[ \sigma = 0.2 \times 10^{-8} \text{ S cm}^{-1} \]

$$\sigma(\text{reported supramolecular polymers}) < 10^{-5} \text{ S cm}^{-1}$$
\[\sigma(\text{distilled water}) = 10^{-6} \text{ S cm}^{-1} \]
\[\sigma(\text{natural rubber}) = 10^{-5} \text{ S cm}^{-1} \]
\[\sigma(\text{gold}) = 10^{7} \text{ S cm}^{-1} \]

**Fig. 4 I-V measurement data.**

ESDA-1/NDI-Py gel had good electrical conductivity.

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Anticancer activity using H-bond 1

About Hedgehog (Hh) Signaling Pathway and Medulloblastomas

Fig. 1 Components of the Hh signal pathway and molecular sites targeted by Hh pathway inhibitors.

Anticancer activity using H-bond 2

Smo inhibitors

Isolated from *Veratrum grandiflorum* by T. Hasammune in 1964

- In clinical trials (Phase II)
- Smo mutation and the resistance was observed in mice.

M. Ruat *et al*, *Molecular Pharmacology* 2010, 78, 658.
Anticancer activity using H-bond 3

Proposed Fitting Model

4. Bioactive compound

AcTU and AcG had the same pharmacophore as the compound reported to be active as Smo inhibitor.

Fig. Compounds in two different conformational layouts (A, B) with the pharmacophoric model for Smo antagonists. HBA features are constituted by a smaller sphere accommodating the hydrogen bond acceptor group, by a directionality vector represented by an arrow, and by a larger sphere intended to allocate the hydrogen bond donor group of the target macromolecule.

HBA: hydrogen bond acceptor groups
HY: hydrophobic regions


**Scheme** Proposed H-Bonding Network for the Three Bio-isosteric Structures AcTU, AcU, and AcG towards a Putative Carboxylate Located on Smo (in Agreement with the Conformations of AcTU and AcG Shown in the previous slide).
Summary

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   - Organocatalyst
   - Urea/Thiourea
   Urea has an ability to play important roles in various areas.

2. Organocatalysis
   - Pioneering Studies
     - Recognizing Carbonyl
     - Nitro Group
     - Sulfonate
     - Hydrogen Cyanide
   Activation of substrates via oxygen atoms.
   Activation of substrates via the ion different from the substrate.
   Activation of reagents via nitrogen atoms.

3. Material
4. Bioactive compound
5. Summary
   - Urea for gel.
   - Urea for anti-cancer activity.

References
「進化を続ける有機分子触媒」化学同人 丸岡啓二 [編]
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Thank you.