A Brief Introduction to the Curtin-Hammett Principle


**Curtin–Hammett Principle**

“The product composition, $P_A$ vs $P_B$ is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies ($\Delta\Delta G^*$) of the respective transition states.”

The C-H principle may be extended to rapidly interconverting diastereomers, or constitutional isomers as well.

**Curtin–Hammett Conditions**

Chem 206, D. A. Evans
"Curtin–Hammett Conditions"

\[ k_1, k_2 \ll k_A, k_B \]  

\[ \begin{align*}  
P_A & \xrightarrow{k_1 \text{ slow}} A & \xrightarrow{k_A} B & \xrightarrow{k_B} P_B \xrightarrow{k_2 \text{ slow}} P_B \end{align*} \]  

(1)

**Case 1:** Less stable conformer leads to the major product.

If reaction rates are much slower than the rate of interconversion, \( \Delta G_{AB}^\ddagger \) is small relative to \( \Delta G_1^\ddagger \) and \( \Delta G_2^\ddagger \), then the A/B ratio is constant throughout the course of the rxn.

**Case 2:** Less stable conformer leads to the minor product.

If reaction rates are much slower than the rate of interconversion, \( \Delta G_{AB}^\ddagger \) is small relative to \( \Delta G_1^\ddagger \) and \( \Delta G_2^\ddagger \), then the A/B ratio is constant throughout the course of the rxn.

The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies \( \Delta \Delta G^\ddagger \) of the respective transition states.
Case 2: Curtin–Hammett Conditions

\( k_1, k_2 << k_A, k_B \): If the rates of reaction are much \textit{slower} than the rate of interconversion, \((\Delta G_{AB}^\ddagger\text{ is small relative to } \Delta G_1^\ddagger\text{ and } \Delta G_2^\ddagger)\), then the ratio of A to B is constant throughout the course of the reaction.

\[
\begin{align*}
P_A & \xrightleftharpoons[k_1, \text{slow}]{k_B, \text{fast}} A \quad \xrightleftharpoons{k_A, \text{fast}} B \quad \xrightleftharpoons[k_2, \text{slow}]{} \quad P_B \\
& \quad \quad \quad \quad \quad \Delta G_1^\ddagger \\
& \quad \quad \quad \quad \quad \Delta G_{AB}^\ddagger \\
& \quad \quad \quad \quad \quad \Delta G_2^\ddagger \\
& \quad \quad \quad \quad \quad \Delta G^\ddagger \\
& \quad \quad \quad \quad \quad \text{Energy} \\
& \quad \quad \quad \quad \quad \text{major} \quad \xrightarrow{\text{Rxn. Coord.}} \quad \text{minor}
\end{align*}
\]

The Derivation:

Using the rate equations \( \frac{d[P_A]}{dt} = k_1[A] \) and \( \frac{d[P_B]}{dt} = k_2[B] \) we can write:

\[
\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]}
\]

or

\[
\frac{d[P_B]}{d[P_A]} = \frac{k_2[B]}{k_1[A]} d[P_A]
\]

Since A and B are in equilibrium, we can substitute \( K_{eq} = \frac{[B]}{[A]} \)

\[
\int d[P_B] = \frac{k_2}{k_1} K_{eq} \int d[P_A] \quad \text{Integrating, we get} \quad \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq}
\]

When A and B are in rapid equilibrium, we must consider the rates of reaction of the conformers as well as the equilibrium constant when analyzing the product ratio.

To relate this quantity to \( \Delta G \) values, recall that \( \Delta G^0 = -RT \ln K_{eq} \) or \( K_{eq} = e^{-\Delta G^0/RT} \). \( k_1 = e^{-\Delta G_1^\ddagger/RT} \) and \( k_2 = e^{-\Delta G_2^\ddagger/RT} \). Substituting this into the above equation:

\[
\frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} K_{eq} = \frac{e^{-\Delta G_2^\ddagger/RT}}{e^{-\Delta G_1^\ddagger/RT}} \Rightarrow \frac{[P_B]}{[P_A]} = e^{\Delta G_2^\ddagger/RT - \Delta G_1^\ddagger/RT} \quad (4)
\]

Combining terms:

\[
\frac{[P_B]}{[P_A]} = e^{-\Delta G^\ddagger/RT} \Rightarrow \frac{[P_B]}{[P_A]} = e^{-\Delta G/RT}
\]

Where \( \Delta G^\ddagger = \Delta G_2^\ddagger + \Delta G^\ddagger - \Delta G_1^\ddagger \)

Curtin - Hammett Principle: The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

Within these limits, we can envision three scenarios:

- If both conformers react at the same rate, the product distribution will be the same as the ratio of conformers at equilibrium.

- If the major conformer is also the faster reacting conformer, the product from the major conformer should prevail, and will not reflect the equilibrium distribution.

- If the minor conformer is the faster reacting conformer, the product ratio will depend on all three variables in eq (2), and the observed product distribution will not reflect the equilibrium distribution.

This derivation implies that you could potentially isolate a product which is derived from a conformer that you can’t even observe in the ground state!
"Non-Equilibrating Conformers"

If the rates of reaction are faster than the rate of interconversion, A and B cannot equilibrate during the course of the reaction, and the product distribution ($P_B/P_A$) will simply reflect the initial equilibrium composition.

\[
\frac{[P_B]}{[P_A]} = \frac{[B]_o}{[A]_o}
\]

The rates of protonation are much faster than the rates of conformation interconversion.

Introduction

Two new classes of potent nonnucleoside reverse transcriptase inhibitors were recently reported by the Merck Research Laboratories: the 3,4-dihydroquinazolin-2(1H)-ones and the 1,4-dihydro-2H-3,1-benzoazin-2-ones. Efforts to enhance the clinical utility of these inhibitor classes by deriving compounds that express both high levels of antiviral activity and augmented pharmacokinetic profiles led to one promising compound from each class—L-738,372 and DMP-266. DMP-266 was ultimately chosen for clinical evaluation and has shown excellent preliminary results for the treatment of HIV when used in combination with indinavir. The potential importance of

A Dramatic case from Merck

JACS 1998, 120, 2028-2038
Tropane alkylation is a well-known example.

The less stable conformer reacts much faster than the more stable conformer, resulting in an unexpected major product!

JOC 1974 319

Enantioselective Lithiation:

Because sparteine is chiral, these two complexes are diastereomeric and have different properties.

Enantioselectivities are the same, regardless of whether or not the starting material is chiral, even at low temperatures. Further, reaction in the absence of (-)-sparteine results in racemic product.

Note that the two alkyl lithium complexes MUST be in equilibrium, as the enantioselectivity is the same over the course of the reaction. If they were not equilibrating, the enantioselectivity should be higher at lower conversions.

This is a case of Dynamic Kinetic Resolution: Two enantiomeric alkyl lithium complexes are equilibrating during the course of a reaction with an electrophile.


Oxidation of piperidines:

When the equilibrium constant is known, the Curtin-Hammett derivation can be used to calculate the relative rates of reaction of the two conformers. Substituting the above data into \[ \frac{[P_B]}{[P_A]} = \frac{k_2}{k_1} \], the ratio \( k_2/k_1 \sim 2 \).

Note that in this case, the more stable conformer is also the faster reacting conformer!

Tet. 1972 573
Tet. 1977 915
The asymmetric hydrogenation of prochiral olefins catalyzed by Rhodium is an important catalytic process.

Enantioselectivities are generally very high when the ligand is a chelating diphosphine. (ee's are given for S,S-CHIRAPHOS)

When a chiral ligand is used, there are two diastereomeric complexes which may be formed:

- **Minor complex** 1
  - $\text{MeO}_2\text{C} \text{NHAc}$
  - $\text{H}_2$ \text{fast}
  - $\text{MeO}_2\text{C} \text{NHAc}$

- **Major complex** 2
  - $\text{MeO}_2\text{C} \text{NHAc}$
  - $\text{H}_2$ \text{slow}

**Observed product**

**Observations:**
- Complex 2 is the only diastereomer observed for the catalyst-substrate complex (1H-NMR, X-Ray crystallography) in the absence of hydrogen
- The enantioselectivity is strongly dependent on the pressure of $\text{H}_2$, and degrades rapidly at higher hydrogen pressures
- The observed enantiomer is exclusively derived from the minor complex 2

*These observations may be explained using the Curtin - Hammett Principle*

The Curtin-Hammett treatment can be extended to ANY case where different products are formed from two rapidly interconverting starting materials, whether they are conformers, tautomers or isomers.

\[
\begin{align*}
\text{PA}_{\text{major}} & \quad \text{k}_1 \quad \text{A} \quad \text{k}_2 \quad \text{PB}_{\text{minor}} \\
\text{k}_a & \quad \text{k}_b
\end{align*}
\]

Stannylene ketals provide an efficient way to acylate the more hindered site of 1,2-diols.

\[
\begin{align*}
\text{Ph} & \quad \text{OCONAr} \\
\text{O} & \quad \text{SnBu}_2\text{Cl} \\
\end{align*}
\]

"It was pointed out by Professor L. P. Hammett in 1950 (private communication) that ..."

David Y. Curtin, 1954

"Because Curtin is very generous in attributing credit, this is sometimes referred to as the Curtin-Hammett principle rather than the Curtin principle."

Louis Plack Hammett, 1970

**Curtin - Hammett Principle:** The product composition is not solely dependent on relative proportions of the conformational isomers in the substrate; it is controlled by the difference in standard Gibbs energies of the respective transition states.

**THE TAKE-HOME LESSON:**

Never assume that the most stable conformation of a compound is the most reactive. It may be, but then again, it may not.