Electron Transfer Catalyzed Cycloadditons Promoted by Radical Cation Salts

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Electron Transfer

- Electron Transfer - Transfer of an electron from one molecular entity to another, or between two localized sites in the same molecular entity.

\[
\text{D} \quad \text{A} \quad \rightarrow \quad \begin{bmatrix} \text{D} \uparrow \end{bmatrix}^+ \quad \begin{bmatrix} \text{A} \end{bmatrix}^- \\
\text{HOMO} \quad \text{LUMO} \quad \text{SOMO} \quad \text{SOMO}
\]
Examples of ET Reactions

- Formation of Grignard reagents
- Barbier coupling
- Sandmeyer reaction
- Birch reduction
- $S_{N2}$
- $S_{RN1}$
Radical Cations

- Are electron deficient
- Very acidic
- Formed by removing an electron from a compound (usually from a pi system)
Promotion of an Organic Radical Cation

- Electrochemically (anode)
- PET – Photoinduced Electron Transfer
- With metals i.e. Fe$^{3+}$ Ce$^{4+}$ Cu$^{2+}$
- Radical cation salts
Radical Cation Salt

- Tris(p-bromophenyl)aminium hexachloroantimononate (aka magic blue, aminium salt)
- 25 $/gram from Aldrich
- Acts as an oxidizer

![Chemical structure of tris(p-bromophenyl)aminium hexachloroantimononate](image)
m+n Terminology

- In [m+n], m and n are the number of electrons contributed by each reacting partner - NOT the number of atoms

\[
\begin{array}{c|c|c}
\text{# atoms} & \text{# e}^- & \text{reaction} \\
4 & 4 & 4+2 \\
2 & 2 & 4+2 \\
3 & 4 & 4+2 \\
2 & 2 & 4+2 \\
2 & 2 & 2+2 \\
2 & 2 & 2+2 \\
\end{array}
\]

\[
\begin{array}{c|c|c}
\text{# atoms} & \text{# e}^- & \text{reaction} \\
4 & 4 & 4+1 \\
2 & 1 & 2+1 \\
\end{array}
\]

Redox Potential

- The lower the redox potential, the easier to oxidize to a radical cation.

Redox potentials and ease of forming radical cations:

1. **OMe**
   - Redox potential: 0.53 V

2. **OMe**
   - Redox potential: 0.85 V

3. **OMe**
   - Redox potential: 1.08 V

Rank of ease of forming radical cations:
1. **OMe**
2. **OMe**
3. **OMe**
Electron Transfer Catalysis (ETC)

• Involves reactions where the initial and final states are at the same oxidation level, and the intervening steps take place at an oxidation level one step above (or below)

Applications to Ring-Forming Reactions

ETC cycloadditions all believed to have activation barriers of 1-5 kcal/mol, often 10-60 kcal/mol lower than corresponding neutral cycloadditions.

An Accidental Discovery

![Chemical Reaction Diagram](image)

Wehrmann, *Montash. Chem.* 95, 1007 (1964)
MO picture

anode/oxidant

---

\[
\begin{align*}
\text{[Chemical Structure]} & \rightarrow \text{[Chemical Structure]} \\
\text{[Chemical Structure]} & \rightarrow \text{[Chemical Structure]}
\end{align*}
\]

Correlation diagram of 2+1

\[ \text{Correlation diagram of } 2+1 \]
Concerted or Stepwise Pathway

cannot be concerted and synchronous

can be concerted, highly asynchronous stereospecific

can be stepwise not stereospecific
Stereospecific Cyclobutanation

\[
\text{MeO-} \begin{array}{c} \text{Me} \\
\text{MeO-} \end{array} \xrightarrow{\text{Ar}_3\text{N}^{+^+}} \begin{array}{c} \text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

\[
\text{CH}_2\text{Cl}_2 \quad -35 \degree \text{C}
\]

\[
\begin{array}{c} \text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} \quad \begin{array}{c} \text{Ar} \\
\text{Ar} \\
\text{Ar} \\
\text{Ar} \\
\end{array}
\]

\[
\text{anti} \\
\text{13:12}
\]

\[
\begin{array}{c} \text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array} \quad \begin{array}{c} \text{Ar} \\
\text{Ar} \\
\text{Ar} \\
\text{Ar} \\
\end{array}
\]

\[
\text{syn}
\]

Stepwise Cyclobutatanation

\[ \text{D} \rightarrow \text{Fe}^3 \rightarrow \text{A} : \text{B} = 4:1 \]

Aryl not as good a donor as amino - the longer lifetime of the amino intermediate allows for bond rotation.
Radical Cation Cyclobutanation

- Not concerted, synchronous
- Many examples are stepwise
- Others may be concerted, asynchronous
- No electron poor olefins known to undergo reaction
Diels-Alder type reactions

\[
\text{Ar}_3\text{N}^+ \xrightarrow{\text{Ar}_3\text{N}} \text{Ar}_3\text{N}
\]

\[
\text{[\text{cyclohexadiene}]}^{\ddagger} \xrightarrow{3\text{e}^-} \text{[\text{cyclohexadiene}]}
\]

\[
\text{[\text{cyclohexadiene}]^{\ddagger}} \xrightarrow{2\text{e}^-} \text{[\text{cyclohexadiene}]}
\]

\[
\text{[\text{cyclohexadiene}]^{\ddagger}} \xrightarrow{1\text{e}^-} \text{[\text{cyclohexadiene}]}
\]
An Early ET Diels-Alder Theory

Woodward, R.B. J. Am. Chem. Soc., 1942, 64, 3058
Another Accidental Discovery

Comparison to Thermal

Sterically Encumbered Dieneophile

Chemoselectivity

Why does the more substituted olefin participate in the Diels-Alder?

Positive Charge Densities are Key

Larger positive charge density indicates reacting olefin

Positive Charge Densities are Key

terminal alkyl groups bring positive charge to the carbon on which it is attached

EXAMPLE: bis alkylated and mono alkylated termini

Radical Cation, or Acid Catalyzed?

If acid is present, is the reaction acid catalyzed?

Acid Catalyzed Pathway

Proof of Acid Catalysis

Are other radical cation salt Diels-Alder products actually just acid catalyzed? Do ETC reactions even exist?

Gassman Revisits Bauld’s Results

\[
\text{HBr trace}
\]

Bauld’s response

• Bauld redid every experiment, adding hindered base to quench any acid
• For every instance except for one, base did little to hinder the reaction, meaning a radical cation Diels-Alder type mechanism was operating
• The only acid catalyzed reaction happened to be chosen by Gassman
• Suggested that in the future, all experiments with radical cation salts should be run in presence of base as a control

An example

Identical yields, therefore, not acid catalyzed
Intramolecular ETC DA


conditions: $\text{Ar}_3\text{N, CH}_2\text{Cl}_2, 0^\circ\text{C, 1 m}$
Expanding the Scope to Allenes

Expanding the Scope to Ketenes

Synthetic Utility - a Formal Synthesis

Stereospecific ETC Diels-Alder

SOMOs have matched symmetry elements therefore 4+1 is a symmetry allowed reaction

SOMOs do not have matching symmetry elements therefore 3+2 is a symmetry forbidden reaction
Assumption:
Allowed pericyclic pathways are lower in energy than corresponding stepwise paths.
First Suggestion of a 3+2

\[
\begin{align*}
\text{Mlcoch, J.; Steckhan, E.} & \quad \text{Tetrahedron Lett.} \quad 1987, \quad 28, \quad 1081 \\
\end{align*}
\]
Could it be Double Electron Transfer?
Proof of 3+2

If D is only product, a 3+2. If E and D are formed, a 4+1 is at play.

Proof of 3+2

- It shouldn’t have been a shock, seeing as how “forbidden” 2+1 reactions took place
- 3+2 is symmetry forbidden by Woodward-Hoffman rules, so cannot be concerted and synchronous
- Most likely is stepwise

\[
\begin{align*}
\text{\(=\)} & \rightarrow \text{\(+\text{\(=\)\)}} \rightarrow \text{\(=\)} \rightarrow \text{\(=\)}
\end{align*}
\]
Radical cation as diene or dieneophile?

"diene" + "dieneophile" → 3+2 4+1
Dissimilar 3+2 and 4+1 Adducts

When both 4+1 and 3+2 pathways are possible, a 4+1 does not necessarily dominate.

A 3+2 can be lower in energy than a 4+1.
Similar 4+1 and 3+2 Adducts

Me
Me
Me
Me
Me
Me
Ar₃N

Why Would a 3+2 Happen When a 4+1 Could?

SOMO MO diagrams have increased complexity – simple symmetry analysis not necessarily correct

4+1 vs. 3+2

- **4+1**
  - Can be concerted
  - Due to SOMO interactions, can be disfavored
  - Requires diene and dieneophile to be identical OR the dieneophile to have a lower redox potential

- **3+2**
  - Stepwise
When Diels-Alder and when cyclobutanation?
More electron rich olefins yield cyclobutane products

Diene Conformation

red olefins have high degree of \( s\text{-}cis \) character

\( \text{MeO} \)
\( \text{Me} \)
\( \text{Me} \)

\( s\text{-}cis \) dienes favor Diels-Alder products

Yang, J.; Bauld, N.L. *Org. Lett.* **1999**, *1*, 1773
Vinylcyclobutane (VCB) rearrangement
PET Induced Vinylcyclobutane Rearrangement

Alternatives
Multiple Potential Pathways to DA

4+1

Ar₃N⁺

2+1

retro 2+2
Could all ETC Diels-Alder products be from VCB rearrangements?

Bauld, Tetrahedron, 1987, 45, 5307
Rearrangement is Stereospecific

Bauld, *Tetrahedron*, 1987, 45, 5307
Intramolecular Shift

1,3 suprafacial are Woodward-Hoffman forbidden

Quenching vs. Rearrangement

Bauld, *Tetrahedron*, 1987, 45, 5307
VCB Rearrangement to DA Product

$\text{Ar}_3\text{N}^+$

-10 °C, 10 m

$\text{Me}$

$\text{OMe}$

$\text{Me}$

$\text{H}$

$\text{Ar}$

$\text{H}$

$\text{Me}$

$\text{Ar}$

1:1

35%

$\text{CH}_2\text{Cl}_2$

Three Pathways
Computational Chemistry

DA Conclusions

- Diels-Alder products can be formed through several pathways
  - 4+1 concerted
  - 3+2 stepwise
  - Vinylcyclobutane rearrangement
Overall Conclusions

- Formal 2+2 and 4+2 products can be made via ETC
- ETC cycloadditions allow access to Diels-Alder and Cyclobutanation products under milder conditions
- Multiple pathways possible due to flat energy surface
- ETC cycloadditions are under explored by synthetic organic chemists
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