Photoinduced Electron Transfer: Strategies for Organic Synthesis

$$D^* + \text{Acc} = D^- + \text{Acc}^+$$

MacMillan Group Meeting
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The First Understandings of Photochemistry

- Priestley was the first to discover photosynthesis, albeit fortuitously

\[
\text{H}_2\text{O} + \text{CO}_2 \xrightarrow{h\nu} \text{O}_2 + \text{C}_6\text{H}_12\text{O}_6
\]

Discovered accidentally while Priestly was studying the “influence of light in the production of ‘dephlogisticated air’ [O\textsubscript{2}] in water by Means of a ‘green substance’.”


- Ingenhousz developed photosynthesis more rigorously

Ingenhousz, along with Saussure, established the requirement of light in macroscopic photosynthesis.

But, despite work by Liebig, Baeyer and Willstatter, electron transfer remained unsolved until the 20th century when J. J. Thompson (1897) and Milikan (1913) convinced the community of the presence of the electron.

Jan Ingenhousz, 1730 - 1799
Dutch chemist, physicist and physician

Joseph Priestley, 1733 - 1804
British chemist
**Electron Transfer and Actinometry**

- Dobereiner foreshadowed photo-redox chemistry with actinometry

\[
\text{Fe}_2\text{O}_3 + \text{Fe}^{3+} + \text{O}^2- + \text{CO}_2^2 \rightarrow \text{FeO} + \text{CO}_2 + \text{CO}_2
\]

Designed the first actinometer that measures the power of electromagnetic radiation

- The place and usefulness of actinometry was fiercely debated and no other photo-redox chemistry was studied in-depth in the 19th century

- Furthermore, prior to the advent of NMR, ESR, and CIDNP the presence of ionic radicals remained highly speculative and their identity often erroneously presumed.

- 20th Century PET contributions were made by Bauer and Weiss. The latter enunciated the basic form of modern PET theory:

  \[
  \text{D}^* + \text{Acc} \rightarrow \text{D}^- + \text{Acc}^+
  \]

  “Fluorescence quenching in solution can be considered as a simple electron transfer process.”

**Photoinduced Electron Transfer: A Representative Mechanism**

- Understanding α-amino radical formation is important for utilizing its reactivity.

\[ \text{1 or } 3 \text{ Sens} \xrightarrow{hv} \text{1 or } 3 \text{ Sens}^* \]

\[ \text{1 or } 3 \text{ Sens}^* + \text{R-N} \xrightarrow{} \text{1 or } 3 \text{ Sens}^- + \text{R-N} \]

\[ \text{Nu} + \text{R-N} \xrightarrow{} \text{Nu-}E + \text{R-N} \]

Further chemistry
**Basics of Photoinduced Electron Transfer**

1. **More efficient as distance decreases**

   \[ {^1}\text{Sens} + A \rightarrow {^1}\text{Sens}^+ + A^- \]

2. **Efficiency dependent on redox potential**

   \[ {^1}\text{Sens} + D \rightarrow {^1}\text{Sens}^- + D^{++} \]

3. **Singlet-excited sensitizer is both a better oxidant AND reductant. Both processes quench fluorescence**

4. **Triplet fluorescence quenching is known**

   \[ {^1}\text{Sens} + A \rightarrow {^1}\text{Sens}^+ + A^- \]

---

Energy Transfer Mechanisms do not Occur Via Polar Intermediates

- Energy Transfer I: Dexter Mechanism

\[
\begin{align*}
\text{3Sens}^* + A & \rightarrow \text{Sens} + \text{3A}^* \\
\text{1Sens}^* + A & \rightarrow \text{1Sens} + A^*
\end{align*}
\]

- Both Energy Transfer Mechanisms Require that E(excited state D) > E(excited state A)

- \[k_{ee} = KJ e^{(-2r_{DA}/L)}, \text{ so } r_{DA} \sim 5 - 10 \text{ A}\]

- Primarily triplet sensitization

- Energy Transfer II: Forster Mechanism

- Can operate at over 50 A via a dipole-dipole (Coulombic) mechanism (transition dipole coupling)

- Basis for FRET

**Reductive PET Bond Cleavage**

Reductive cleavage proceeds by electron transfer to benzyl halide or pseudo-halide

\[
\text{Me}_3\text{Cl} + \text{Me}_3\text{NO}_2^\text{+Na} \xrightarrow{\text{PET}} \text{Me}_3\text{NO}_2^\text{+Na} + \text{Me}_3\text{NO}_2
\]

\[
\text{Me}_3\text{NO}_2^\text{+Na} \xrightarrow{\text{ambient light}} \text{Me}_3\text{Cl} + \text{Me}_3\text{NO}_2
\]

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark</td>
<td>0%</td>
</tr>
<tr>
<td>ambient</td>
<td>63%</td>
</tr>
<tr>
<td>fluorescent light (20 W)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Reductive PET Reactions and Non-Halide Examples

- NBoc substituents stabilize benzylic radical formation

- OMe groups stabilize benzylic nucleofuges toward tandem epoxide ring openings

**Reductive PET Bond Cleavage**

- Homobenzylic chlorides also participate in reductive PET chemistry

- Besides anti/syn considerations, differences occur between homopara vs. homometa C-X bonds

Oxidative PET Bond Cleavage

- A representative and early example of oxidative PET bond cleavage

\[
\begin{align*}
\text{PET} & \quad \text{ClO}_4^- \quad \text{NMePh} \quad + \quad \text{SiMe}_3\text{CH} = \text{CH} \quad \rightarrow \quad \text{NMePh} \quad + \quad \left[ \text{SiMe}_3\text{CH} = \text{CH} \right]^+ \\
\text{Nu}^- & \quad \rightarrow \quad \text{SiMe}_3 \quad + \quad \text{NuSiMe}_3 \\
\text{PET} & \quad \text{NMePh} \quad + \quad \text{CH} - \text{CH} \quad \rightarrow \quad \text{NMePh} \quad + \quad \text{CH} - \text{CH}
\end{align*}
\]

**Oxidative Intramolecular PET Bond Cleavage**

- Intramolecular C-C bond formation to form indolizidines

- Intramolecular organocatalytic Hiyama-type coupling


- Difficult to perform this chemistry as efficiently with a non-PET approach (polar reagents)
Oxidative PET Bond Cleavage

Less polar and aprotic solvents (MeCN alone) afford product retaining silyl group

Application to Macroyclic Ring Closures


**Application to Poison Frog Therapeutics**

- Carbohydrate-mimetic hydroxylated indolizidines

![(+)-Pumiliotoxin](image)

- Antidiabetics, antiviral, anticancer, immunosuppressant, transplantation medicine

- Pyrrolizidines also offer opportunities for synthetic application

![Alexine and Riddelliine](image)

- Potent glycosidase inhibitor, antiviral, anti HIV, anticancer

- Insect defense agent

Intermolecular Non-Silylated, Simple Amino-Alkyl Additions

- Triplet sensitizers have very specific transition energies and can markedly improve reaction efficiency

MenthO\(\text{F} \rightarrow \text{O}\) + \text{Me}\(\text{Me}\) \(\text{PET}\) \(\text{Ph} \rightarrow \text{Ph}\)

\[\text{RO} \quad \text{H} \quad \text{H} \quad \text{NMe} \quad \text{2} \quad \text{60\%}\]

\[\text{O} \quad \text{Ph} \quad \text{Ph} \quad \text{OMenth}\]

\[\text{1} \quad : \quad \text{1.2} \quad \text{94\%}\]

\[\text{MeO} \quad \text{OMe} \quad \text{MeO} \quad \text{OMe}\]

\[\text{(-)-Isoretronecanol}\]

\[\text{(+)Laburnine}\]

Proposed Mechanism for Pyrrolidine Addition

- The catalytic cycle may provide more than one opportunity for a product forming step

Further Development of Amine Coupling Partners

- Triethyl amine, piperidone and other amines are a viable coupling partner in PET C-C bond construction.

\[
\text{PET} \quad \begin{array}{c}
\text{MenthO} \quad + \quad \text{TEA} \\
\text{PET} \quad \text{350 nm sensitizer} \\
\end{array} \\
\begin{array}{c}
\text{RO} \quad + \quad \text{RO} \\
\text{H} \quad \text{H} \\
\text{H} \quad \text{H} \\
\end{array} \\
\begin{array}{c}
\text{NMe} \quad \text{NMe} \\
\text{1 : 1 dr} \\
\end{array}
\]

2.5 : 1 constitutional isomeric products favoring tertiary radical.

With SMeEtO

\[
\begin{array}{c}
\text{N} \\
\text{EtO} \quad \text{SMe} \\
\text{1 : 1} \\
\end{array} \quad 60\% \\
\begin{array}{c}
\text{No S} \\
\text{EtO} \quad \text{SMe} \\
\text{1} \\
\end{array} \quad 48\% \\
\]

**Intramolecular Trapping of Presumed Oxy-allyl Radical**

When trapping oxy-allyl radical acetone was necessary to act as benign oxidant

\[
\text{MentO} + \text{Me}_{2}N\text{NMe}_{2} \xrightarrow{\text{PET}, 350 \text{ nm}} \text{Michler's ketone} \\
\]

Without acetone: 38% : 2% : 18%

With acetone: 74% : 3% : 0%

Non-Direct Methods for Enantioinduction in PET Reactions

- Cascade cyclization of terpene polyolefins via photoinduced electron transfer
  
  ![Chemical Structure](image)

  1) PET, DCTMB
  BP, MeCN/H\textsubscript{2}O
  -25 °C
  2) removal of (-)-menthone

  Perfect diastereoinduction
  Only 2 of 256 possible isomers formed and 8 stereocenters set
  Shortest steroid route
  Remarkably far reaching asymmetric induction

- Memory of chirality PET study explained by rigidity of amide and aniline bonds toward rotation
  
  ![Chemical Structure](image)

  PET, acetone/H\textsubscript{2}O

  $X = \text{H, 45\%, 86\% ee}$
  $X = \text{Cl, 50\%, 79\% ee}$

  With ethylene di-ortho linker: 0\% ee

The Bach example is the only method thus far for a direct, catalytic, asymmetric reaction with chemical yields above 1%.

Evidence Supporting the Occurrence of Charge Separation

- Why should we trust that charge separation is occurring?

2 Fluoresces upon irradiation and is quenched upon increasing concentration of 1 in solution. This levels off at 1 molar equivalent of 1.

Quenching of simple anthracene* fluorescence by addition of aniline only occurs at 2%.

If masked donor (R = COCHMe₂) is used, little quenching occurs.

Thus, diffusion controlled collisional quenching cannot be responsible for electron transfer.

\[
\Delta G^0_{CS} = -0.41 \text{ eV}; \Delta G^0_{CR} = -2.5 \text{ eV}
\]

PET Projects in Total Synthesis

- Selected natural products formed by PET bond-constructive key steps

Conclusions

• Photoinduced electron transfer (PET) utilizing alpha-amino radicals was shown to be applicable to problem solving in organic synthesis.
• Alpha oxo- and alpha thio-radicals are also useful.
• Advantages - unique and/or expedited carbon-carbon bond construction; vastly underexploited asymmetric potential for interesting reactivity.
• Disadvantages - Limited substrate scope and/or specific wavelength for some methods.