Design Concepts of Nitrooxyl Radicals

Literature Seminar
2018/3/10
B4 Katsuya Maruyama
Contents

1. Introduction
2. TEMPOs and AZADOs
3. Design Concept of Nitroxyl Radicals
4. Summary
1. Introduction
1. Introduction

Nitroxy radicals (nitroxides, aminoxyl radicals)

KO₃S·N·SO₃K

Fremy's salt

The first nitroxy radical (1845)
Use of Nitroxy Radicals

Tuning design for each purpose can improve the efficacy.

**Chemical use**
- Oxidation catalyst
- Nitroxide mediated radical polymerization (NMP)
- Radical coupling
- Mechanism analysis

**Biological use**
- Spin probe
- Superoxide dismutase mimics
- Antioxidant

**Material use**
- Dye-sensitized solar cells
- Organic radical battery

![Nitroxy radical structure](image)
Property of Nitrooxyl Radicals

- TEMPO is stabilized both thermodynamically and kinetically.

Thermodynamic stabilization
- Delocalization of unpaired electron

- Resonance stabilization
  - $120 \text{ kJ mol}^{-1}$

- Bond length
  - $\text{N}–\text{O} : 1.25 \text{ Å}$
  - $\text{N}–\text{O} : 1.20 \text{ Å (single bond)}$
  - $\text{N}=$\text{O} : 1.44 \text{ Å (double bond)}$

Kinetic stabilization
- $4 \alpha$-methyl groups

- Four Me shield the radical.

- N-O bond contains three electrons.
- Bond order of N-O is 1.5.

Property of Nitrooxyl Radicals

TEMPO
• Thermodynamic driving force for direct H-abstraction is low.

PINO
• Stronger H-abstraction reagent, but unstable. (generated in situ)
• Used in transition-metal mediated C-H functionalization with Co, Mn.

Oxidation State of Nitroxyl Radicals

Oxidation states of nitroxyl radical

- Oxoammonium ion acts as an active species in oxidation.
- Oxoammonium salt can be isolated with proper counteranion. (e.g. BF$_4^-$)

Generation of oxoammonium salt

- Acid cause disproportionation.
- Nitroxy radical and hydroxylamine are oxidized into oxoammonium salt.
2. TEMPOs and AZADOs
2-1. TEMPOs

TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl)

- Alcohol oxidation catalyst.
- 1° alcohol > 2° alcohol.
- Terminal oxidant: NaOCl, PhI(OAc)$_2$, oxone, I$_2$, O$_2$, etc.
Alcohol Oxidation by TEMPO

Oxoammonium as active species

Catalytic cycle

pH < 4

Hydride-transfer to oxoammonium cation

pH > 5

Cope-type elimination from alcohol adduct


Alcohol Oxidation by TEMPO

Aerobic oxidation with Cu

(bpy)Cu\(^{+}\) 5 mol%  
TEMPO 5 mol%  
NMI 10 mol%  
air or O\(_2\)  
MeCN, rt

NMI: N-methylimidazole

- Cu(II) isn’t sufficiently strong oxidant for the oxidation of TEMPO to TEMPO\(^{+}\).
- Oxoammonium cation isn’t generated.

Simplified catalytic cycle

2-2. AZADOs

Problems with TEMPO

-reactivity

steric repulsion between Me and R1, R2
-> 1° alcohol > 2° alcohol

-development of AZADOs

AZADO: 2-azaadamantane N-oxyl

AZADO
1-Me-AZADO
1,3-diMe-AZADO

Steric hindrance

Catalytic Activity

\[
\text{OH} \quad \xrightarrow{\text{nitroxide (1 mol%), NaOCl (150 mol%), KBr (10 mol%), Bu}_4\text{NBr (5 mol%)}} \quad \text{O}
\]

DCM, aq.NaHCO₃
0 °C, 20 min

Redox Property

Cyclic Voltammetry (CV)

- Stable for >100 measurement cycles.

Redox Potential ($E^0$ vs Ag/Ag$^+$)

<table>
<thead>
<tr>
<th>Nitroxide</th>
<th>$E^0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>a: TEMPO</td>
<td>294</td>
</tr>
<tr>
<td>b: AZADO</td>
<td>236</td>
</tr>
<tr>
<td>c: 1-Me-AZADO</td>
<td>186</td>
</tr>
<tr>
<td>d: 1,3-diMe-AZADO</td>
<td>136</td>
</tr>
</tbody>
</table>


High catalytic activity is mainly due to kinetic factors.

Development of ABNO and Nor-AZADO

<table>
<thead>
<tr>
<th>nitrooxide (X mol%), NaOCl (150 mol%), KBr (10 mol%), Bu₄NBr (5 mol%)</th>
<th>DCM, aq.NaHCO₃ 0 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitrooxide X mol%</td>
<td>TEMPO</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
</tr>
<tr>
<td>1</td>
<td>97%</td>
</tr>
<tr>
<td>0.01</td>
<td>28%</td>
</tr>
<tr>
<td>0.005</td>
<td>n.d.</td>
</tr>
<tr>
<td>0.003</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>nitrooxide X mol%</th>
<th>TEMPO</th>
<th>1-Me-AZADO</th>
<th>AZADO</th>
<th>ABNO</th>
<th>Nor-AZADO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5%</td>
<td>95%</td>
<td>99%</td>
<td>94%</td>
<td>99%</td>
</tr>
<tr>
<td>0.01</td>
<td>n.d.</td>
<td>61%</td>
<td>98%</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td>0.005</td>
<td>n.d.</td>
<td>41%</td>
<td>96%</td>
<td>92%</td>
<td>96%</td>
</tr>
<tr>
<td>0.003</td>
<td>n.d.</td>
<td>25%</td>
<td>87%</td>
<td>8%</td>
<td>92%</td>
</tr>
</tbody>
</table>

- Nor-AZADO showed higher catalytic activity than AZADO.

5-F-AZADO

Introduction of electron-withdrawing group

\[ \text{AZADO} \rightarrow \text{EWG} \]

\[ \text{e}^- \text{ poor oxoammonium salt} \]

A: 5-F-AZADO (5 mol\%)  
NaNO\(_2\) (10 mol\%)  
AcOH (1 M), Air (balloon), rt

B: 5-F-AZADO\(^+\)NO\(_3\)^- (5 mol\%)  
AcOH, Air (balloon), rt

- NOx works as reoxidant.

wider scope of substrate

Mechanism Analysis with 5-F-AZADO

Proposed mechanism

5-F-AZADO -> Lower basicity prevents the formation of IV and V.

General Trend of Redox Property

Redox potential $E_0$ (vs Ag/Ag$^+$)

**EWG**
- $\rightarrow$ destabilization of N$^+=O$
- $\rightarrow$ higher redox potential

**EDG**
- $\rightarrow$ stabilization of N$^+=O$
- $\rightarrow$ lower redox potential

Catalytic Activity vs Redox Potential

The lower the redox potential, the higher the catalytic activity. (Probably because reoxidation into oxoammonium species is favorable.)

Redox potential
AZADO 236 mV
5-F-AZADO 412 mV
5,7-diF-AZADO 591 mV

• Redox potential is an important factor.

2-3. Steric Effect vs Driving Force

Cyclic voltammogram

Increment of oxidation current and disappearance of reduction current -> electrocatalysis

Oxidation Under Electrochemical Conditions

**Electrochemical oxidation**

- TOFs of alcohol oxidation

<table>
<thead>
<tr>
<th></th>
<th>1° benzyl</th>
<th>2° benzyl</th>
<th>1° aliphatic</th>
<th>sterically hindered 1° aliphatic</th>
<th>2° aliphatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABNO</td>
<td>1088</td>
<td>238</td>
<td>588</td>
<td>337</td>
<td>87</td>
</tr>
<tr>
<td>AZADO</td>
<td>1128</td>
<td>358</td>
<td>488</td>
<td>298</td>
<td>78</td>
</tr>
<tr>
<td>TEMPO</td>
<td>853</td>
<td>118</td>
<td>568</td>
<td>198</td>
<td>18</td>
</tr>
<tr>
<td>ACT</td>
<td>1228</td>
<td>378</td>
<td>708</td>
<td>388</td>
<td>73</td>
</tr>
</tbody>
</table>

**Nitroxy Redox Potentials ($E_{mp}$)**

- AZADO 0.45
- ABNO 0.48
- TEMPO 0.53
- Keto-ABNO 0.63
- ACT 0.65
- 4-oxo-TEMPO 0.69

Oxidation Under Chemical Conditions

Chemical oxidation

1-Butanol oxidation with NaClO

<table>
<thead>
<tr>
<th>Radical</th>
<th>Relative Rate</th>
<th>$k_{obs}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZADO</td>
<td>&gt;</td>
<td>0.0232</td>
</tr>
<tr>
<td>ABNO</td>
<td>&gt;</td>
<td>0.0112</td>
</tr>
<tr>
<td>TEMPO</td>
<td>&gt;</td>
<td>0.0051</td>
</tr>
<tr>
<td>ACT (4-acetamido-TEMPO)</td>
<td></td>
<td>0.003</td>
</tr>
</tbody>
</table>

Concentration in the presence of NaClO


Poor catalytic activity of 4-acetamido-TEMPO
Formation of N-O$^-$ -> N$^+$=O (reoxidation) is slow.
Intrinsic Catalytic Activity of 4-Acetamido-TEMPO

Chemical conditions vs electrochemical conditions

Oxidation of 1-butanol

- Oxidation with NaClO
- Electrochemical Oxidation

Compared with TEMPO...

High reactivity

Low reactivity

- Intrinsic reactivity can overcome the steric effect.

Use of Stoichiometric Amount of Oxoammonium

Rate of oxidation ($k \times 10^4 \text{ s}^{-1}$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Value 1</th>
<th>Value 2</th>
<th>Value 3</th>
<th>Value 4</th>
<th>Value 5</th>
<th>Value 6</th>
<th>Value 7</th>
<th>Value 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-acetamido-TEMPO$^+$</td>
<td>1.73</td>
<td>9.14</td>
<td>0.385</td>
<td>18.9</td>
<td>19.1</td>
<td>28.2</td>
<td>145</td>
<td>365</td>
</tr>
<tr>
<td>4-trifluoroacetamido-TEMPO$^+$</td>
<td>3.71</td>
<td>16.7</td>
<td>0.965</td>
<td>33.3</td>
<td>33.3</td>
<td>58.0</td>
<td>2666</td>
<td>980</td>
</tr>
</tbody>
</table>

- 1.7-3.2 times faster than 4-acetamido-TEMPO.

Short Summary

• AZADOs were designed to achieve higher reactivity.
• Steric property and electric property are important for them.
3. Design Concepts of Nitroxyl Radicals
3-1. Effect of Direct Conjugation on Redox Property

Piperidine, isoindoline, azaphenalene derivatives
• SOMO is localized on N-O bond.
• Substituent effects: σ-inductive effects.

2-Pyridyl nitroxy radicals
Direct conjugation of N-O with Py.

• Over 4 times sensitive to substituent effect than isoindoline.
  -> easy to tune the reactivity and stability.

SOMOs of 2-Pyridyl nitrooxides

SOMO delocalizes at 1-, 3-, 5- position.

--> Substituent at 1-, 3- and 5- position can affect the energy of SOMO and enables redox property tuning.

3-2. Twisted Diaryl-Nitrooxyl Radical

Diaryl-Nitrooxyl radical

- Normally unstable due to spin delocalization on Ar.

Decomposition pathway

- Substituent at $p$-position can prevent this pathway.


Calculated Structure and SOMO

- One ring with o-substituent is out of conjugation due to its bulkiness.
  -> Spin delocalization over the ring is prevented.

Redox Property

Redox potential $E^0$ (vs $\text{Ag/Ag}^+$)

Oxidation ($\text{N-O}^-$ $\leftrightarrow$ $\text{N}^+=\text{O}$) : $E^0_{\text{ox}}$

Reduction ($\text{N-O}^-$ $\leftrightarrow$ $\text{N-O}^-$) : $E^0_{\text{red}}$

**Effect of twist**

Interesting Property

1: twisted

\[ \Delta E = E_{ox}^0 - E_{red}^0 \]

\[ E_{red}^0 = -919 \text{ mV} \]
\[ E_{ox}^0 = 952 \text{ mV} \]

\[ \Delta E = 1871 \text{ mV} \]

5: non-twisted

\[ \Delta E = 1674 \text{ mV} \]

\[ E_{red}^0 = -866 \text{ mV} \]
\[ E_{ox}^0 = 808 \text{ mV} \]

- \( \Delta E = E_{ox}^0 - E_{red}^0 \) increases when twist exists.

\(<->\) Inductive substituent normally shifts \( E_{ox}^0 \) and \( E_{red}^0 \) to the same direction.

Torsion Angle

O-N-C-C torsion angle (θ) : θ is larger. --> conjugation is less.

Torsion angle θ depends on
• Position of substituents
• Electronic property of substituents

Relationship Between θ and Redox Potential

found:
\[ \sigma_o(CF_3) = 0.60 \]
\[ \sigma_o(iBu) = -0.21 \]

\[ 1/2(E_{ox}^{0} + E_{red}^{0}) = 0.504\Sigma\sigma + 0.129 \]
\[ R^2 = 0.93 \]

- Plotted \( E_{ox}^{0} + E_{red}^{0} \) vs \( \Sigma(\sigma_p + \sigma_o \cos \theta) \)
- Such \( \sigma_o \) was determined that makes \( R^2 \) minimum.

3-3. $\alpha$-Hydrogen Nitroxy radicals

Nitroxy radicals with tertiary alkyl group

- Stable but highly encumbered.

Conventional $\alpha$-hydrogen nitroxy radicals

- Only acyclic and bicyclic system had been reported.
- The examples aren’t abundant.

Disproportionation of α-Hydrogen Nitroxy Radicals

Disproportionation of α-hydrogen nitroxy radicals

\[
\text{R}_2\text{N}-\text{O}^\cdot + \text{O}^\cdot\text{N-R}_2 \rightarrow \text{R}_2\text{N}^-\text{O}^\cdot + \text{HO}^-\text{N-R}_2
\]

• Bridgehead H inhibit the formation of nitrone. (Bredt’s rule)

But...

• bridgehead H strategy isn’t necessarily effective.

Design Concept of α-Hydrogen Nitroxy1 Radicals

New α-hydrogen nitroxy1 radicals

- Isoindoline nitroxide (II NO)
- 2,3-dihydro-isoazaphenalene nitroxide (IAPNO)

Design concept

1: pushing out the substituent
- $R_6$ push $R_5$ away from the plane.
- $H$ abstraction by another molecule is inhibited.

2: 1,3-allylic strain
- Nitrone formation is disfavored due to A(1,3) strain.

Design Concept of $\alpha$-Hydrogen Nitrooxyl Radicals

3: H-C-N-O angle ($\Phi$)

Ideal angle for C-H abstraction:

- C-H bond overlaps SOMO.
- H abstraction is favored.

This case:

- C-H bond is orthogonal to SOMO.
- H abstraction is disfavored.

Based on these concepts, improved stability of was expected.

Results

Synthesized molecules

Disproportionation is thermodynamically favored.

Stable for months.

DFT calculation

- Stability of the nitroxyl radicals is due to kinetic factors.

Potential as Catalyst

**Aerobic alcohol oxidation**

**Stahl’s conditions**

\[
\begin{align*}
\text{air} & \quad 5 \text{ mol\% nitroxide} \\
& \quad 5 \text{ mol\% CuBr} \\
& \quad 5 \text{ mol\% BiPy} \\
& \quad 10 \text{ mol\% NMI}
\end{align*}
\]

MeCN, T °C

\[
\begin{align*}
(\text{BiPy: bipyridine} & \quad \text{NMI: N-methylimidazole})
\end{align*}
\]

**Further investigation**

\[
\begin{align*}
\text{air} & \quad 5 \text{ mol\% 32 or 35} \\
& \quad 5 \text{ mol\% CuBr} \\
& \quad 5 \text{ mol\% ligand} \\
& \quad 10 \text{ mol\% base}
\end{align*}
\]

MeCN, T °C

\[
\begin{align*}
R_1 \quad R_2 & \quad \text{up to 96%}
\end{align*}
\]

- In some Nitroxides, catalytic activity is better than TEMPO.

<table>
<thead>
<tr>
<th>Nitroxide</th>
<th>Reaction time (h)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (TEMPO)</td>
<td>3</td>
<td>25</td>
<td>95</td>
</tr>
<tr>
<td>25a</td>
<td>6</td>
<td>55</td>
<td>82</td>
</tr>
<tr>
<td>25b</td>
<td>1.5</td>
<td>25</td>
<td>92</td>
</tr>
<tr>
<td>32</td>
<td>2</td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td>35</td>
<td>1</td>
<td>25</td>
<td>96</td>
</tr>
</tbody>
</table>

- Nitroxide 35 shows 2~3 times higher catalytic activity than TEMPO.
4. Summary

• Reactivity and stability of nitroxy radical can be tuned by the parameters here and maybe by other parameters.
• The examples of the use of fine-tuned nitroxy radicals aren’t many, so the best design of nitroxy radicals for the purpose could improve the efficiency.
Appendix: Cyclic Voltammetry

Caution
<- The direction of x (potential) and y (current) axis is inversed with the figures in this seminar.