Triplet Oxygen in Organic Synthesis

Oxygen

15.9994

8

- First discovered by Scheele in 1773 "fire air"
- Member of the Chalcogen family (S, Se, Te, Po)
- 21% of the earth's atmosphere by volume, third most abundant element in the universe
- BP = −183 °C, exists as a pale blue liquid below this temperature
- Exists in as a diatomic molecule
- Paramagnetic due to triplet nature of ground state

Rocket Fuel

liquid O₂ (LOX) combined with RP-1 (refined hydrocarbons) in 1st stage rocket boosters

Its magnetic!

ground state

excited state

triplet oxygen

( relativley inert)

metalloenzymes

O₂

HO⁻

HHO⁻

respiration

metabolism

detoxification

activated oxygen species

SpaceX Falcon 9

Triplet Oxygen, a deceptively stable species

- Ground state of triplet oxygen bears two unpaired electrons with parallel spins
- Interaction with singlet organic molecules is symmetry forbidden (Wigner spin conservation rule)
- Triplet oxygen can overcome this obstacle in a variety of ways:
  1. Direct substrate oxidation via low energy triplet state
  2. Direct substrate oxidation via SET
  3. Photooxygenation
  4. Pradical chain reaction (autooxidation)
  5. Interaction with a paramagnetic transition metal

A Brief History of Oxygen on Earth

- 3.5 billion years ago anaerobic bacteria relied on H₂S as H-atom source for photosynthesis
- Aprox. 1 billion years later, cyanobacteria evolved the ability to use water instead

2 H₂O → PS II under hv → O₂ + 4(H⁺ + e⁻)

- This resulted in the "Great Oxidation Event" leading to a rise in global O₂ levels
- Anaerobic organisms perished or retreated to oxygen free environments, aerobes emerged
- Reaction of oxygen with solar radiation created the ozone layer, land-based life emerged


Me₂N

NMe₂

Me₂N

NMe₂

air

neat 6 hrs.

proposed intermediate

- TDAE = strong single electron organic reductant
- Reaction with triplet oxygen produces chemiluminescence
- Mechanistic studies suggests possible charge transfer complex (Fletcher, J. Phys. Chem. 1967, 71, 1507)


- no differences in yield were observed when reaction run under light/dark conditions

2. Direct substrate oxidation via single electron transfer (SET)
- Possible only for highly reducing substrates (anions)
- Proceeds via SET substrate oxidation and generation of reduced superoxide radical anion

\[
\begin{align*}
\text{O}_2 && \text{O}^- \\
\text{O}^- + \text{R} &\xrightarrow{\text{SET}} \text{R} - O^- \\
\text{R} - O^- &\xrightarrow{\text{O}_2} \text{R} - \text{O}_2^-
\end{align*}
\]
- triplet oxygen is a poor oxidant \( E^\circ = -0.33 \) V
- weaker than:
  \( \text{Ni}^{2+} (E^\circ = -0.25 \) V
  \( \text{Co}^{2+} (E^\circ = -0.28 \) V


- \( n \text{EWG} = \uparrow \text{ionization, } \downarrow \text{reducing ability (rate)} \downarrow \)
- \( R(\text{aryl,Ph}) = \uparrow \text{radical stability (rate)} \uparrow \)

Oxidations of Stabilized Carbanions
Aromatization

\[
\begin{align*}
\text{Me} && \text{Me} \\
\text{Me} &\xrightarrow{\text{t-BuOK, } \text{THF}} \text{Me} + \text{Me}
\end{align*}
\]
- rate calculated based on oxygen consumption


Configurationally stable organometallics

\[
\begin{align*}
\text{Ph} - \text{M} &\xrightarrow{\text{\text{^3}O}_2, \text{Ac}_2 \text{O, } \text{Et}_2 \text{O or THF, } 78 \text{ °C, 1 hr}} \text{Ph} - \text{M} + \text{Ph} - \text{M} \\
\text{Ph} - \text{M} &\xrightarrow{\text{SET}} \text{Ph} - \text{M} + \text{O}_2 \\
\text{Ph} - \text{M} &\xrightarrow{\text{H}_2 \text{O}_2} \text{Ph} - \text{M} + \text{O}_2 \\
\end{align*}
\]
- Gives mixtures of diastereomers
- Retention of configuration using alternative t-BuOOLi oxenoid

Triplet Oxygen in Organic Synthesis

3. Photooxygention
- Light promoted oxidation of organic molecules with molecular oxygen
- Three sub-categories (types I, II and III)

Examples of Type I Photooxygention.
Light promoted diazo decomposition-trapping with molecular oxygen

Examples of Type II Photooxygention.
Singlet oxygen generation and general reactivity

Examples of Type III Photooxygention.
Selective endo-peroxide formation from 1,3-dienes using triplet oxygen and Lewis acids

Examples of Type III Photooxygention.
PET (see Yan GM, 2014)

Type/I/II Norrish-Yang reactivity

Enone photoexcitation - $\text{O}_2$ trapping

Examples of Type II Photooxygention.

Reaction of activated olefins to form [7,6.2] peroxy-bicycles

Photoxidation in food.
- Common photochemicals in food can act as photosensitizers to cause spoilage

Role in milk spoilage (Skibsted, Food Funct. 2012, 3, 487)

- type II dominant $\uparrow[\text{O}_2]$

- type III RF$^+$ + $\text{O}_2$
Triplet Oxygen in Organic Synthesis

4. Radical chain reaction (autoxidation)
- Most prevalent means of triplet oxygen-mediated oxidation
- Relevant in food spoilage, industrial chemical production, polymer stability etc.

**Autoxidation**: spontaneous oxidation of a substance at ambient temperatures in the presence of oxygen.

- Radical chain reaction process involving three key events:

  **A. Initiation**
  
  \[ R-H \xrightarrow{\text{initiator}} R^\cdot \]  
  - radical initiators vary and can sometimes be difficult to identify (vida infra)

  **B. Propagation**
  
  \[ R^\cdot + 3\text{O}_2 \rightarrow R-\text{OO}^\cdot + R-H \rightarrow R-\text{OOH} + R^\cdot \]

  **C. Termination**
  
  \[ 2R-\text{OO}^\cdot \rightarrow R=O + R-OH + 3\text{O}_2 \]

**Autoxidation initiation**
- Mechanism of initiation not always clear, often due to trace impurities
- Common autoxidation initiators:

  **Excited Photosensitizers**
  
  \[ ^1\text{sens} \xrightarrow{hv} ^3\text{sens}^* \xrightarrow{3\text{O}_2} \text{ROOH} \]  
  \[ ^1\text{sens} \xrightarrow{R} \rightarrow ^1\text{sens}^* \xrightarrow{3\text{O}_2} \text{RO}^\cdot + \cdot\text{OH} \]
  - sensitizers can be dyes, trace organic impurities or the substrate itself

  **Environmental Pollutants**
  
  \[ \text{NO}_2 \xrightarrow{^{3}\text{sO}_2} \text{HOONO} + \text{OO}' \]  

  \[ \text{O}_3\text{O}_2 \rightarrow \text{OO}' \]  

  **Trace Metal Contaminants**
  
  - Triplet oxygen reacts with paramagnetic metal species to generate reactive oxygen species
  

**Autoxidation inhibition**
- Inhibitors work by trapping radical initiation species, block chain propagation
- Hindered phenols often used
- Phenoxy radical stable, not prone to C–H abstraction
- Phenoxy radicals do not readily react with \(^3\text{O}_2\)

**Mechanism of action**

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

\[ \text{R}^\cdot \text{O}_2^- + \text{ROOH} \rightarrow \text{RO}^\cdot + \text{R} \text{OH} \]

\[ \text{BDE} = 80 \text{ kcal/mol} \]

\[ \alpha\text{-tocopherol} \text{BDE} = 78 \text{ kcal/mol} \]

**Autoxidation of weak sp\(^3\) C–H Bonds.**
- Most relevant to food spoilage, industrial processes, small molecule stability

**Rate limiting step**

\[ \text{RH} \xrightarrow{\text{initiator}} \text{R}^\cdot \xrightarrow{3\text{O}_2} \text{RO}^\cdot \xrightarrow{\text{RH}} \text{ROOH} \]


- Reaction of \(\text{R}^\cdot\) with \(^3\text{O}_2\) at rate of diffusion
- Chain propagation limited by H-atom abstraction ability of peroxy radical

**Examples**

**Mann, J. Prakt. Chem. 1963, 20, 210**

\[ \text{HCO}_2\text{Me} \xrightarrow{3\text{O}_2} \text{HOOC}_2\text{Me} \]

**Bellefon, RSC Adv. 2013, 3, 18931**

\[ \text{HCO}_2\text{Me} \xrightarrow{3\text{O}_2} \text{HOOC}_2\text{Me} \]

**Dörwald, Side Reactions in Organic Synthesis, Wiley, 2005**

\[ \text{R}^\cdot \text{X} \xrightarrow{87} \text{R} \text{OH} \]

\[ \text{R} = \text{alkyl} \]

\[ 90–94 (\text{X} = \text{O}) \]

\[ 87–93 (\text{X} = \text{NH}) \]

**Becker, Tet. Let. 1975, 16, 3745**

\[ \text{H}^\cdot \text{Me} \xrightarrow{3\text{O}_2} \text{HO}\text{Me} \]

- Autoxidation is generally a slow process
- Can be accelerated with high temperature, metal catalysts and organic mediators
**Triplet Oxygen in Organic Synthesis**

**Accelerators of Autoxidation**

**Temperature**
- High temperature promotes organoperoxide O–O homolysis = higher concentration of ROS
- Resulting alkyl/hydroxy radicals able to oxidize strong C–H bonds

\[
\text{T} \geq 130^\circ C \quad \text{ROH} \quad \text{ROOH}^{+} \quad \text{OH}^{-} \quad \text{ROH} + \text{H}_2\text{O} \\
\text{ROH (BDE = 100–110 kcal/mol)} \quad \text{H}_2\text{O (BDE = 119 kcal/mol)}
\]

**Transition Metal Catalysts**
- TM catalysts are used to promote organoperoxide cleavage to enhance reactivity (see above)
- Common metals include: Mn, Fe, Co, Ni, Cu
- Based on the Haber-Weiss cycle

\[
\text{Weckhuysen, J. Cat. 2010, 270, 16}
\]

**Organic Mediators**
- NHPI most commonly used, requires a redox co-catalyst (RDX) to initiate reaction
- Circumvents peroxo radical (RO') generation = enhanced selectivity over metal catalyst only

\[
\text{RDX} \quad \text{NHPI} \quad \text{RDX-OOH} \quad \text{RDX-OO}^{+} \quad \text{CO(OAc)}_2^{+} (1 \text{ mol%)}
\]

**Autoxidation by Functional Group**

**Benzylc**
- Generally requires high temperature, metal catalyst or mediator for unactivated sites
- α-heteroatom substituted benzylc sites undergo facile benzylic oxidation

**Industrial synthesis of phenol/acetone (Hock process)**

\[
\text{Me} \quad \text{Me} \quad \text{Me}_2\text{C} \quad \text{OH} \quad \text{OH} \quad \text{Me} \quad \text{Me}
\]

\[
\text{Me} \quad \text{Me} \quad \text{Me}_2\text{C} \quad \text{OH} \quad \text{OH} \quad \text{Me} \quad \text{Me}
\]

\[
\text{conc. to 80%\%} \quad \text{then H}^+ \quad 11 \times 10^5 \text{ t/yr}
\]

**Application in methodology**

\[
\text{PG} = \text{Bn or allyl} \\
\text{R} = \text{alkyl, H}
\]

**Application in synthesis**

\[
\text{Zhu, Synlett, 2006, 1691}
\]

**Allylic**
- Less common for unactivated allylic positions (1O₂, SeO₂)
- Enones and doubly-allylic positions readily autoxidize with triplet oxygen

\[
\text{Smith III, J. Am. Chem. Soc. 2000, 122, 11254}
\]

**Recent example**

\[
\text{Stahl, Chem. Sci. 2017, 8, 1282}
\]

**Review**
- Recupero, Chem. Rev. 2007, 107, 3800

**Baran Group Meeting**
- 12/01/18
**Triplet Oxygen in Organic Synthesis**

**Ethers and Amines**
- α-C–H bonds undergo slow autoxidation in the presence of oxygen under ambient conditions
- Organic mediators are often used

**Ether oxidation**
- primarily benzylic ethers and acetics (Recupero, Chem. Rev. 2007, 107, 3800)

**Amine oxidation**
- only a few examples using autoxidation (Hermans, ACS Catal. 2012, 2, 1108)

**Phenols and Anilines**
- Highly facile autoxidation (low X–H BDE)
- Generally react via carbon centered radical resonance form

**Strain release**

**Synthesis of (-)-hamigeran B**
- if \( R^1 = O H, R^2 = O M e \)
- Han, Org. Lett. 2018, 20, 3687

**Unexpected rearrangement/autoxidation leading to the synthesis of (-)-merscarpine**

**Aldehydes and Ketones**
- Aldehydes are easily oxidized by molecular oxygen (not commonly used)
- α-keto C–H bond autoxidation requires a catalyst or mediator, if there is an α-heteroatom (captodative) the autoxidation is facile

**Aldehyde oxidation**
- R = alkyl, aryl
  - heptane (0.8 M), rt, 61–91% in flow
  - Favre-Réguillon, Org. Lett. 2013, 15, 5978

**α-keto oxidation**

**Captodative effect**

**Kinetics**
- 10% aqu. HCl then aqu. NaOH, extract (EtOAc)
- solution in EtOAc unstable

**EPR**
- DPPH (5 mol%), 
  - \( \text{WO}_3/\text{Al}_2\text{O}_3 \) (1 mol%), 
  - \( \text{O}_2/\text{N}_2 \) (50 atm)
  - \( \text{CH}_3\text{CN}, 80^\circ \text{C} \)

**Kinetics**
- Creary, Org. Lett. 1999, 1, 1615

**Kinetics**
- Han, Org. Lett. 2018, 20, 3687
Triplet Oxygen in Organic Synthesis

Synthesis of complex flavonoids from Daemonorops "dragon's blood"


Autooxidation of a masked amino-furan yields the 1st maleic anhydride of the CP molecules


(Hetero)arene Oxidation
Electron poor (hetero)arenes
- React via hydroxide radical substitution at high temperature (generally messy)

Example

Sulfide Oxidation
- Thiols undergo facile air oxidation to disulfides (accelerated by base, metal catalysts)
- Sulfides to sulfoxides/sulfones requires metal catalyst (Choudary, Chem. Comm. 2003, 754)

Example

Electron rich (hetero)arenes
- SET oxidation in air via generation of superoxide (O$_2^-$)
- CV can be used to approximate if a substrate will air oxidize

Examples

Dörwald, Side Reactions in Organic Synthesis, Wiley, 2005

Miwa, Tetrahedron, 1971, 27, 775


Lei, Angew. Chem. Int. Ed. 2012, 124, 4744

Ruano, Green Chem. 2008, 10, 706
5. Interaction with a paramagnetic transition metal (TM catalysis)

**DISCLAIMER:** The purpose of this section is not to exhaustively review the field of aerobic TM catalysis. It seeks to present general reactivity and highlight interesting synthetic examples.

**Useful reviews:**
- Aerobic Pd catalysis (Stahl, Chem. Rev. 2018, 118, 2636)
- Fe catalysis (Knößer, Chem. Rev. 2015, 115, 3170)

- Aerobic oxidation in TM catalysis can be broadly divided into two categories:

**Oxygenase type:** Molecular oxygen is incorporated into the substrate being oxidized, generally proceeds via a metal-oxo/peroxo (not covered in this GM)

- Oxidase type: Molecular oxygen serves as an electron sink for the TM catalyst allowing catalyst turnover, it is not directly incorporated into the substrate

**A. Nucleometalation**
- Metal promoted addition of a nucleophile across an olefin/alkyne
- Pd and Cu most common metals used

**Wacker process**

\[ \text{H}_2\text{O} + \text{R} \rightarrow \text{MeO or } \text{R} \rightarrow \text{MeO} \rightarrow \text{2 Cu}^+ \]

- requires redox co-catalyst (Cu or BQ)
- DMSO and pyridine based ligands reduce need for redox co-catalyst

**aldehyde vs ketone control see:**

**Example**

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{Pd(OAc)}_2 (40 \text{ mol}) \quad \text{Pd(OAc)}_2 (10 \text{ mol}), \quad \text{O}_2 (1 \text{ atm}), \quad \text{Na}_2\text{CO}_3 \\
\text{dioxane, 70 °C, 24 hrs.} & \quad 57-96% \\
\end{align*}
\]

**B. Dehydrogenation**
- Desaturation of C–C or C–X bonds via formal removal of H₂

**Alcohol oxidation**

\[
\begin{align*}
\text{Cu-TEMPO system selectively oxidizes primary alcohols} \\
\text{O}_2 (1 \text{ atm}) & \quad \text{CuCl (0.14 eq.)} \\
\text{TEMPO (0.15 eq.)} & \quad \text{DMF, rt, 3 hrs.} \\
\text{MeOH} & \quad 40\% \text{ in H}_2\text{O} \\
\text{55\%} & \quad \text{Porco, Org. Lett. 2002, 4, 3267} \\
\end{align*}
\]

**Cationic Pd catalyst selectively oxidizes secondary alcohols in unprotected carbohydrates**

\[
\begin{align*}
\text{O}_2 (1 \text{ atm}) & \quad \text{Pd cat. (2 mol%), 2,5-iPr-phenol (0.5 eq.)} \\
\text{CH}_2\text{CN, 60 °C} & \quad 2\text{ hrs.} \\
\text{20 hrs.} & \quad 60\% \\
\end{align*}
\]

- 2⁺β-H elimination more facile than 1⁺
- works on various unprotected carbohydrates
- regioselectivity substrate dependent (generally high)

**Waymouth, ACS Catal. 2016, 6, 4653**

**Alkane dehydrogenation**

**Aerobic Pd catalyzed dehydrogenation of cyclic hydrocarbons**

\[
\begin{align*}
\text{H}_2\text{N-EEEDA} & \quad 2 \text{ AcOH} \\
1) \text{ EDDA (0.1 eq.)} & \quad \text{grounding, 10 mins} \\
2) \text{ SiO}_2, 150 °C & \quad 5 \text{ hrs.} \\
& \quad 37\% (2 \text{ steps}) \\
\end{align*}
\]

**initial conditions**
20 mol % Pd/C, PhMe, 110 °C, 48 hrs. 20% yield

**Mischne, J. Org. Chem. 2016, 81, 7977**

**C. Cross-coupling**
- Oxygen promotes TM catalyst turnover via two general pathways

**Yang, Org. Lett. 2011, 13, 2134**

**Triplet Oxygen in Organic Synthesis**

**Pd catalyzed homocoupling of aryl boronic acids to form strained macrocycles**
- Reaction applied to various other strained macrocycles (35–75%)
- Formal synthesis of aceroginin E
- Previous route: via Ar–I, B$_2$Pin$_2$ 10 mol% Pd, DMSO, 100 °C, 24 hrs. = 34% yield


**Cu catalyzed aerobic alkyne homocoupling - Glaser-Hay reaction**
- Reaction conditions:
  - CuCl$_2$ (1 eq.)
  - Ni(NO$_3$)$_2$ 6H$_2$O (25 mol%)
  - Et$_3$N, Pyr, O$_2$ (1 atm)
  - PEG$_{400}$/MeOH (0.03 M)
  - 60 °C, 2 d, 60%


**Pd catalyzed oxidative Heck reaction**
- Preservation of stereochemistry


**Improved Cu catalyzed aerobic coupling of anilines with aryl boron nucleophiles - Chan-Lam**


**Pd catalyzed aerobic C–H activation**
- Aerobic turnover possible in Pd(II)–(0)
- Aerobic turnover not observed in Pd(II)–(IV)


**Arylation using BF$_3$K salts/O$_2$**


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