POLITECNICO DI MILANO

Free-Radicals: Chemistry and Biology

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http://iscamap.chem.polimi.it/citterio/education/free-radical-chemistry/

Content

1. **Introduction**
   - Current Status of Radicals Chemistry
   - What is a Radical
   - Free Radicals and Life
2. **Historical Aspects**
3. **Electronic Structure and Bonding**
4. **Active Oxygen Specie,**
   - O_2, $O_2 \bullet^-$, $HO_2^{\bullet}$, $^1O_2$, H_2O_2, $HO^{\bullet}$
   - Chemistry
   - H_2O_2 and peroxides
5. **Radical Reactions**
   - Atom transfer
   - Addition to multiple bonds
   - Homolytic Aromatic Substitution
   - Electron Transfer (oxidation-reduction)
6. **Thermodynamics**
7. **Free Radical Kinetics**
   - First-order Reaction
   - Second-order Reaction
   - Steady-State
   - Chain-reactions
   - Redox chain reactions
   - Inhibition
8. **Radiation Chemistry**
   - Tools
   - Specie: $e^-(aq)$, $H^{\bullet}$, $HO^{\bullet}$, H_2O_2, H_2, $O_2^{\bullet-}$
   - Pulse Radiolysis/Flash Photolysis

9. **Lipid Peroxidation**
   - Chemistry
   - Measurement
   - Effects
10. **Antioxidants**
    - Preventive
    - Chain-breaking
    - Small molecule (Vit. C/E, CoQ, Urate).
    - Enzymes
    - Chelates
11. **Metals and Free Radical Chemistry**
    - Reactions
    - Complexes and redox chemistry
12. **DNA and Protein** (As radical targets)
13. **Photo reactions**
    - Photochemistry
    - Photosensitization
14. **Detection of Radicals**
    - TBARS
    - Fluorescence
    - Cyt. C /NBT
    - Strategies 1. SOD, CAT
15. **EPR Detection of Radicals**
    - Direct Detection
    - Spin Trapping
    - Transition metal
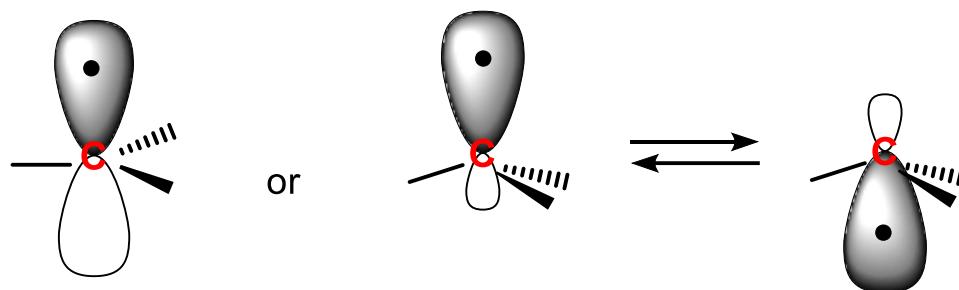16. **Nitric Oxide/NOS**
17. **Oxygen radicals/ROS**

Radicals: Electronic Structure and Bonding

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- As we have seen in cap. 1A, the bonds around a carbon centered alkyl radical are more or less sp^2-hybridized, with the radical occupying the $2p_z$ orbital
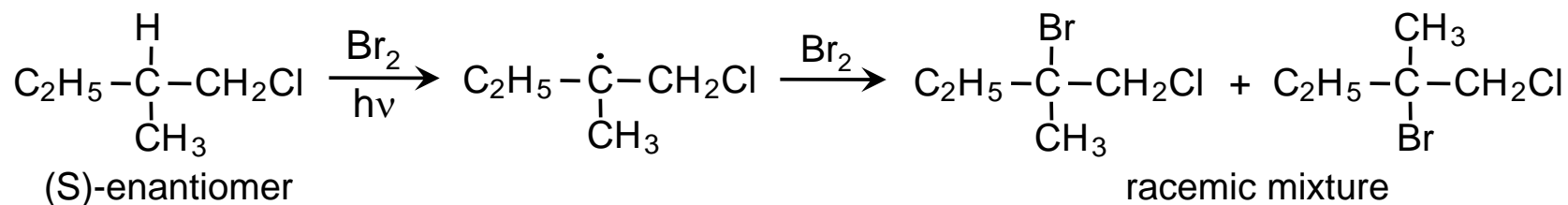

planar …. or   very shallow pyramid

This conclusion arises from:

1) Loss of optical activity when generated at an asymmetric carbon

2) Electronic and infrared spectra of gas phase generated methyl radicals
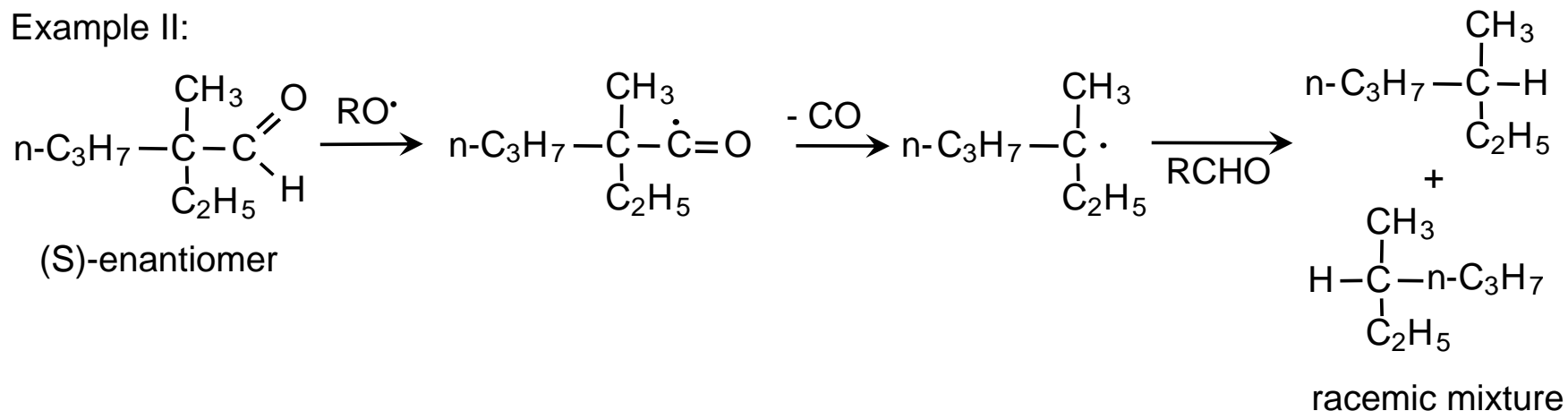
3) ESR spectra of simple alkyl radicals.

Geometry

Example I:

$$C_2H_5 - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}} - CH_2Cl \xrightarrow[h\nu]{Br_2} C_2H_5 - \overset{\cdot}{\underset{\underset{\displaystyle CH_3}{|}}{C}} - CH_2Cl \xrightarrow{Br_2} C_2H_5 - \overset{\overset{\displaystyle Br}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}} - CH_2Cl \; + \; C_2H_5 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle Br}{|}}{C}} - CH_2Cl$$

(S)-enantiomer   racemic mixture

Example II:

$$n\text{-}C_3H_7 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}} - \overset{\overset{\displaystyle O}{\parallel}}{\underset{\underset{\displaystyle H}{}}{C}} \xrightarrow{RO^\cdot} n\text{-}C_3H_7 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}} - \overset{\cdot}{C} = O \xrightarrow{-CO} n\text{-}C_3H_7 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}}\cdot \xrightarrow[RCHO]{}$$

(S)-enantiomer

$$n\text{-}C_3H_7 - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}} - H$$

+

$$H - \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}} - n\text{-}C_3H_7$$

racemic mixture

Explanation I:

Participation by a planar radical species capable of undergoing "top" or "bottom" attack with equal likelihood

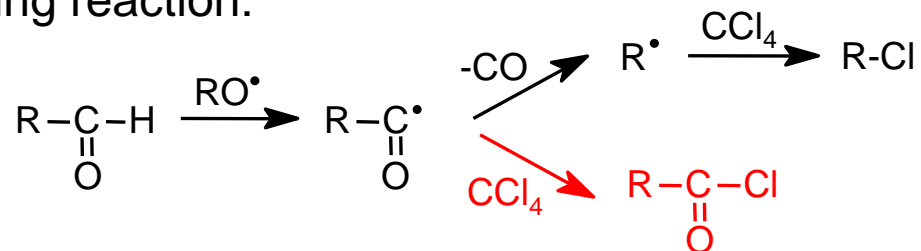$$Z_{\cdots\cdots}\overset{\bullet}{C}\!-\!X$$
$$Y$$
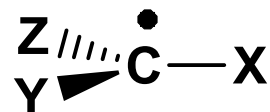
Explanation II:

Participation by a rapidly equilibrating pair of enantiomeric pyramidal radical species that would lead to racemic products
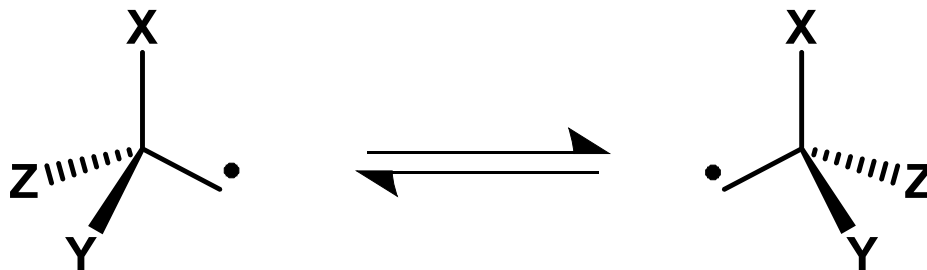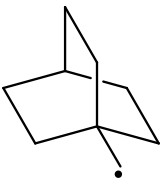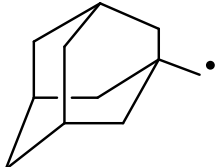
Consider the following reaction:

Object: Change R- from a group that can easily adopt a planar geometry to one that cannot. If the first is favored for free radicals, a low RCl:RCOCl ratio should be obtained.

Observations: R-group	RCl: RCOCl ratio	Stability of R•
$(CH_3)_3C–\cdot$	12.3:1.0	1.0 (ref.)
	15.2:1.0	1.2
	30.5:1.0	2.5

Conclusion: The formation of pyramidal radicals is **not** accompanied by adverse energy considerations. In fact, the opposite is true.

Consider the following observation:
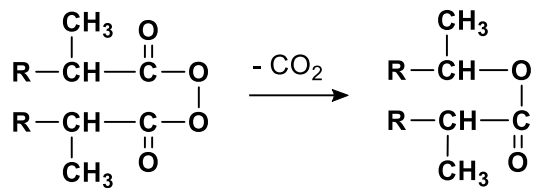
Both stereogenic centers remain intact

Plausible explanation: Loss of CO_2 leads to a pyramidal alkyl radical that rapidly recombines with incipient oxyradical before inversion of configuration can occur ("cage effect").
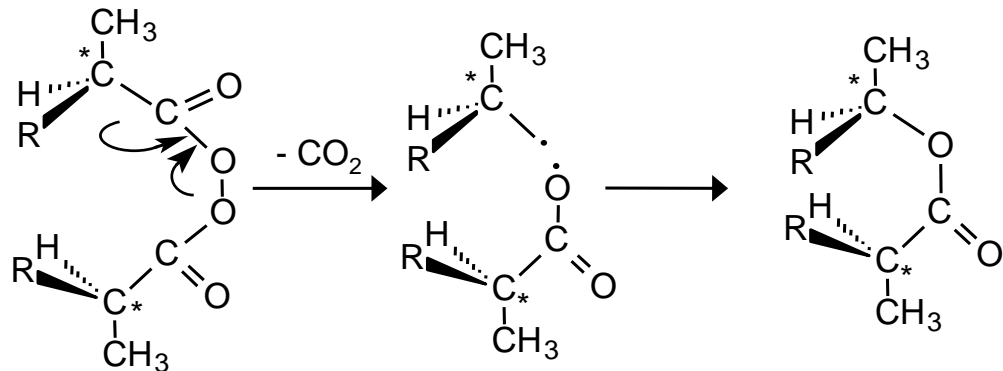
Alternate explanation
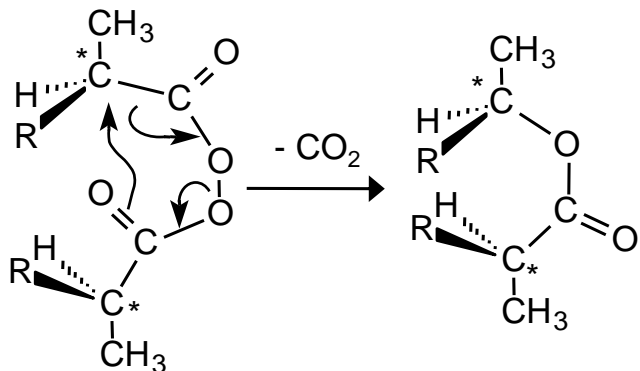
a concerted non-radical process

- **Normally, configurational isomers are only obtained by breaking covalent bonds, this is not the case with radicals**

- **With radicals, bond rotation determines the geometry and hybridisation of molecules.**

Tetrahedral ← **Pyramidal**   **Planar**   **Pyramidal** → Tetrahedral

sp^3 ← sp^2 → sp^3

+ _p_-character   **+ _p_-character**

Similarly,

$$AX_2 \quad X\!-\!\dot{A}\!-\!X \longrightarrow \underset{X \qquad\qquad X}{\overset{\dot{A}}{\diagdown}}$$

Linear Radical   **Non-Linear**
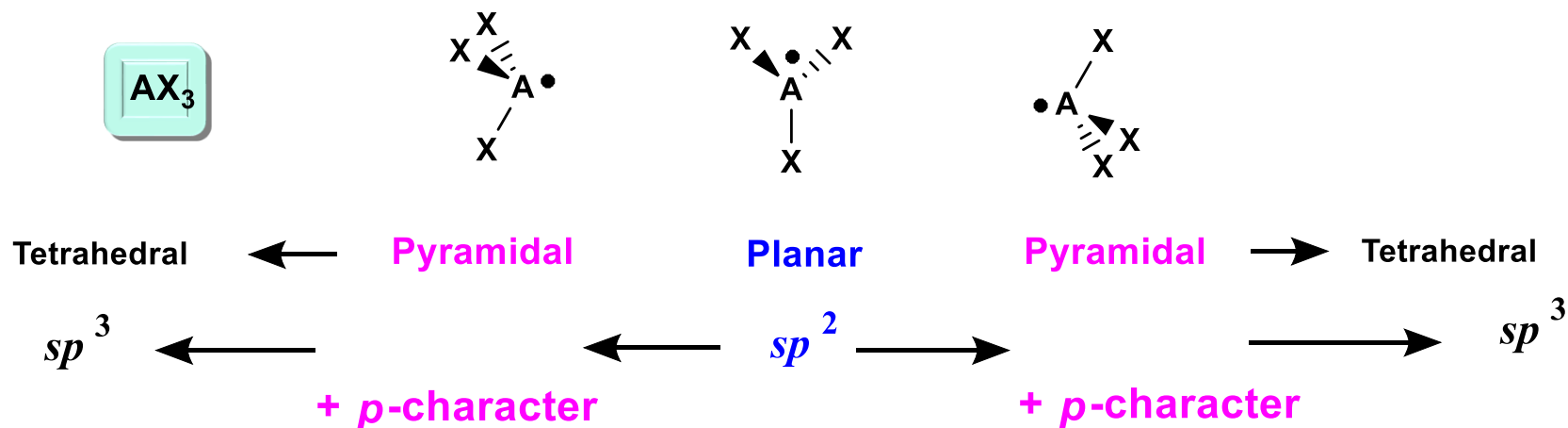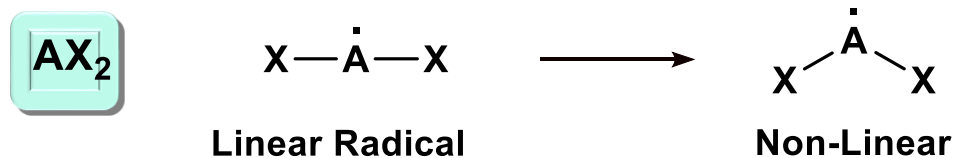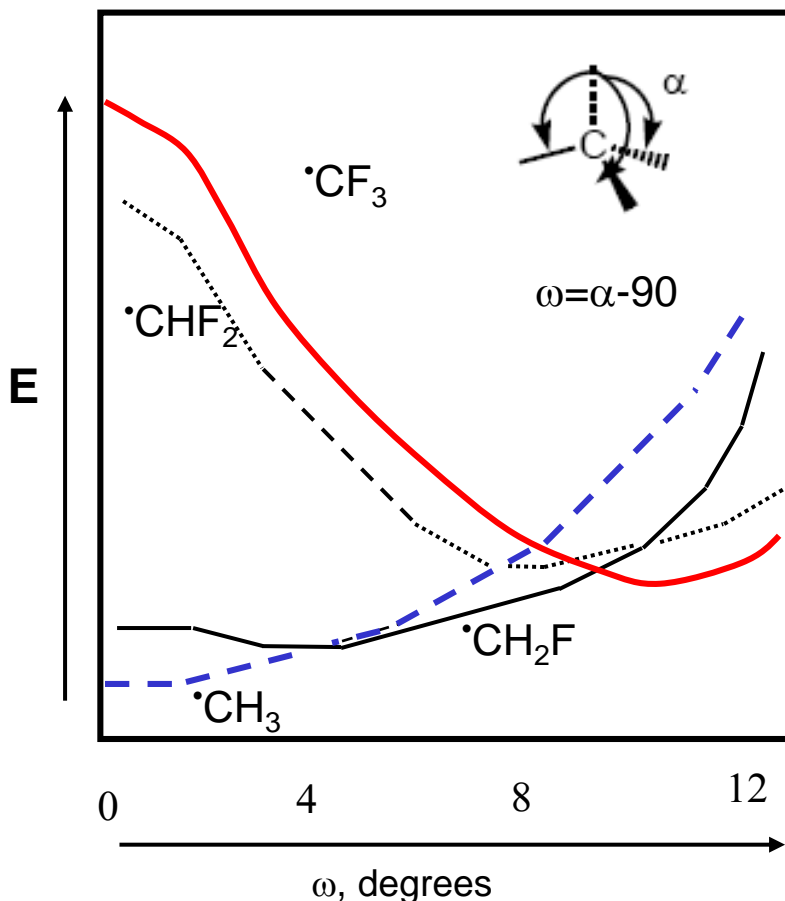
- ESR coupling

- Computations

- MO picture

- Polarization proportional to dipole moment
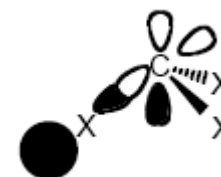
SOMO - filled lone pairs repulsion pyramidalization helps to stabilize the SOMO by the interaction of p-$\sigma*$

Zheng, X.; Phillips, D. L. *J. Phys. Chem. A.***2000,***104*, 1030.
Cramer, C. J. *J. Org. Chem.,***1991**, *56*, 5229.
Rozum, I.; Tennyson, J. *J. Phys. B.***2004,***37,*957.

The main factors which determine stability are Conjugation, Hyperconjugation, Hybridisation and Captodative effects

Hydrocarbon	Radical	BDE (kJ·mol^{-1})
CH_3-H	$CH_3^\bullet$	435
CH_3CH_2-H	$CH_3CH_2^\bullet$	406
$(CH_3)_2CH$-H	$(CH_3)_2CH^\bullet$	395
$(CH_3)_3C$-H	$(CH_3)_3C^\bullet$	380

- The order of stability of radicals is (in decreasing order):

  tertiary > secondary > primary > methyl   (**?**)

BDE

Filled C-H σ bond

Half-filled 2*p*

2*p*-Hybrid overlap
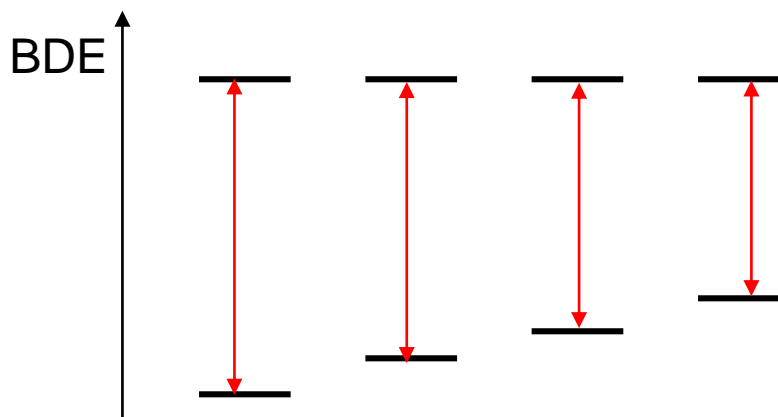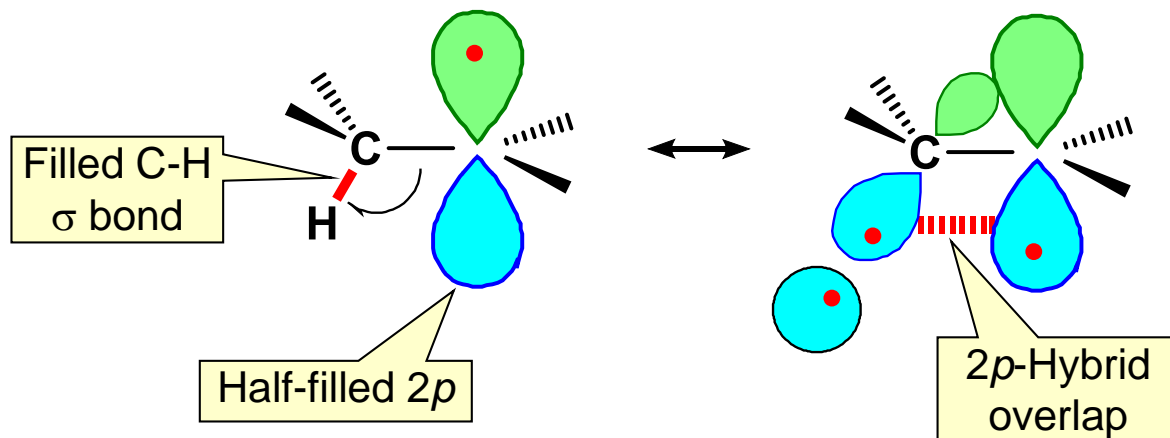
- The explanation resembles the stabilization through hyperconjugation in carbocations: the radical is stabilized by overlap with the *s*-bond of the adjacent CH's.

- A general behavior of radical center with exploit delocalization through interaction with electron pair on *beta* atom (both as non-bonded pair on a single atom or as bond pair, if appropriate geometry could be obtained).

Bond Dissociation Energy (kJ·mol^{-1})

$H_3C \text{—} CH_2CH_3 \longrightarrow CH_3 + CH_2CH_3$ — **355**

$H_3C \text{—} CH_2\text{-}CH{=}CH_2 \longrightarrow {}^{\bullet}CH_3 +$ allyl radical — **301**

1-butene

allyl radical

$H_2C{=}CHCH_2 \text{—} CH_2CH{=}CH_2 \longrightarrow 2$ — **259**

1,5-Hexadiene
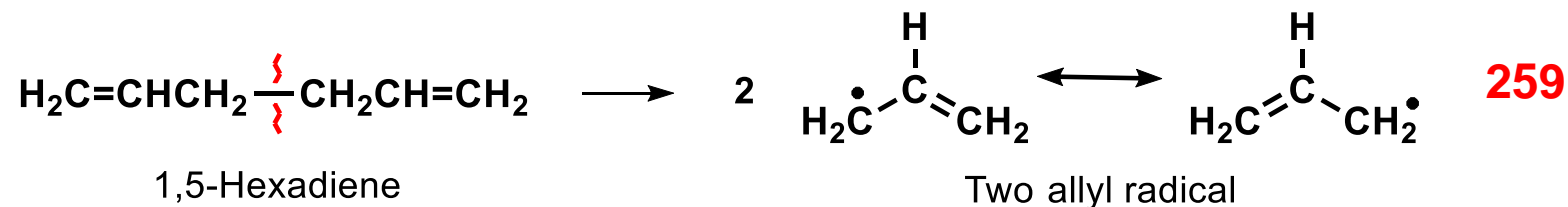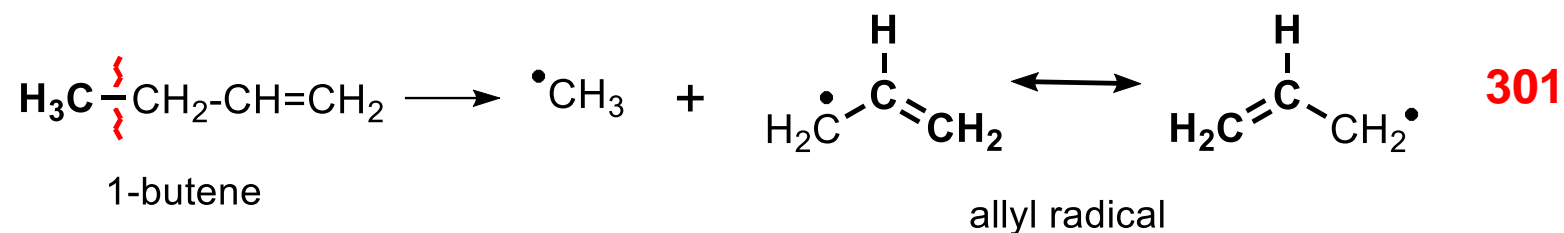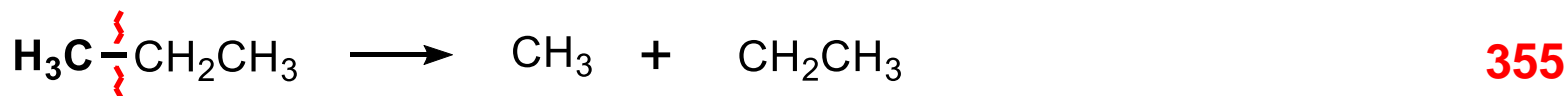
Two allyl radical

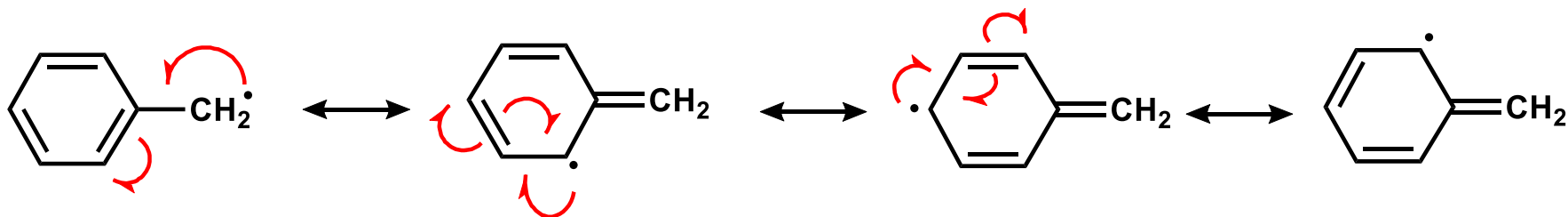- Just as with cations and anions, radicals are also stabilized by resonance; therefore, allylic radicals are more stable than simple alkyl radicals

An orbital view of the allyl radical. The p orbital on the central carbon can overlap equally well with a p orbital on either neighboring carbon because the structure is electronically symmetrical
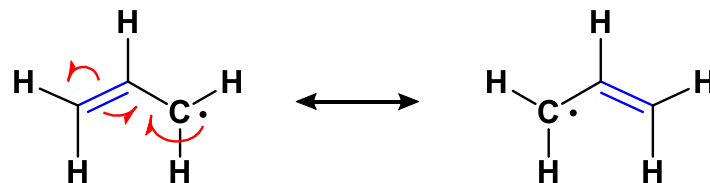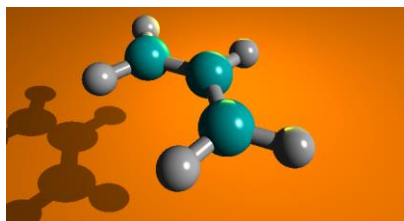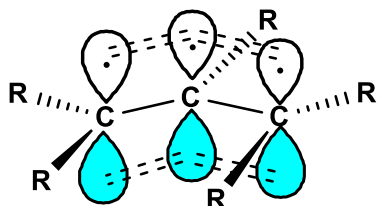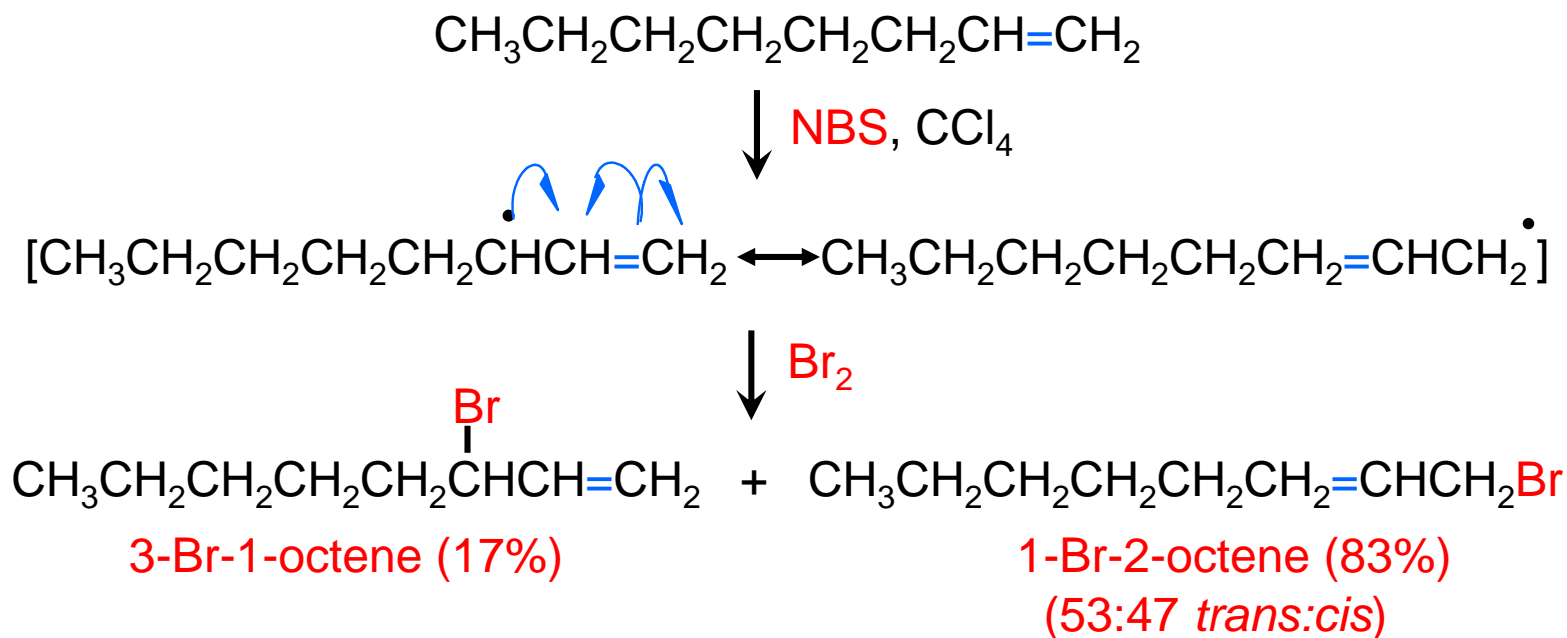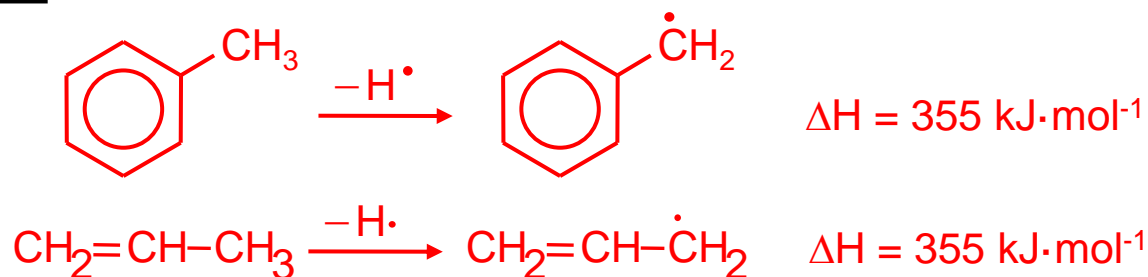

benzyl radical

Two products are formed in the bromination of unsymmetrical alkenes, i.e. 1-octene, but, because the intermediate allylic radical is not symmetrical and the reaction at the two ends is not equally likely, the substitution at the less hindered, primary end is favored.
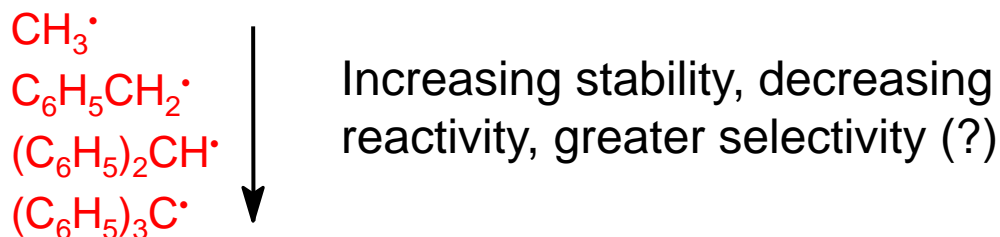
$$CH_3CH_2CH_2CH_2CH_2CH_2CH=CH_2$$

$\downarrow$ NBS, CCl_4

$$[CH_3CH_2CH_2CH_2CH_2\overset{\bullet}{C}HCH=CH_2 \longleftrightarrow CH_3CH_2CH_2CH_2CH_2CH_2=CH\overset{\bullet}{C}H_2]$$

$\downarrow$ Br_2

$$\overset{\displaystyle Br}{\underset{\displaystyle }{CH_3CH_2CH_2CH_2CH_2CHCH=CH_2}} \quad + \quad CH_3CH_2CH_2CH_2CH_2CH_2=CHCH_2Br$$

3-Br-1-octene (17%)   1-Br-2-octene (83%)

(53:47 *trans:cis*)

Observation:

$$\text{C}_6\text{H}_5\text{CH}_3 \xrightarrow{-\text{H}^\bullet} \text{C}_6\text{H}_5\overset{\bullet}{\text{CH}}_2 \qquad \Delta H = 355 \text{ kJ·mol}^{-1}$$

$$\text{CH}_2{=}\text{CH}{-}\text{CH}_3 \xrightarrow{-\text{H}\cdot} \text{CH}_2{=}\text{CH}{-}\overset{\bullet}{\text{CH}}_2 \qquad \Delta H = 355 \text{ kJ·mol}^{-1}$$

Basis: Abstraction of either benzylic or allylic hydrogen atoms to produce benzyl or allylic radicals is a lower energy process than that for corresponding saturated systems due to the possibility of π-delocalization of the odd electron in the former systems.

Observation:

$$\text{CH}_3{}^\bullet$$
$$\text{C}_6\text{H}_5\text{CH}_2{}^\bullet$$
$$(\text{C}_6\text{H}_5)_2\text{CH}^\bullet$$
$$(\text{C}_6\text{H}_5)_3\text{C}^\bullet$$

Increasing stability, decreasing reactivity, greater selectivity (?)

Basis: The greater the possibility for π-delocalization, the greater the stability of the radical species.

Observation:

$$\rho = -0.38$$

Relative stabilities:

Z =	CH_3	OCH_3	H	Br	CN	NO_2
	1.9	1.2	1.0	1.8	3.7	4.0

Conclusions:

1. Based on the measured rho (ρ) value for benzyl radical formation, the reaction is relatively insensitive to substituent electronic effects.

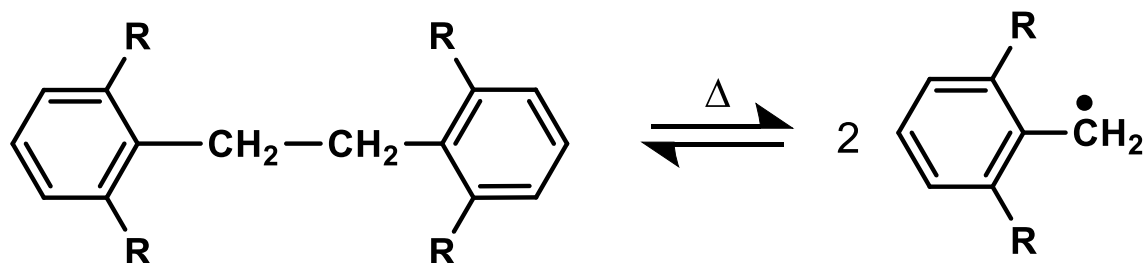2. Both electron donating and withdrawing substituents stabilize the benzyl radical.

Rationale:

Consider the following dissociation reaction:

Observations: As the size of R increases (methyl, ethyl, isopropyl, t-butyl),

    a) the magnitude of the equilibrium constant increases
    b) the reactivity of the resulting benzyl radical decreases
    c) the radical with the largest *ortho*-substituents forms fastest (at a fixed T)
    d) the benzyl radical with the largest *ortho*-substituents is formed under the mildest reaction conditions (under variable temperature conditions)

Rationale: As R increases in size, the reactant is destabilized. Production of the substituted benzyl radical serves to relieve steric strain.

    Once formed, the benzyl radical with the largest *ortho*-substituents will experience the greatest steric hindrance to recombination or to other reactions at the radical site.

Substituent Effects

F (+M)

π **-Donors (+M) ,** $\sigma-$ **Attractors (-I)** $\longrightarrow$ **- F, - Cl , - Br , - I**

- OH

- NH$_2$

π **-Acceptors (-M) ,** $\sigma-$ **Acceptors (-I)** $\longrightarrow$ **HC≡C——**

N≡C——

SOMO energy is raised by electron donating groups, Radical is repelled by substituents

SOMO energy is raised by electron withdrawing groups, Radical is stabilized Inductive effects

E

"C" centered SOMO

n or filled σ orbital

π^*

π^*

π

X type
NR_2, OR
Cl, Me, I

Z type
COR, CN
SOR, NO, NO_2

C type
$C=CH_2$
Ph, etc.
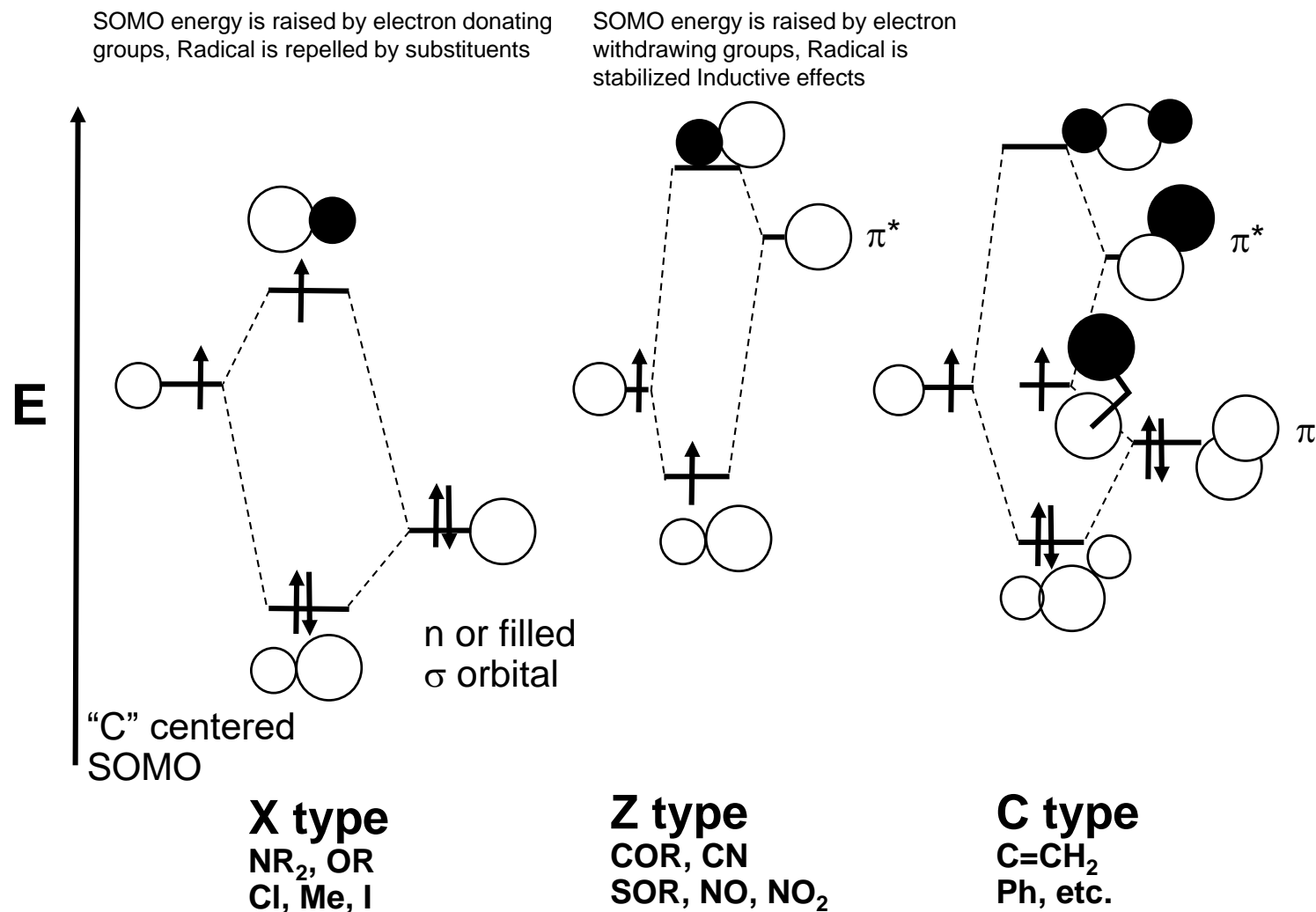
"Orbital Interaction Theory in Organic Chemistry'" **2001**, 2nd Ed, Rauk, A. Wiley & sons. Inc.,

Group IV Hydrides

$\overset{\cdot}{CH_3}$ < $\overset{\cdot}{SiH_3}$ < $\overset{\cdot}{GeH_3}$ < $\overset{\cdot}{PbH_3}$

→ *Pyrimidized*

Alkyl Radicals

Staggered   *Eclipsed*

Pyrimidized rotamer
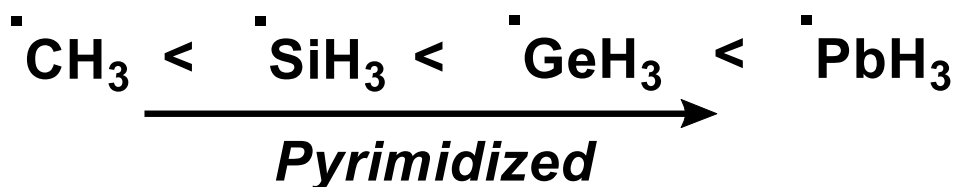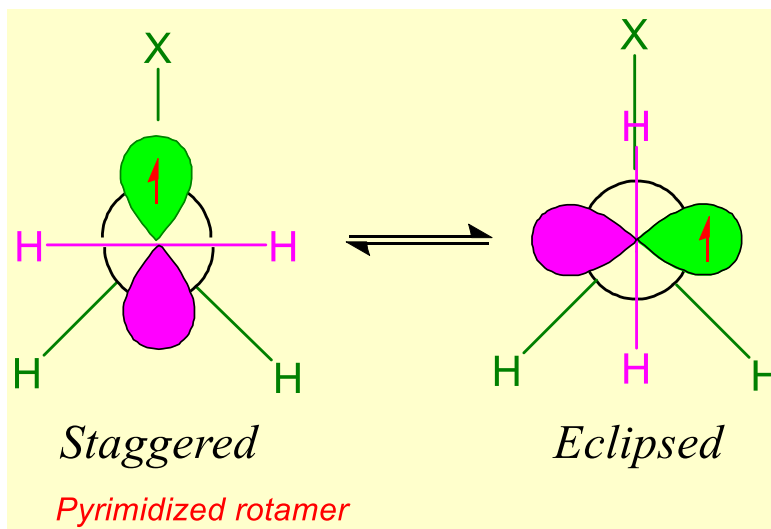
As alkyl radicals become more substituted so they become more pyramidal.
Also, when X = SR , Cl , SiR_3 , GeR_3 or SnR_3 – delocalisation of the unpaired electron into the C-X bond increases. The eclipsed rotomer becomes the transitional structure for rotation

Lewis Structure

- or -

?

$2\pi g$

$1\pi u$

$3\sigma g$

$2\sigma u$

$1\sigma g$

$4\sigma u$
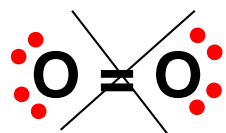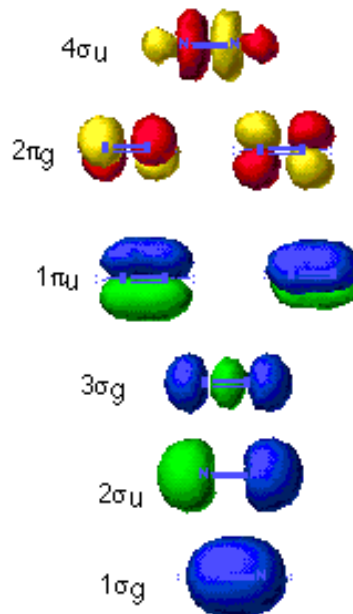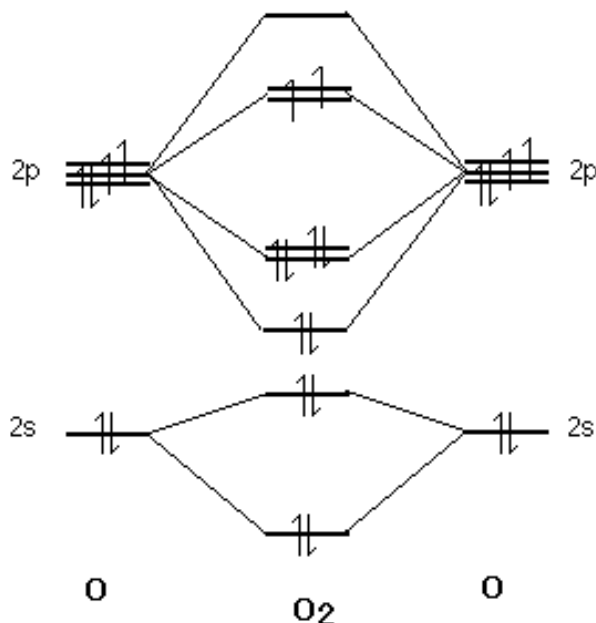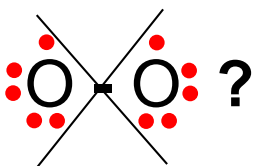
Bond Order = (1/2) [10 – 6] = 2
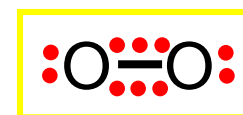
- Two "3 electron" bonds
- One σ bond

- 12 valence electrons in $2s$ and $2p$ orbitals
- From Hund rule, electrons fill the two low lying π antibonding orbitals.
- This lives two unpaired electrons (paramagnetic molecule – electronic state $X^3\Sigma_g^-$).

Persistent radical, until 1989 considered only a pollutant. Then, identified as a fundamental signaling agent in cells biochemistry with relevant physiological roles.

$$\sigma_{2p}^{*}$$

$$\pi_{2p}^{*}$$

$$\sigma_{2p}$$

$$\pi_{2p}$$

$$\sigma_{2s}^{*}$$

$$\sigma_{2s}$$

E

Bond Order = (1/2) [8– 3] = 2.5

:O≡N:

1 σ bond
1 π bond
1 "3 electrons" bond
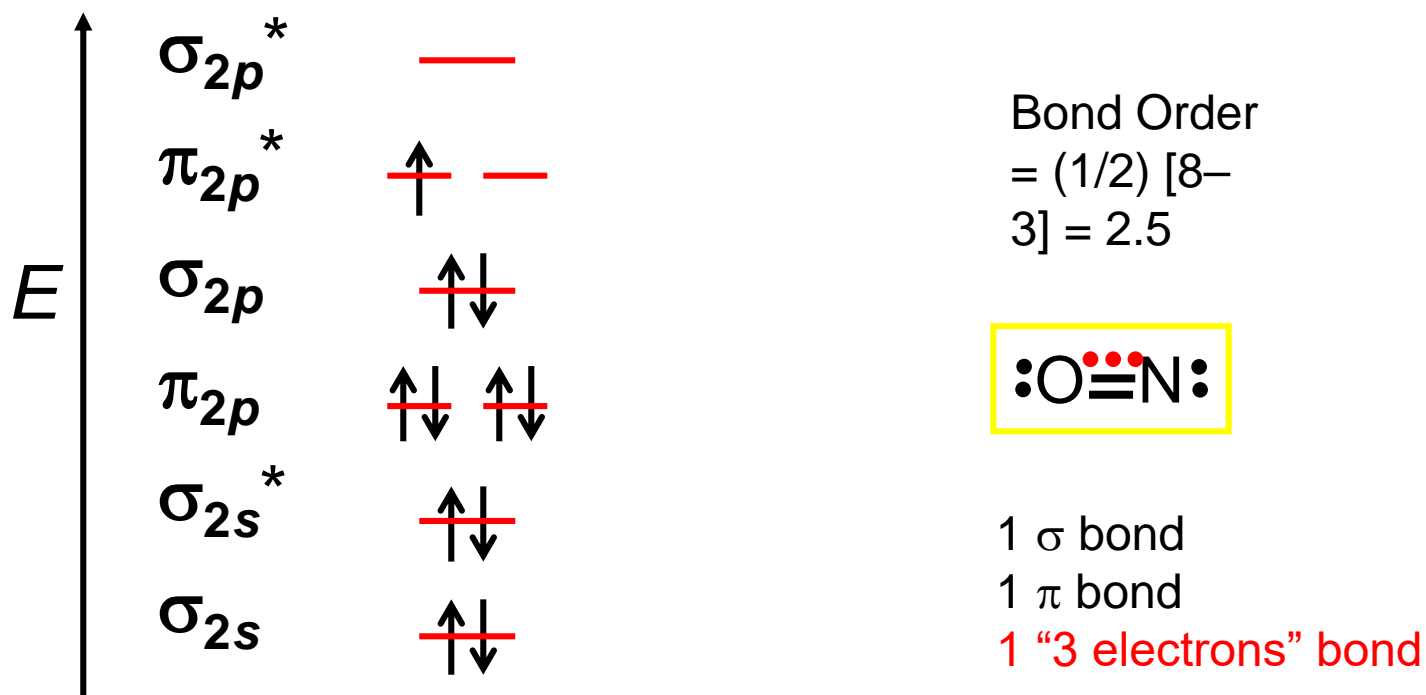
Nitric oxide: a molecule of millennium! *Circ Res* **2000**, *87*, 85-7.

- **In the formation and breaking of chemical bonds radicals, even the uncharged ones, develop a significant charge transfer in the transition state showing significant polarity.**

a) *Electrophilic Radicals*

$$R^{\bullet} + B \rightarrow [R^{-} \cdots B^{\bullet+}] \rightarrow R\text{-}B^{\bullet}$$

R•

SOMO

HOMO

3e   Low IP
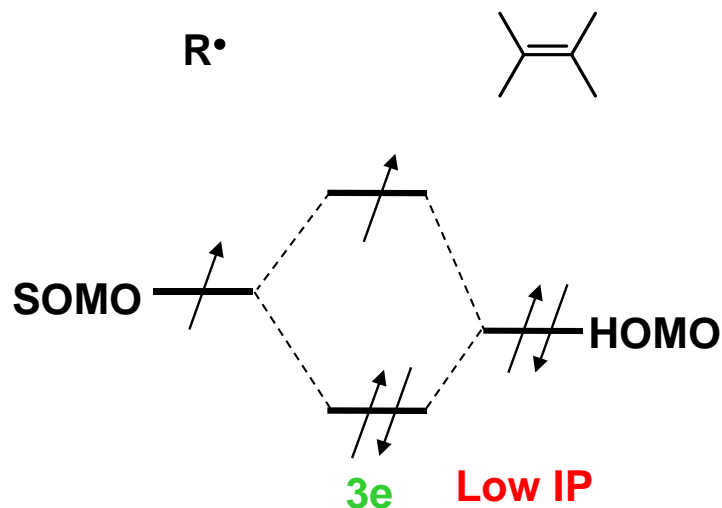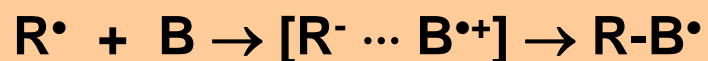
b) *Nucleophilic Radicals*

$$R^{\bullet} + A \rightarrow [R^{+} \cdots A^{\bullet-}] \rightarrow R\text{-}A^{\bullet}$$

R•

LUMO

1e   high AE
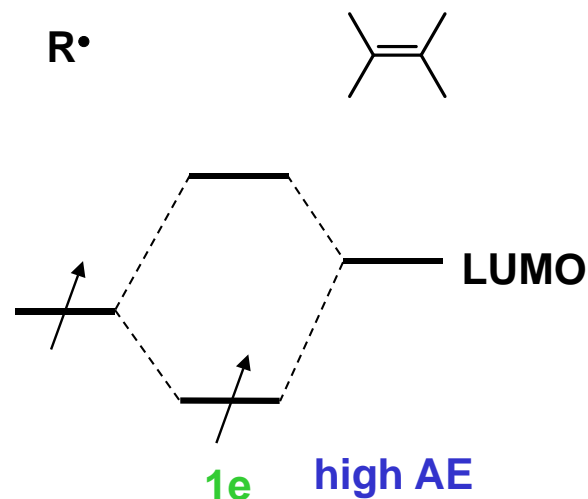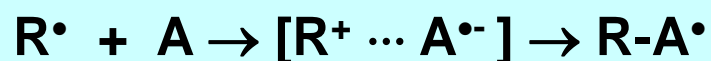
Aminium Radical cation $H_3N^{\bullet+}$

Association with NH_3 to give the dimer radical cation $[H_3N \therefore NH_3]^+$

MO Model:
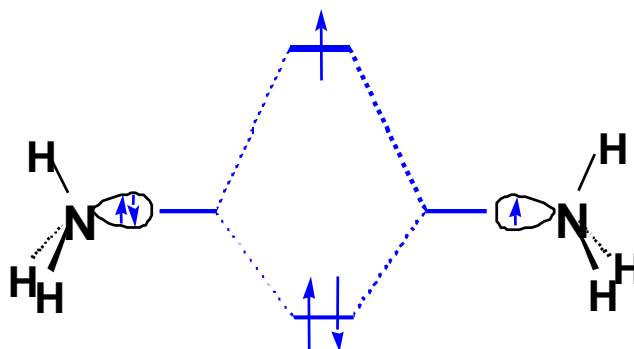
2 bonding electrons,
1 antibonding electron

$\Rightarrow$ Stability

Bond index: 0.5 « hemi-bond »

Valence Bond Model:

$H_3N \cdots NH_3^+$ $\longleftrightarrow$ $H_3N^+ \cdots NH_3$
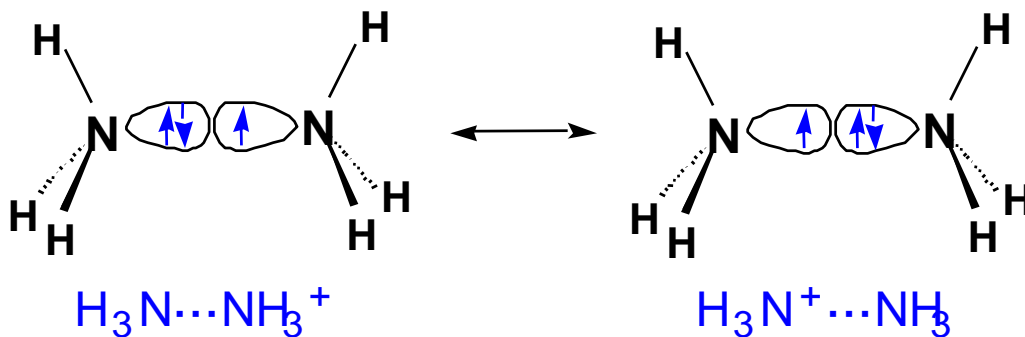
Resonance between
2 VB structures

$\Rightarrow$ Stability

$$\diagdown N \overset{+}{\underset{\cdot\cdot}{}} N \diagup \qquad \diagdown O \overset{+}{\underset{\cdot\cdot}{}} O \diagup \qquad F \overset{+}{\underset{\cdot\cdot}{}} F \qquad Ne \overset{+}{\underset{\cdot\cdot}{}} Ne$$

$$\diagdown P \overset{+}{\underset{\cdot\cdot}{}} P \diagup \qquad \boxed{\diagdown S \overset{+}{\underset{\cdot\cdot}{}} S \diagdown} \qquad Cl \overset{+}{\underset{\cdot\cdot}{}} Cl \qquad Ar \overset{+}{\underset{\cdot\cdot}{}} Ar$$

$$[A \overset{\cdot\cdot}{} B]^+ \xrightarrow{\Delta E} A{:} \ + \ B^{\bullet+} \qquad\qquad [A \overset{\cdot\cdot}{} B]^- \xrightarrow{\Delta E} A{:}^- + \ B^{\bullet}$$
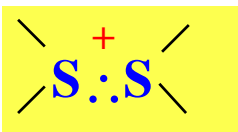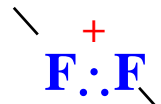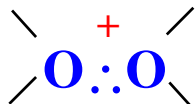
Cations: $[Rg \overset{\cdot\cdot}{} Rg]^+$ $\Delta E = 96\text{-}130 \ \text{kcal}\cdot\text{mol}^{-1}$
(Rg = Ne, Ar, Xe….)

Anions: $[X \overset{\cdot\cdot}{} X]^-$ $\Delta E = 100\text{-}125 \ \text{kcal}\cdot\text{mol}^{-1}$
(X = F, Cl, Br, I)

$$F^- + F^\bullet \longrightarrow [F \cdots F]^-$$

$$F \because F ,^{\ominus} \quad Cl \because Cl ,^{\ominus}$$

$$Br \because Br ,^{\ominus} \quad F \because Cl ,^{\ominus}$$

$$+ \text{ isoelectronic } ...$$

$$RS \because SR ,^{\ominus}$$
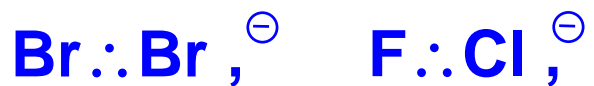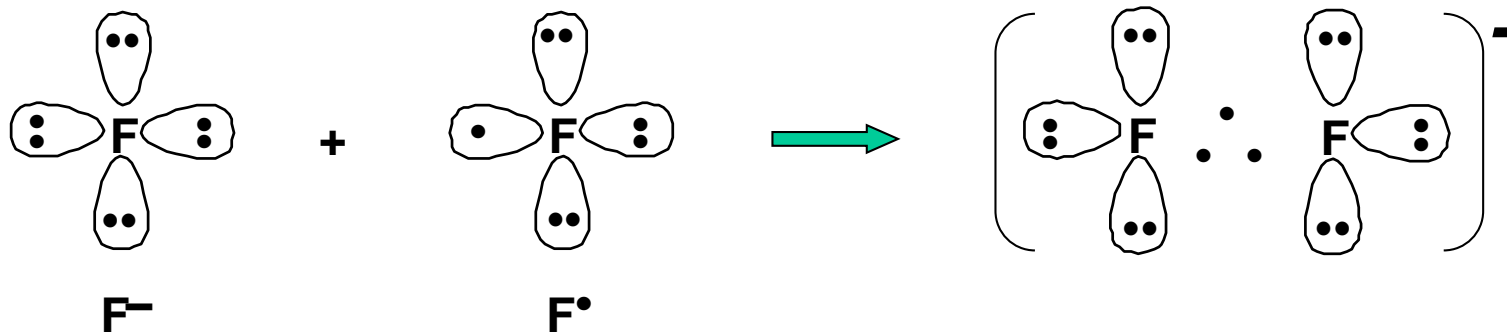
- HOMO(A) ≈ same energy as HOMO(B)
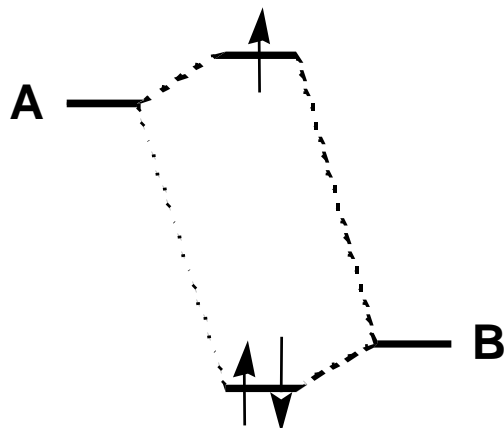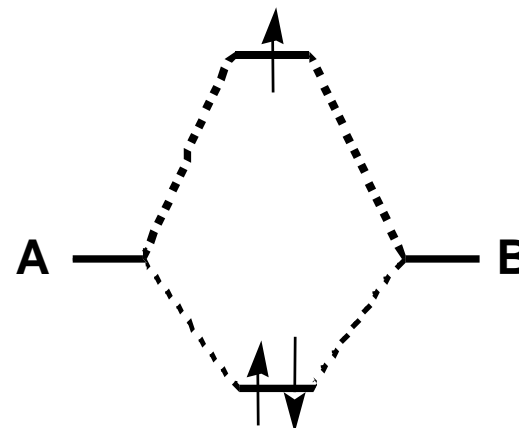
unfavorable **favorable**

IP(A) ≈ IP(B) (cations)   or :   EA(A) ≈ EA(B) (anions)

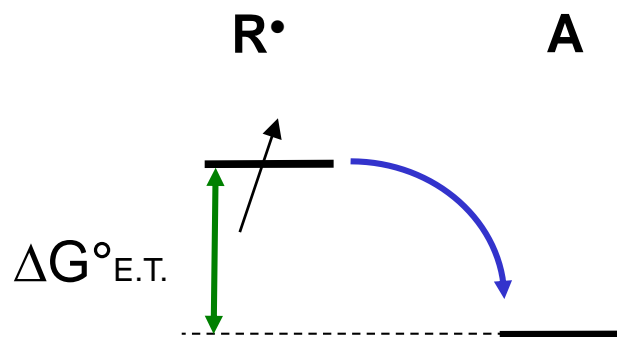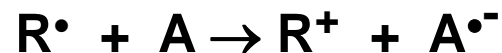## Met-Gly
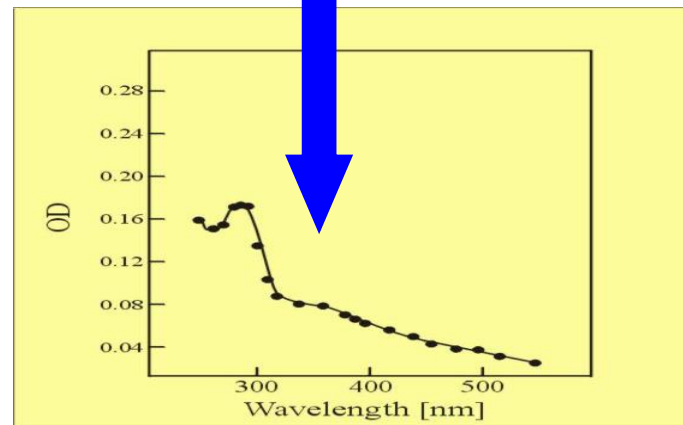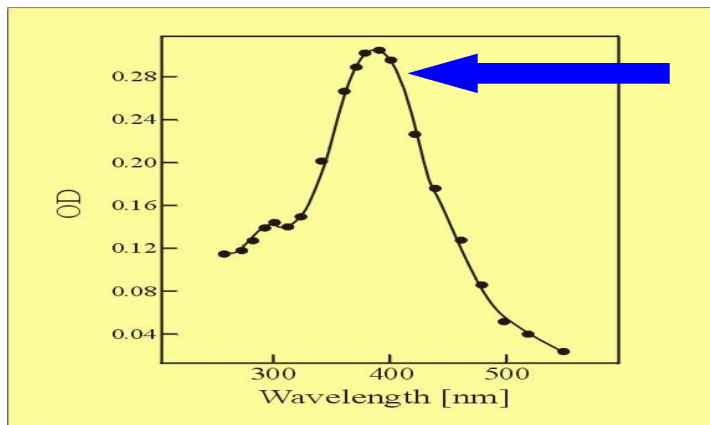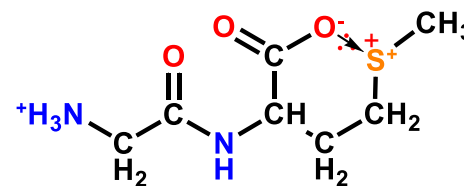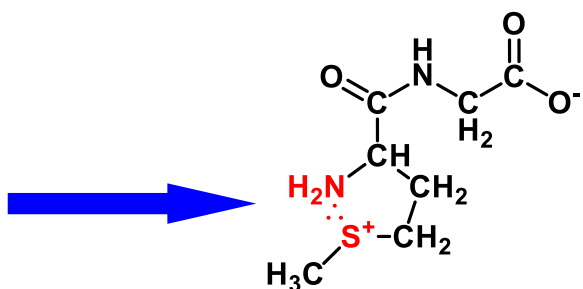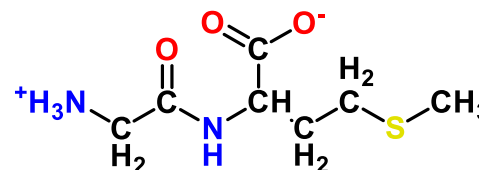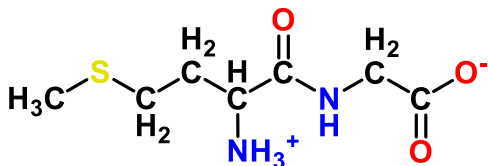
- Radicals, even the uncharged ones, are easily involved in electron transfer (redox) processes owing their ability to gain electrons from reducing species (when centered on electronegative atoms) or transfer electrons to oxidant species (when centered on electropositive atoms).

a') *Oxidant Radicals*

$$R^\bullet + B \rightarrow R^- + B^{\bullet+}$$

R$^\bullet$ B

$\Delta G°_{E.T.}$
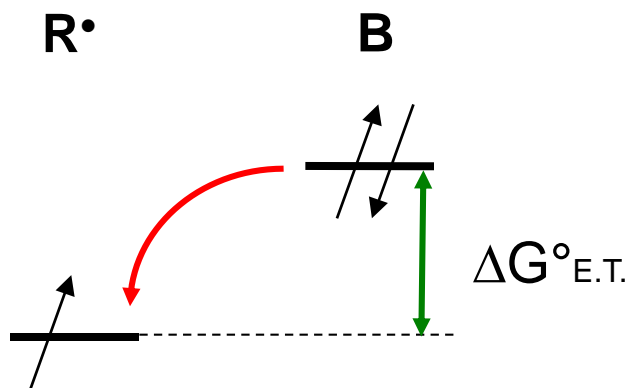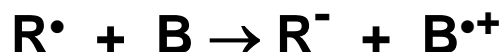
b') *Reducing Radicals*

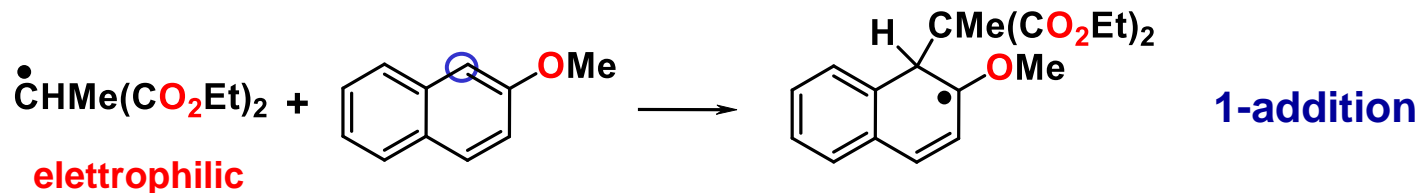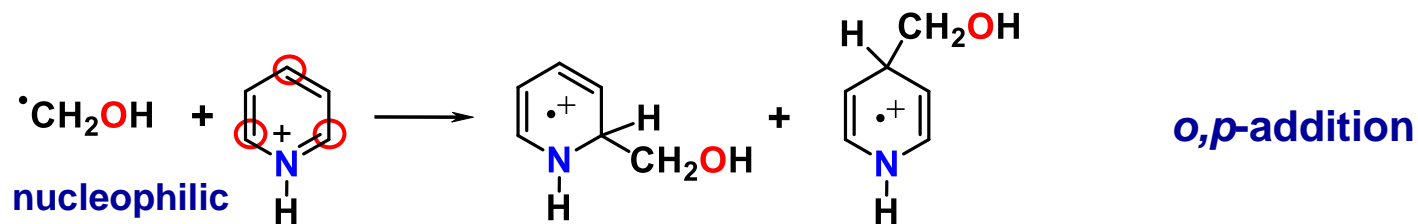$$R^\bullet + A \rightarrow R^+ + A^{\bullet-}$$

R$^\bullet$ A

$\Delta G°_{E.T.}$

a) POLAR EFFECTS

(related to the sensitivity of radicals to electron density of substrates, Hammett correlations with positive ρ (electrophilic) and negative ρ (nucleophilic), partial electron transfer in the transition state)

nucleophilic
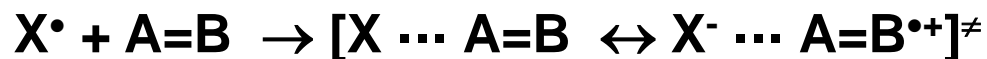
o,p-addition

elettrophilic

1-addition

The sensitivity to polar effects depend upon the exothermicity of the reaction: when $\Delta H \ll 0$ a low selectivity is observed (Evan-Polany relationship):

$$E^{\neq} = -\alpha \cdot \frac{1}{\Delta H^0}$$

$$X^{\bullet} + A{=}B \rightarrow [X \cdots A{=}B \leftrightarrow X^{-} \cdots A{=}B^{\bullet+}]^{\neq}$$

Name	Structure	Substrates from which they form by	
		Displacement	Addition
Chlorine atom	$Cl^{\bullet}$	Cl-Cl, H-Cl	- -
Bromine atom	$Br^{\bullet}$	Br-Br, HBr, R_2NBr	- -
Alkoxy	$RO^{\bullet}$	RO-X, RO-OR	- -
Tiyl	$RS^{\bullet}$	RS-H, RS-SR	- -
Trihalomethyl	$X_3C^{\bullet}$	X_3C-X, X_3C-H	- -
α-Haloalkyl	$X{-}CR_2^{\bullet}$	XCR_2-X, XCR_2-H	$XCR{=}CH_2$
α-Cyanoalkyl	$NC{-}CR_2^{\bullet}$	$NCCR_2$-X, (H)	$NCCR{=}CH_2$
α-Ketoalkyl	$R{-}OC{-}CR_2^{\bullet}$	R-OC-CR_2-X ,(H)	R-OC-CR$=CH_2$

Examples of Nucleophilic Radicals

$$X^\bullet + A=B \rightarrow [X \cdots A=B \leftrightarrow X^+ \cdots A=B^{\bullet-}]^{\neq}$$

Name	Structure	Substrates from which they form by	
		Displacement	Addition
Alkyl primary	$RCH_2^\bullet$	$RCH_2\text{-}H$	$CH_2=CH_2$
Alkyl second.	$R_2CH^\bullet$	$R_2CH\text{-}H$	$RCH=CH_2$
Alkyl tertiary	$R_3C^\bullet$	R_3C	$RR'C=CH_2$
Allyl	$CR_2=CH\text{-}CR_2^\bullet$	$CR_2=CH\text{-}CR_2$	$CH_2=CH\text{-}CH=CR_2$
Benzyl	$PhCH_2^\bullet$	$PhCH_2\text{-}H$	$ArCR=CH_2$
α-Hydroxyalkyl	$HO\text{-}CR_2^\bullet$	$HO\text{-}CR_2\text{-}H$	$HOCR=CH_2$
α-Alkoxyalkyl	$RO\text{-}CR_2^\bullet$	$RO\text{-}CR_2\text{-}H$	$ROCR=CH_2$
α-Aminoalkyl	$R_2N\text{-}CR_2^\bullet$	$R_2N\text{-}CR_2\text{-}H$	$R_2N\text{-}CR=CH_2$
Acyl	$R\text{-}^\bullet C=O$	$R\text{-}CO\text{-}H$	$O=C=CH_2$

Cl•   ↓   ↓   ↓   ↓

CH$_3$-CH$_2$-CH$_2$-CH$_2$Y
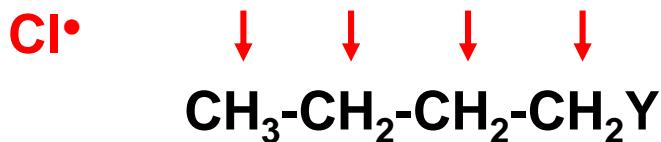
Y				
H	1	4	4	1
Cl	1	4	2	1
C(O)Cl	1	4	2	0.2
COOH	1	4	1.5	0

Kim, S. S.; Choi, S. Y.; Kang, C. H. *J. Am. Chem. Soc.* **1985,** *107*, 4234.

Selectivity Me$_2$NH^{+}$^•$

CH$_3$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$Y

2	72	19	7	0	0
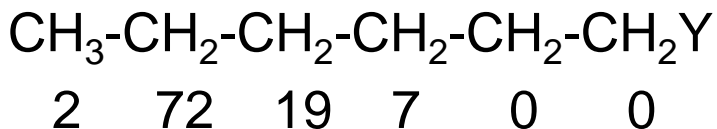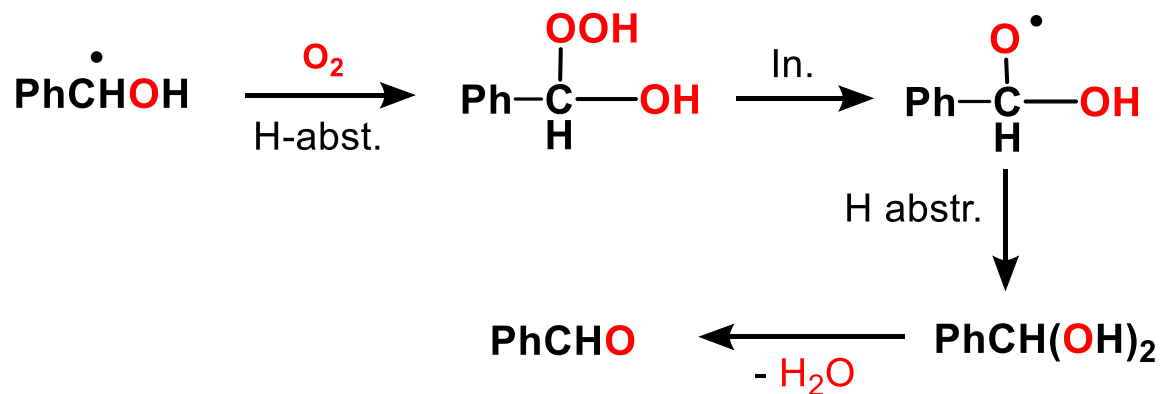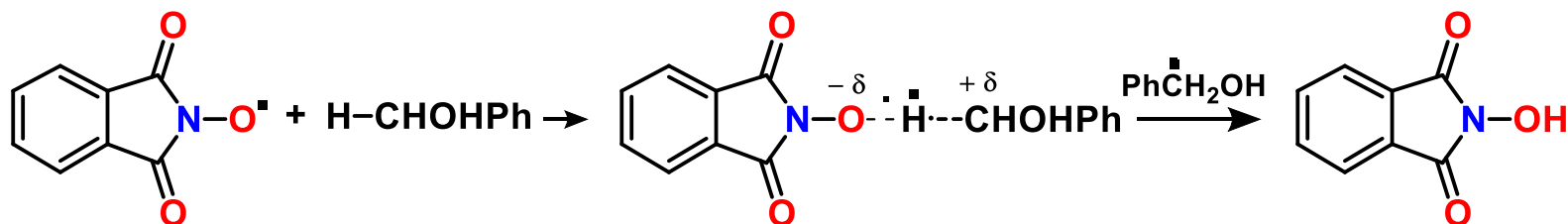
Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *J. Org. Chem.* **2002**, *67*, 2671.
Annunziatini, C.; Gerini, M. F.; Lanzalunga, O.; Lucarini, M. *J. Org. Chem.* **2004**, *69*, 3431.
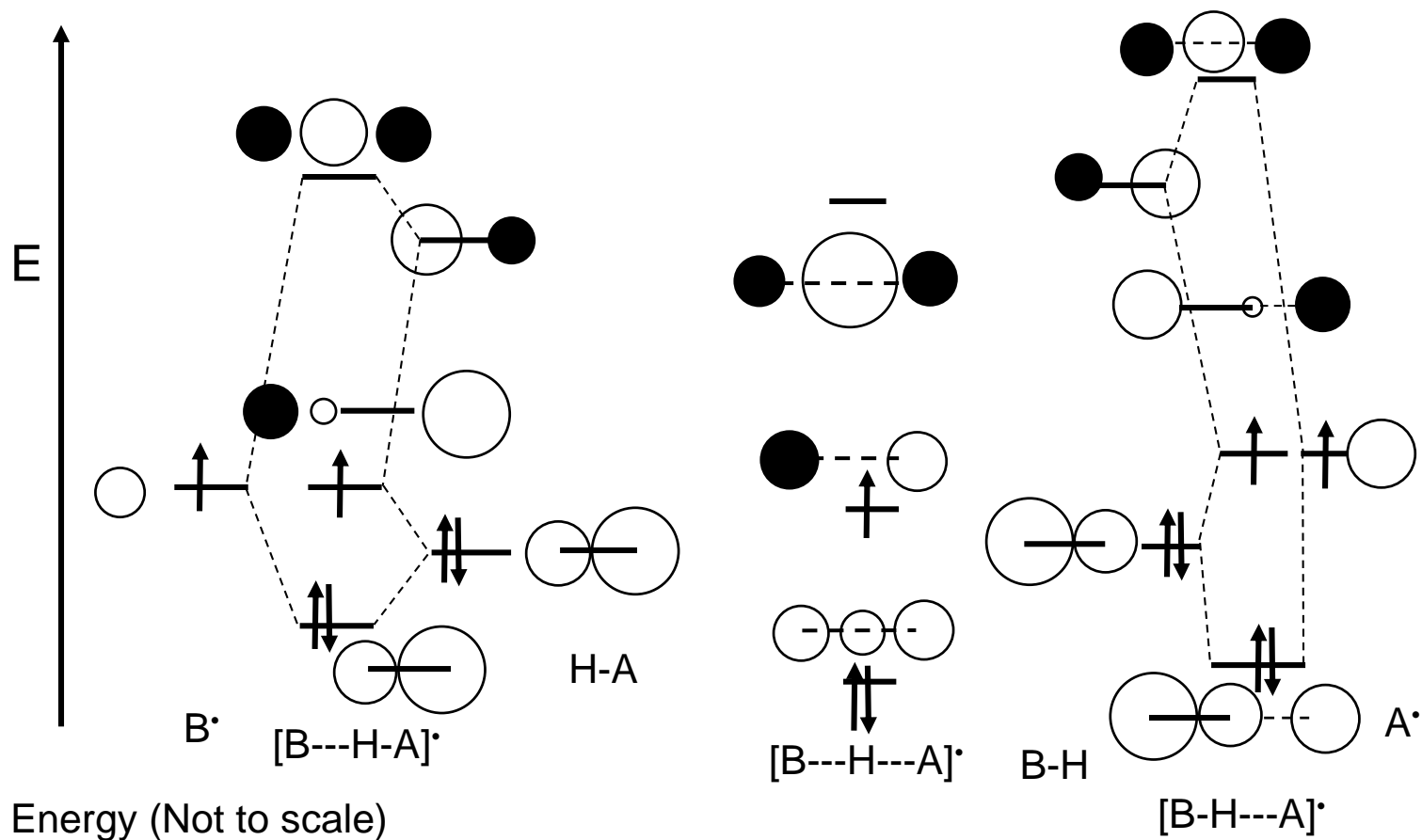Hermans, I.; Vereecken, P. A.; Jacobs, A.; Peters, *J. Chem. Commun.*, **2004**, 1140.

PINO → **NHPI**
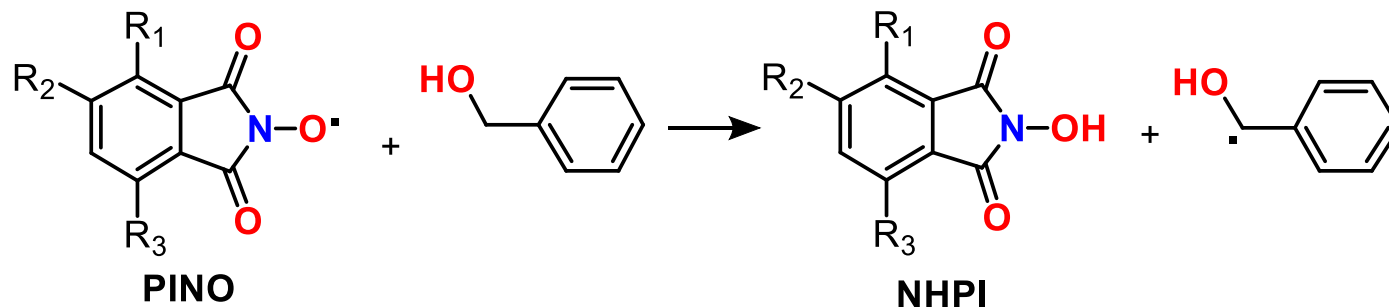
Entry	R_1	R_2	R_3	ρ
1	H	MeOCO	H	-0.70
2	F	H	H	-0.69
3	H	H	H	-0.68
4	MeO	H	H	-0.60
5	MeO	MeO	H	-0.54

$\rho = -0.69$

BDE   69.6   79.2   88.1
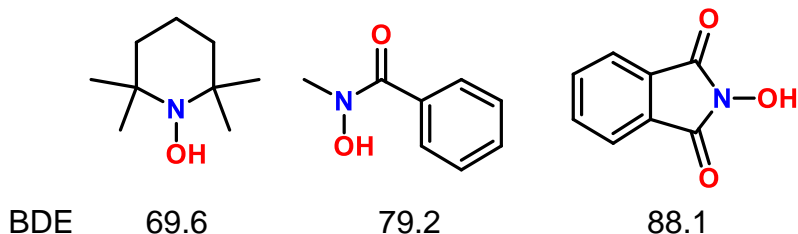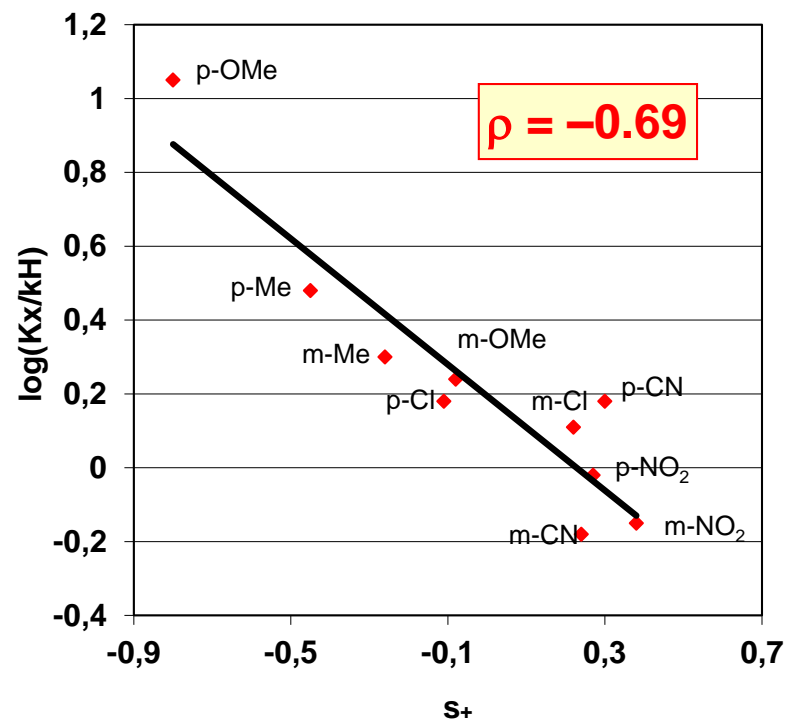
Minisci, F. et al. *Eur. J. Org. Chem.* **2004**, 109.

E

H-A

B•   [B---H-A]•

[B---H---A]•   B-H

A•

[B-H---A]•

Energy (Not to scale)

"The stability of alkyl radicals", Tsang, W. J. Am. Chem. Soc.,1985, 107, 2872.

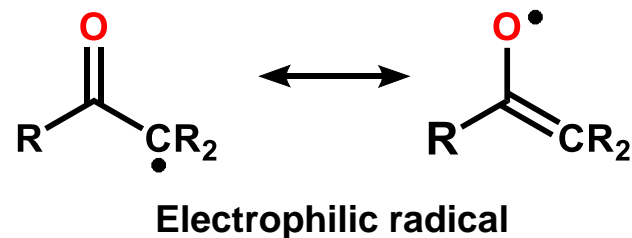"Kinetics and Thermochemistry of CH_3, C_2H_5, i-C_3H_7, Study of equilibrium of $R^\bullet$ + HBr

"Russel, J. J.; Seetula, J. A.; Gutman, D. J. Am. Chem. Soc., 1990, 112, 1347.

| X = Cl | 1 | 50 |
| X = CH$_3$ | 5.2 | 1 |

Umpolung Reactivity

Electrophilic cation

Nucleophilic anion

Nucleophilic radical

Electrophilic radical
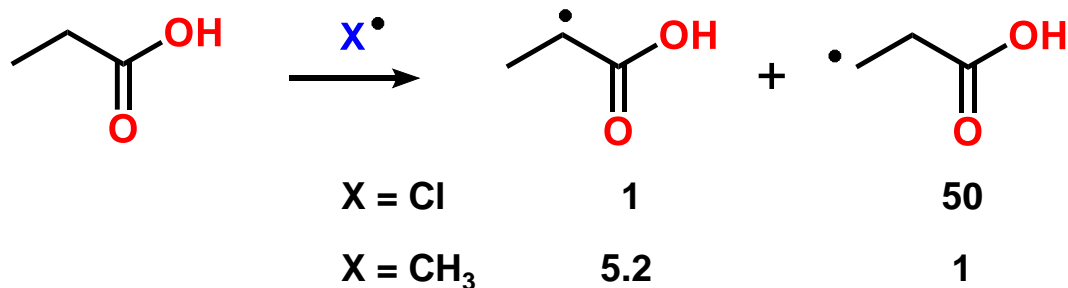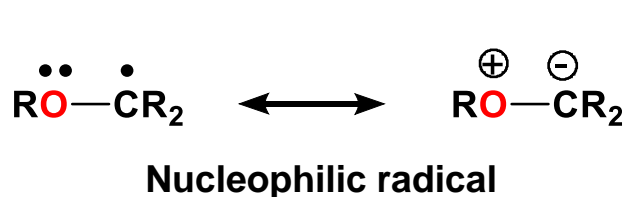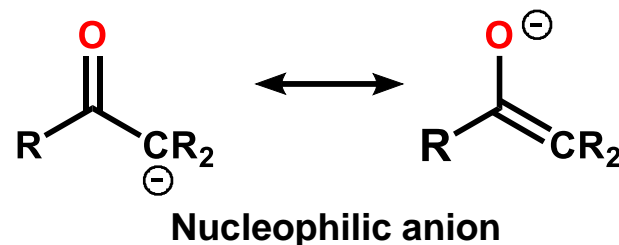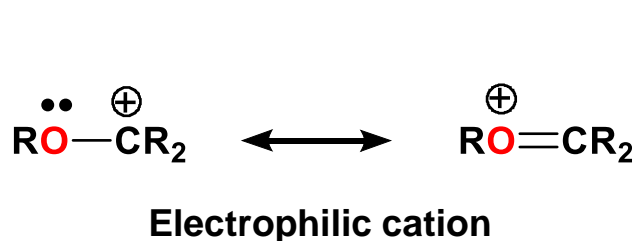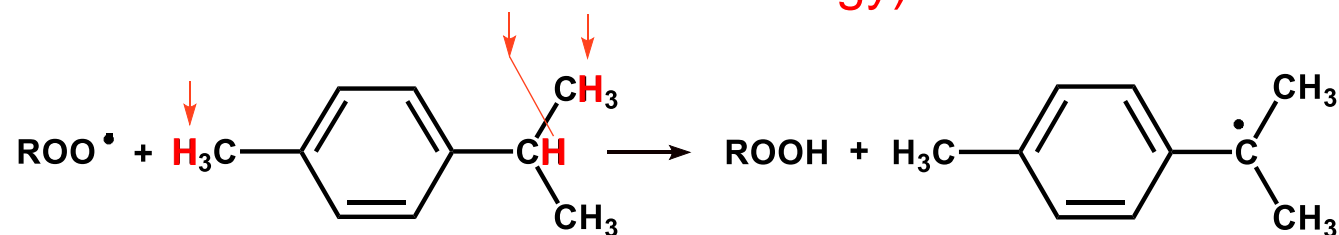
Parsons, A.F., An Introduction to Free Radical Chemistry, Blackwell Science, Oxford, 2000.

b) <u>RESONANCE EFFECTS</u>
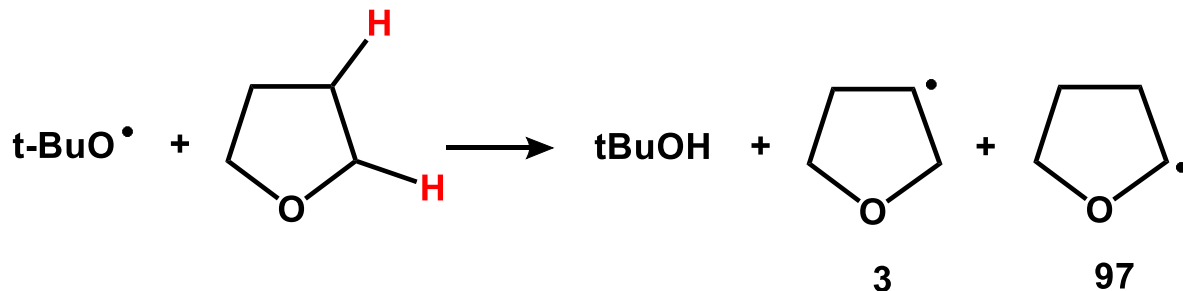
(connected to radical stabilization energy)

Tertiary benzyl radical (90-100%)
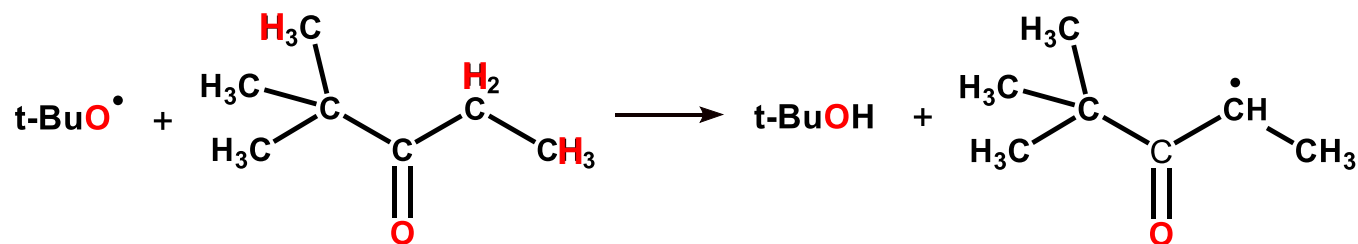
α-Carbonylalkyl radical (95%)
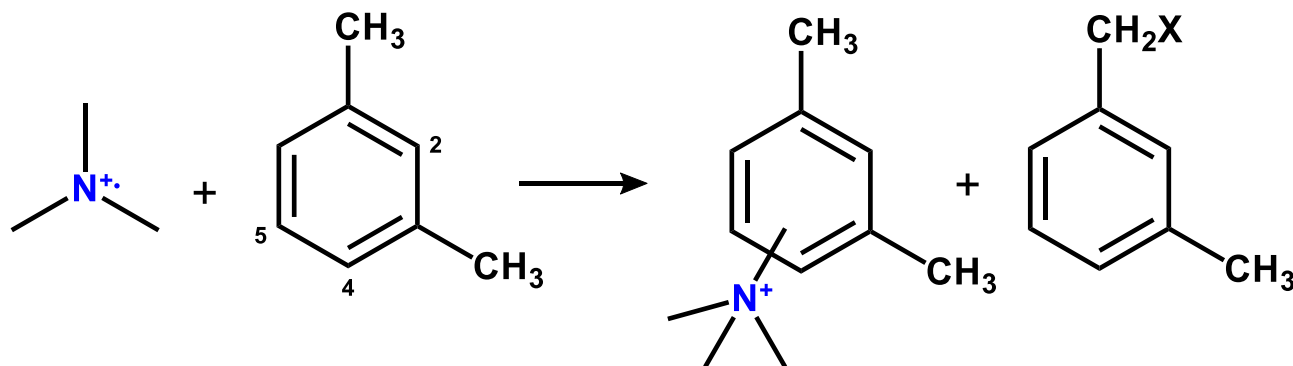

α-Oxyalkyl Radical

3   97

c) STERIC EFFECTS

Radical	----------- Regioselectivity for position -----------			
	4	5	2	CH$_3$
NH$_3$$^{•+}$	70	19	11	-
MeNH$_2$$^{•+}$	60	25	14	-
(Me)$_2$NH$^{•+}$	24	70	6	2
(c-C$_6$H$_{11}$)$_2$NH$^{•+}$	-	-	-	100

Fate of diffusive cage pair:

$$R^\cdot + R^\cdot \underset{k_{-diff}}{\overset{k_{diff}}{\rightleftharpoons}} (\dot{R}/\dot{R})_{cage} \nearrow^{k_{dim}} R\text{-}R$$
$$\searrow_{k_{disp}} R_{-H} + R_{+H}$$

for ^{t}Bu radical
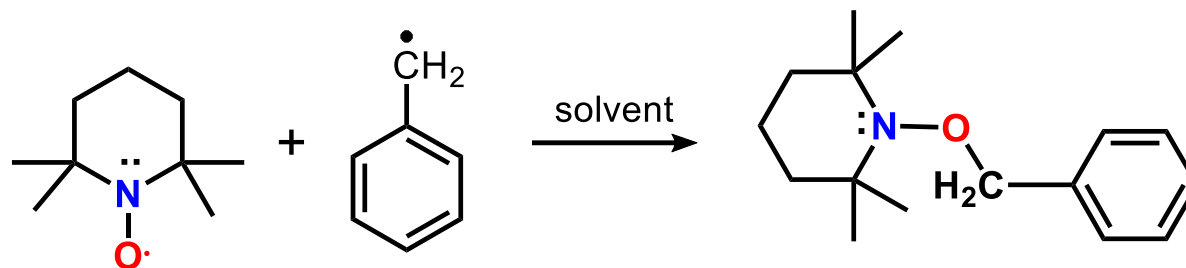
for 2-Propyl radical

k_{disp}/k_{dim}

η (cP)
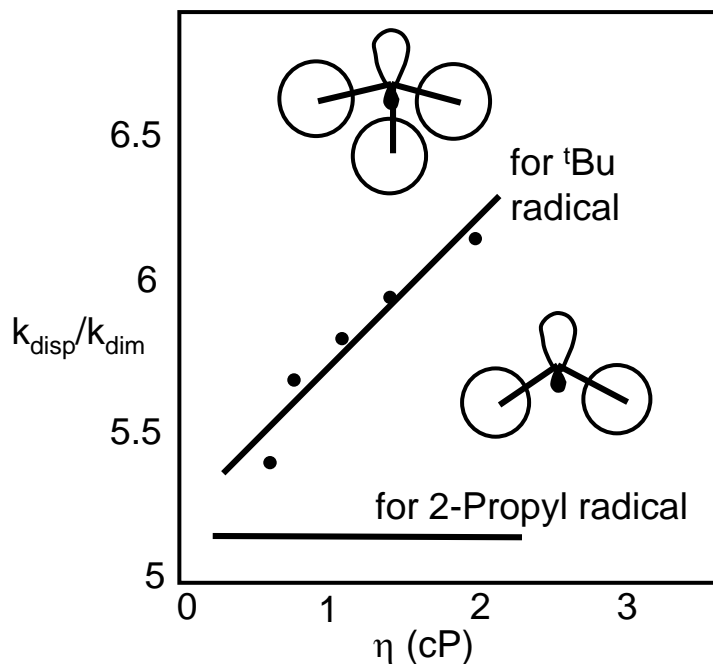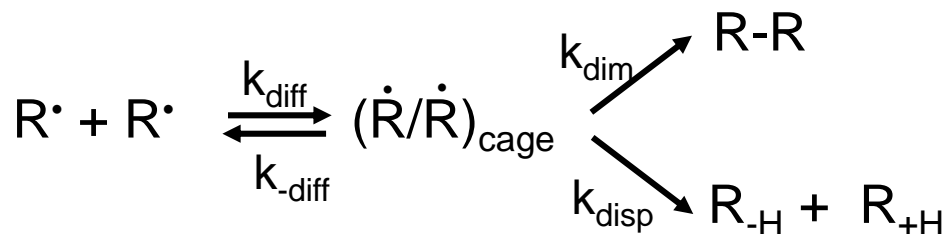
- Variation of k_{disp}/k_{dim} with viscosity
- Shape matters: t-Bu radical an ellipsoid, isopropyl "V" shaped
- Similar trend observed for polar radical reactions

Shuch, H. H.; Fischer, H. *Helv. Chim. Acta* **1978**, *61*, 2463.

Polar Solvents Reduce the Rate

TEMPO

Entry	Solvent	$k_T \times 10^{-7}$, $M^{-1} \cdot s^{-1}$
1	n-pentane	50 +1.5
2	Cyclohexane	41 ± 2
3	Benzene	18 +1
4	Chlorobenzene	17 +2
5	Tetrahydrofuran	23 +3
6	Acetonitrile	9.5 +0.7

Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U *J. Am. Chem. Soc.* **1992**, *114*, 4983.
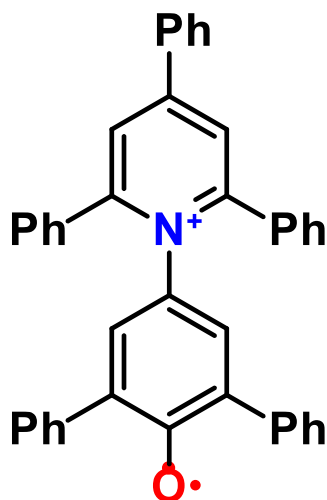
POLITECNICO DI MILANO

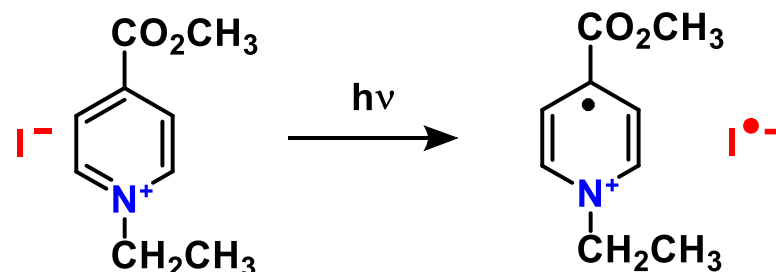| Radical Species	Dipole Moments in Debye
$CH_3\bullet$	0.00141
$CF_3\bullet$	0.00615
$CH_3CH_2\bullet$	0.43937
$CH_2=CHCH_2\bullet$	0.07868
$CH_2=CHC\bullet HOH$	2.38577
$ClCH_2C\bullet HCH_3$	2.87736
$ClCH=CHCH_2\bullet$	1.25684
$HC\equiv C\bullet$	0.80287
$N_3\bullet$	0.00103
$HOO\bullet$	2.52010

- Energy of charge transfer as a intramolecular (ET) or intermolecular (Z) process

E_T Scale

Z Scale

Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.