POLITECNICO DI MILANO

Department CMIC

Lecture 6 – FR6





Free-Radicals: Chemistry and Biology

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Thermodynamic Data

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Thermodynamic Values Useful in Free Radicals Chemistry

a) **Ionization Potential** (IP) $R^{\bullet} \rightarrow R^{+} + e^{-}$

b) **Electron Affinity** (AE) $R^{\bullet} + e^{-} \rightarrow R^{-}$

c) **Redox Potential** ($E°_{ox}$) $R^{\bullet}_{(sol)} + e^{-} \rightleftarrows R^{-}_{(sol)}$

($E°_{red}$) $R^{\bullet}_{(sol)} \rightleftarrows R^{+}_{(sol)} + e^{-}$

d) **Bond Energy** (BDE) $R\text{-}X \rightarrow R^{\bullet} + X^{\bullet} \quad (+ q)$

e) **Formation Enthalpy** ($\Delta H°_f$) $\text{Elements} \rightarrow R^{\bullet} \quad (+ q)$

f) **Radical Stabilization** (H_r) $\Delta(\Delta H°_f(R^{\bullet}) - \Delta H°_f(R^{\bullet}_{rif}))$

Δ(BDE) in homolog series

g) **Acid strength** (pK_a) $RH^{\bullet} \rightleftarrows R^{\bullet -} + H^{+}$

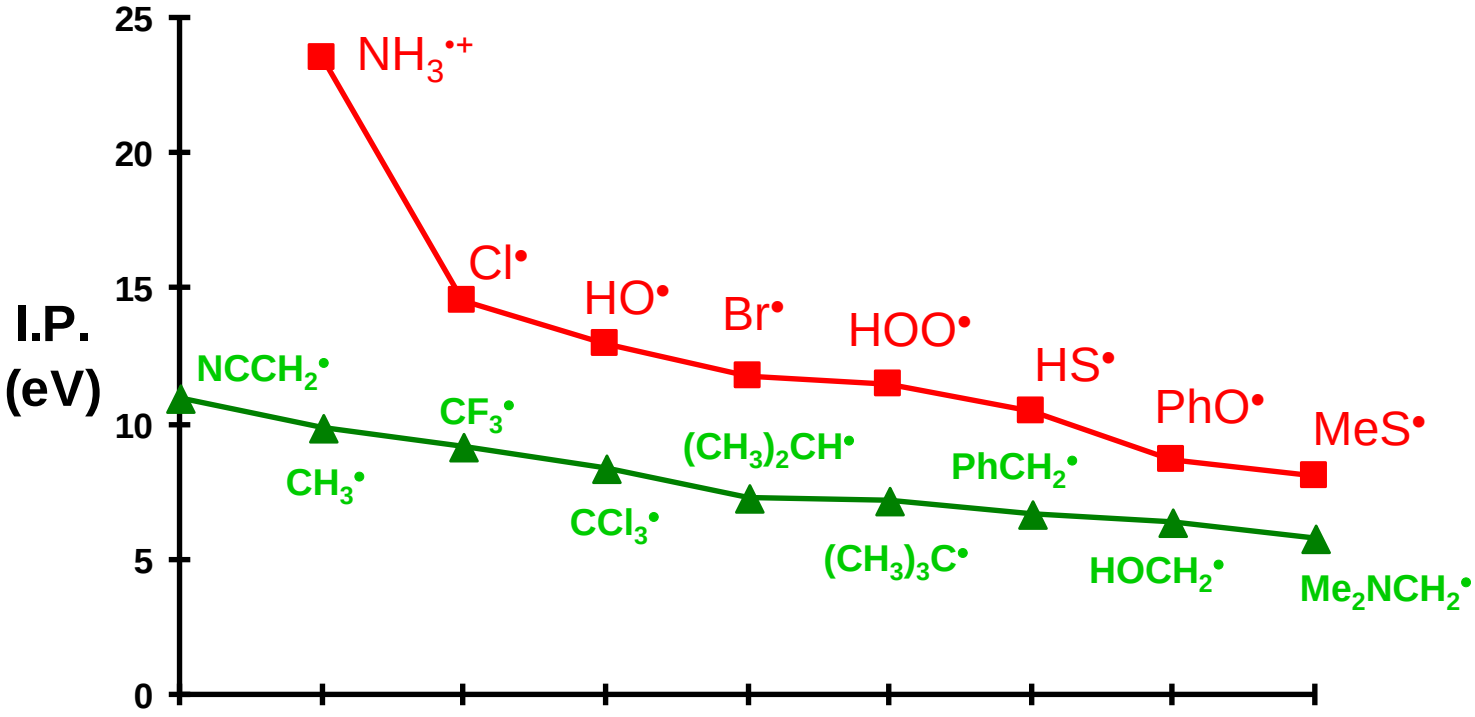
$RH^{\bullet +} \rightleftarrows R^{\bullet} + H^{+}$

h) **Coordination Constants** (pK_c) $R^{\bullet} + A^{+} \rightleftarrows R\text{-}A^{\bullet +}$

$R^{\bullet} + B^{-} \rightleftarrows R\text{-}B^{\bullet -}$

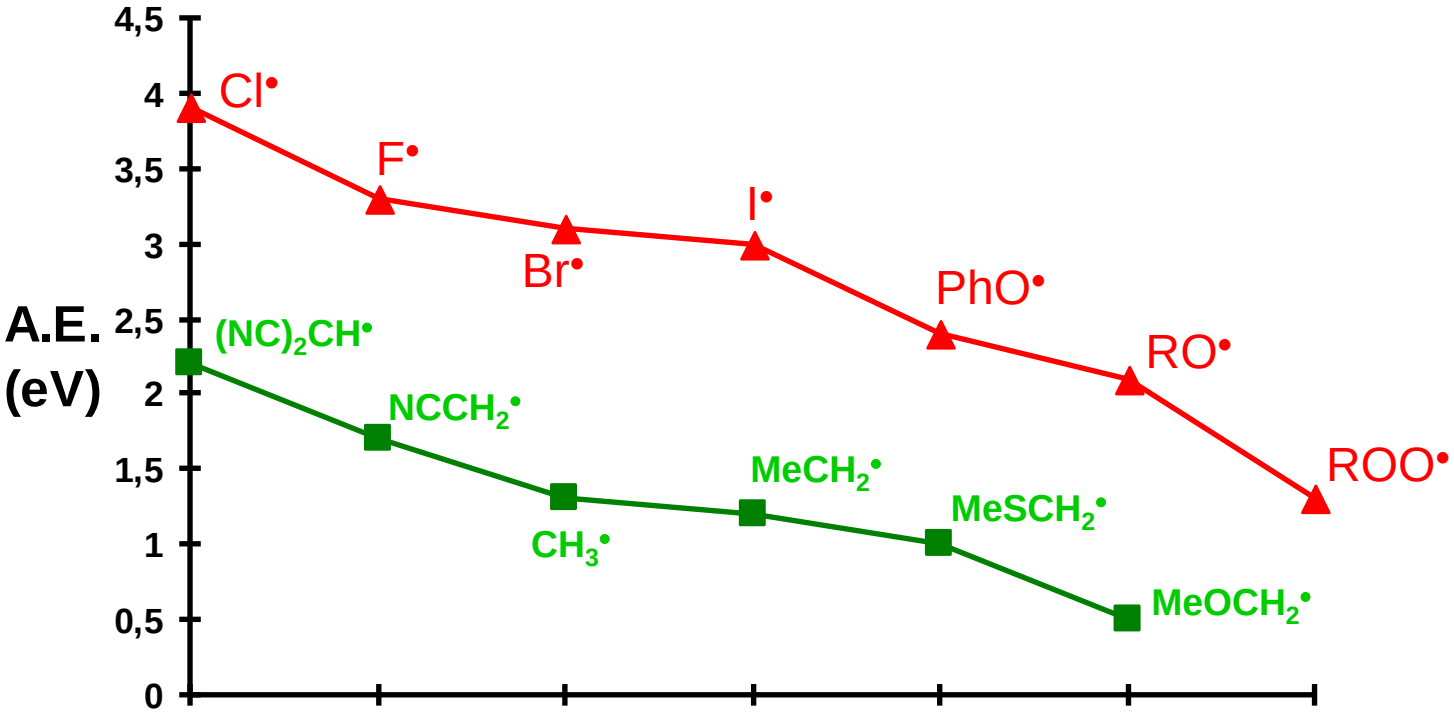
Ionization Potential of Some Radicals

- **Radicals centered to electronegative elements show high IP**
- **Radicals *alfa*-substituted with electron-withdrawing groups show high IP**
- **Radicals substituted by electron-donor groups show low IP (easily oxidized species, involved in redox reactions).**



Electron Affinity of Some Radicals

- **Radicals centered to electronegative elements show high AE**
- **Carbon centered radicals *alfa*-substituted with electron-withdrawing groups show high AE**
- **Oxygen centered radicals show an AE in the order: phenoxy > alkoxy > peroxy.**



Bond Dissociation Energy of Selected Molecules (kcal·mol^{-1})

Specie	BDE*	Specie	BDE*	Specie	BDE*
H--H	104	HO--H	119	Me--Me	88
Me--H	104	CH_3CO_2H	112	Et--Me	85
Et--H	98	CH_3OO--H	102	Pr--Me	84
^{n}Pr--H	96	O_2NO--H	102	Bu^{t}--Me	80
^{i}Pr--H	95	HO_2--H	90	Bu^{t}--Bu^{t}	68
^{t}Bu--H	91	PhO--H	85	$PhCH_2$--Me	72
$PhCH_2$--H	85	ONO--H	79	CH_2=$CHCH_2$--Me	72
CH_2=$CHCH_2$-H	85	ClO--H	78	MeCO--Me	82
Ph_2C--H	75	F--H	136	MeCO--COMe	70
C_7H_7--H	74	Cl--H	103	$HOCH_2$--Me	83
HC=C--H	125	Br--H	88	$C_{10}H_{10}$--CPh_3	15
Ph--H	112	I--H	71	Ph--Ph	100
CH_2=CH--H	103	H_2N--H	103	Ph--Me	93
CH_3CO--H	88	HS--H	90	Me--F	106
HOCO--H	90	Cl--Cl	58	Me--Cl	84
$HOCH_2$--H	93	Br--Br	46	Me--I	56
F_3C--H	104	I--I	36	Me--OH	92
Cl_3C--H	96	F--F	38	Me--NH_2	79
		MeS—SMe	73		

Bond Dissociation Energies (kcal·mol^{-1})

sp^3 Carbons	
CF_3-H	106.6
CH_3-H	104.9
CH_3CH_2-H	100.9
$(CH_3)_2CH$-H	98.5
$(CH_3)_3C$-	96.1
CH_3OCH_2-H	93.0
N≡CCH_2-H	93.0
CH_3COCH_2-H	92.0
$C_6H_5CH_2$-H	88.4
CH_2=$CHCH_2$-H	86.5
$(CH_2$=$CH)_2CH$-H	82.9
sp^2 Carbons	
CH_2 =C-H	111.1
C_6H_5-H	111.1
***sp* Carbons**	
CH≡C-H	132.9

π Bonds	
C≡C	199.6
C=C	**148.2**
C=O	173.0
C≡N	204.1
C=N	**142.9**

C-X Bonds	
C-Cl	78.9
C-Br	**65.7**
C-I	**52.6**

Halogens	
F-H	136.2
Cl-H	103.0
Br-H	87.5
I-H	71.0
O-H Bonds	
HO-H	119.0
CH_3O-H	105.2
HOO-H	88.0
C_6H_5O-H	85.1
$(t\text{-}Bu)_2NO$-H	71.7
S-H Bonds	
CH_3S-H	87.5
M-H Bonds	
$(CH_3)_3Si$-H	92.7
$(CH)_3Sn$-H	**74.1**

Perkins, J.M., Radical Chemistry: The Fundamentals, Oxford University Press, Inc., New York, 2000. March, J.; Smith, M.B., March's Advanced Organic Chemistry, John Wiley & Sons, Inc., New York 2001.

Alkane ΔH_f values (kcal·mol^{-1})

Carbon number n →

Branching ↓

1	2	3	4	5	6	7	8
-17.9	-20.04	-25.02	-30.37	-35.08	-39.96	-44.89	-49.82
			-32.07	-36.73	...	...	...
				-40.14	-44.35	-48.96	-53.99

Octanes:

Octane	-49.82		
		2,2-dimethylhexane	-53.71
2-methylheptane	-51.50	3,3-dimethylhexane	-52.61
3-methylheptane	-50.82	3-ethyl-3-methylpentane	-51.38
4-methylheptane	-50.69		
3-ethylhexane	-50.40	2,3,4-trimethylpentane	-51.97
2,5-dimethylhexane	-53.21	2,2,3-trimethylpentane	-52.61
2,4-dimethylhexane	-52.44	2,2,4-trimethylpentane	-53.57
2,3-dimethylhexane	-51.13	2,3,3-trimethylpentane	-51.73
3,4-dimethylhexane	-50.91		
3-ethyl-2-methylpentane	-50.48	2,2,3,3-tetramethylbutane	-53.99

Bond Dissociation Energies (BDEs)

		52.1	**19.0**	**29,0**	**26,7**	**25,5**	**9,3**	**45,5**	**35,1**
		34.7	-59,5	-54,4	-50,9	-45,1	-32,8	27,1	33,3
H	**52.1**	0,0	-65,3	-22,1	-8,7	6,3	-57,8	-11,0	-17,9
	365.7	0,0	-65,3	-22,1	-8,7	6,3	-57,8	-11,0	-17,9
CH_3	**35.1**	-17,9	-56,0	-20,0	-8,2	3,4	-48,0	-5,5	-20,0
	262.0	-17,9	-56,0	-20,0	-8,2	3,4	-48,0	-5,5	-20,0
CH_3CH_2	**28.4**	-20,0		-26,8	-15,2	-1,7	-56,2	-13,0	-25,0
	215.6	-20,0		-26,8	-15,2	-1,7	-56,2	-13,0	-25,0
$(CH_3)_2CH$	**22.0**	-25,0	-70,1	-34,7	-22,9	-9,5	-65,2	-20,0	-32,1
	191.5	-25,0	-70,1	-34,7	-22,9	-9,5	-65,2	-20,0	-32,1
$(CH_3)_3C$	**11.0**	-32,1		-43,0	-31,6	-17,2	-74,7	-28,8	-40,1
	165.5	-32,1		-43,0	-31,6	-17,2	-74,7	-28,8	-40,1
$H_2C{=}CHCH_2$	**40.9**	4,9		-1,3	11,4	23,8	-29,6		-0,2
	229.5	4,9		-1,3	11,4	23,8	-29,6		-0,2
$PhCH_2$	**49.5**	12,0	-30,2	4,5	20,0	30,4	-22,6	21,0	7,1
	216.5	12,0	-30,2	4,5	20,0	30,4	-22,6	21,0	7,1

Value in bold: group contribution; $kJ \cdot mol^{-1}$

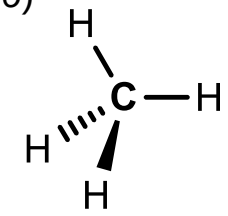
Heats of Formation of Some Radicals

		H	F	Cl	Br	I	OH	NH_2	CH_3
		52,1	**19,0**	**29,0**	**26,7**	**25,5**	**9,3**	**45,5**	**35,1**
		34,7	-59,5	-54,4	-50,9	-45,1	-32,8	27,1	33,3
H	**52,1**	104,2	136,4	103,2	87,5	71,3	119,2	108,6	105,1
	365,7	400,4	371,5	333,4	323,5	314,3	390,7	403,8	416,9
CH_3	**35,1**	105,1	110,1	84,1	70,0	57,2	92,4	86,1	90,2
	262,0	314,6	258,5	227,6	219,3	213,5	277,2	294,6	315,3
CH_3CH_2	**28,4**	100,5		84,2	70,3	55,6	93,9	86,9	88,5
	215,6	270,3		188,0	179,9	172,2	239,0	255,7	273,9
$(CH_3)_2CH$	**22,0**	99,1	111,1	85,7	71,6	57,0	96,5	87,5	89,2
	192,0	251,2	202,1	171,8	163,5	155,9	223,9	238,6	256,9
$(CH_3)_3C$	**11,0**	95,2		83,0	69,3	53,7	95,0	85,3	86,2
	165,5	232,3		154,1	146,2	137,6	207,4	221,4	238,9
$H_2C{=}CHCH_2$	**40,9**	88,1		71,2	56,2	42,6	79,8		76,2
	229,5	259,3		176,4	167,2	160,6	226,3		263,0
$PhCH_2$	**49,5**	89,6	61,2	74,0	56,2	44,6	81,4	74,0	77,5
	216,5	239,2	-17,3	157,6	145,6	141,0	206,3	222,6	242,7

Value in bold: group contribution; $kJ \cdot mol^{-1}$

Challenge: $CH_4 \rightarrow CH_3OH$

105.1
(314.6)

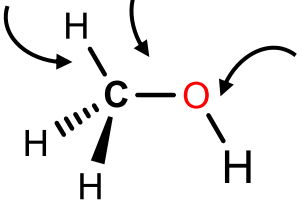


^2H_f = -17.9 kcal·mol^{-1}
IE = 12.61 eV (290.8 kcal·mol^{-1})
PA = 129.9 kcal·mol^{-1}

98.1
(*254.3*)

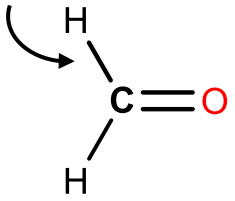
92.4 (*277.2*)

104.2
(*382*)



^2H_f = -48.0 kcal·mol^{-1}
IE = 10.84 eV (250.0 kcal·mol^{-1})
PA = 180.3 kcal·mol^{-1}

90.2
(*259.4*)



^2H_f = -27.7 kcal·mol^{-1}
IE = 10.88 eV (250.9 kcal·mol^{-1})
PA = 170.4 kcal·mol^{-1}

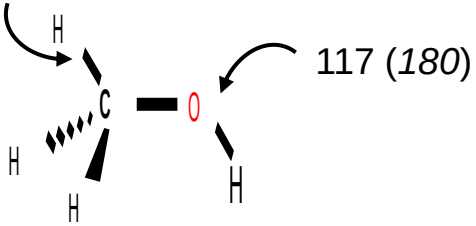
Reagents?

Radicals
Acids
Bases

110

130.6 (*66.6*)

117 (*180*)



^2H_f = 137.4 kcal·mol^{-1}

Radical Stabilization (H_r, Kcal·mol^{-1})

- Best evaluated comparing Bond Dissociation Energies in homologous series.

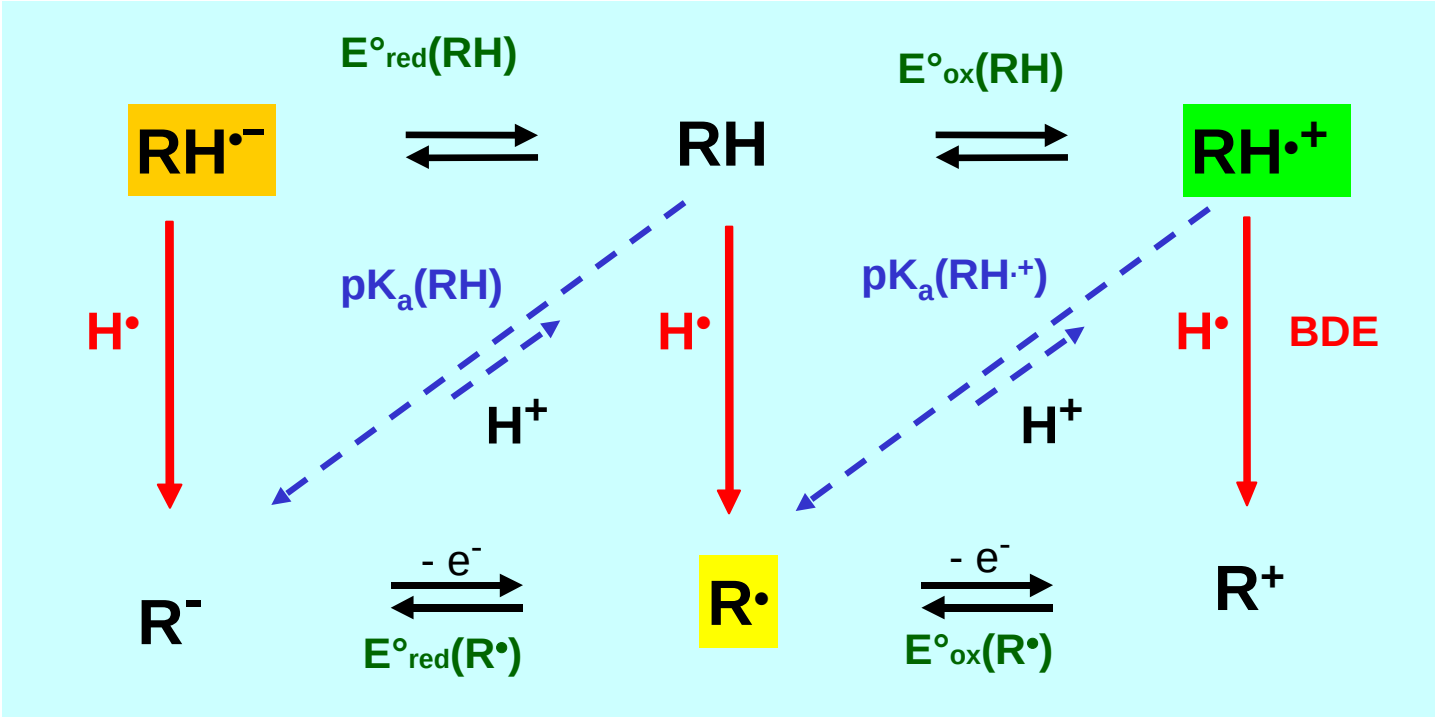
X	H	OH	I	CH_3	C_2H_5	$^iC_3H_7$	$^tC_4H_9$	C_6H_5
CH_3-X	104	91	56	88	85	84	80	93
Benzyl-X	85	77	40	72	69	67	64	78
Allyl-X	85	77	41	72	69	67	63	77
Δ(Me/Benzyl)	19	14	16	16	16	17	16	15
Δ(Me/Allyl)	19	14	15	16	16	17	17	16

X	CH_3	CH_2OH	COOR	CN	COR	Ph	Vinyl	$(Ph)_2$	$(Ph)_3$	OR	SR
H_r	0	1.0	3.1	5.5	6.5	8.4	8.5	12	19	1.3	10

Resonance saturation effect →

Correlations between Thermodynamic Quantities

Acidity, Bond Energies and Redox Potentials



The following typical inequalities hold:

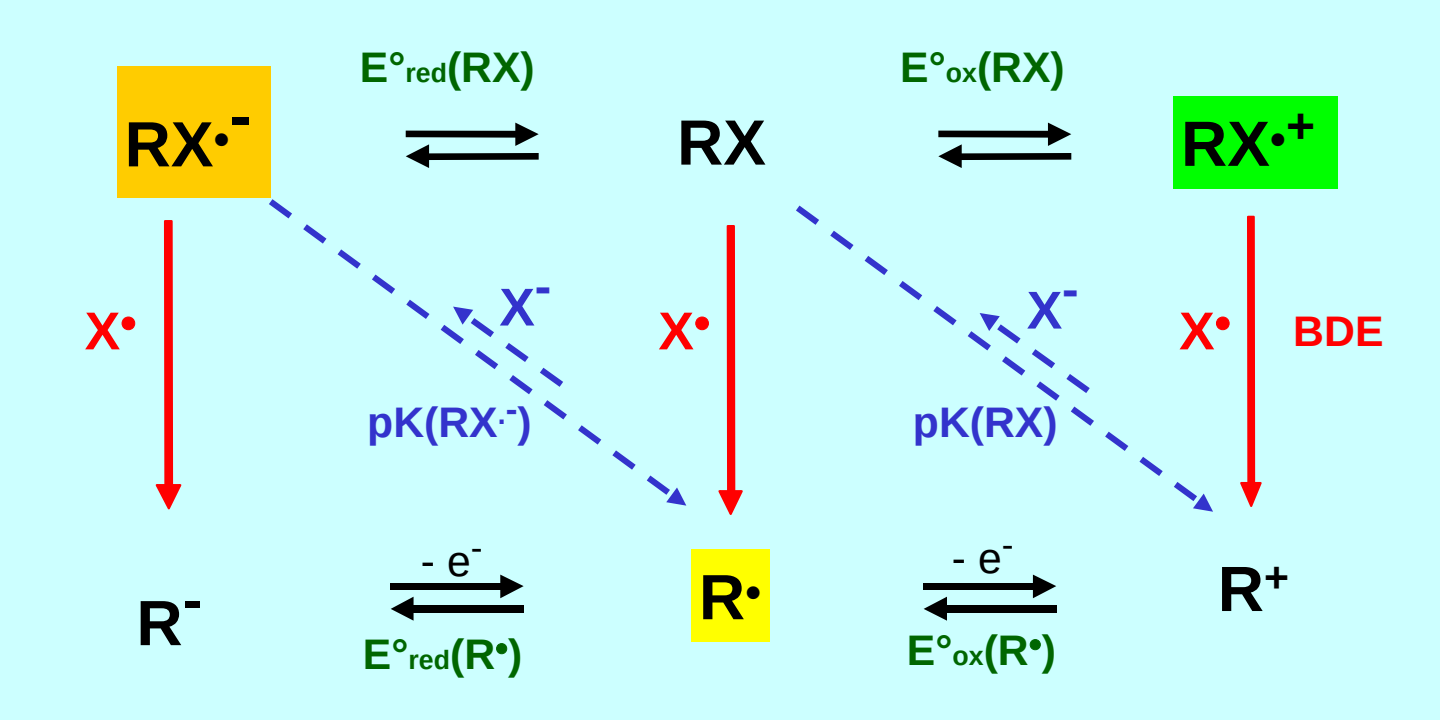
a) $E°_{ox/red}(RH) \neq E°_{ox/red}(R^{\bullet})$

b) $BDE(RH) > BDE(RH^{\cdot+}$ o $RH^{\cdot-})$

c) $pK_a(RH^{\bullet+}) >> pK_a(RH)$

Correlations between Thermodynamic Quantities

Elect. group loss, *Bond Energies* *and Redox Potentials*



The following typical inequalities hold:

a) $E°_{ox/red}(RX) \neq E°_{ox/red}(R^{\bullet})$

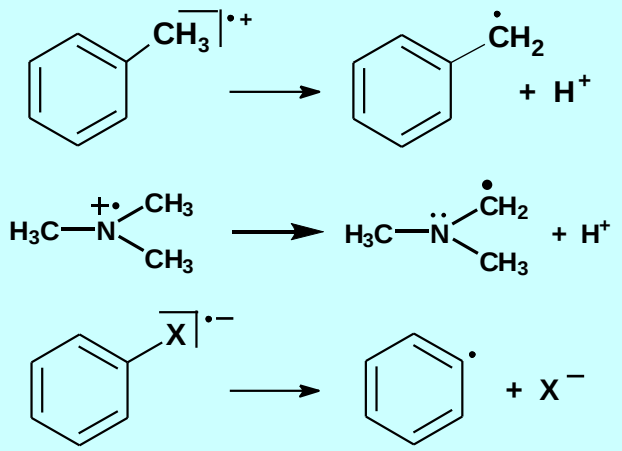
b) $BDE(RX) > BDE(RX^{\bullet+}$ o $RX^{\bullet-})$

c) $pK(RX^{\bullet-}) >> pK(RX)$

BDE in Uncharged Radicals, Cation Radicals and Anion Radicals

Uncharged Radicals

Radical	BDE kcal·mol^{-1}
$^{\bullet}CH_2$–Me	96
$^{\bullet}CH_2CH_2$–H	39
$^{\bullet}CH_2CH_2$–Me	26
$^{\bullet}OCH_2$–Me	12
$^{\bullet}OCMe_2$–Me	7
O=C$^{\bullet}$–Me	11



Cation radicals

$R\text{-}H^{\bullet+}$ (σ o π) → $R^+ + H^{\bullet}$; $R^{\bullet} + H^+$ (cation radical acidity)

RH^+	$PhCH_3$	Ph_2CH_2	$PhH(CH_3)_2$	Me_3N	Et_3N
(A)	52	43	36	34	30
(B)	-17	-18	-19	6	3

Anion radicals

$R\text{-}X^{\bullet-}$ (σ o π) → $R^- + X^{\bullet}$; $R^{\bullet} + X^-$ (anion radicals basicity)

$RX^{\bullet-}$	CH_3-Cl	CCl_4	CH_3I	C_6H_5Cl	Et_3N
(A)	58	42	49	40	31
(B)	- 2	- 8	- 20	12	6

Acid-Base Properties of Radicals

Uncharged Radicals

$$^{\bullet}R\text{-}X\text{-}H + S \rightarrow RX^{\bullet -} + SH^{+}$$

Cation Radicals

$$^{\bullet +}R\text{-}X\text{-}H + S \rightarrow RX^{\bullet} + SH^{+}$$

Radical	pK_a	Molecule	pK_a
$^{\bullet}CH(O\text{-}H)\text{-}$	11-12	$H\text{-}OCH_2\text{-}$	16-17
$^{\bullet}CH_2CH_2O\text{-}H$	14.7	$CH_3CH_2O\text{-}H$	16
$^{\bullet}CH(O\text{-}H)CN$	~ 4	$H\text{-}OCH_2CN$	~ 9
$^{\bullet}CH_2COO\text{-}H$	4.3	$CH_3COO\text{-}H$	4.5
$^{\bullet}CH(NH_3^{+})COOH$	6.6	$CH_2(NH_3^{+})COOH$	2.3
$^{\bullet}CR_2\text{-}NHCO\text{-}$	12-13	$CHR_2\text{-}NHCO\text{-}$	15-18
$PhCH_3^{\bullet +}$	-10	$PhCH_3$	50
$PhOH^{\bullet +}$	-2	PhOH	9.89
$NH_3^{\bullet +}$	2.3	NH_3 (NH_4^{+})	18 (9.2)

Redox Properties of Radicals (vs. S.C.E.)

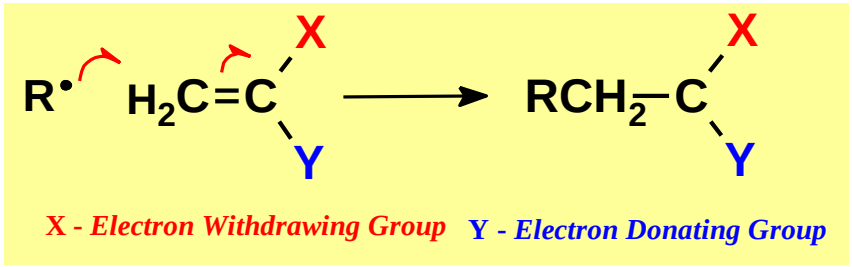
Radical	$E_{1/2\ ox}$ (V)	$E_{1/2\ red}$ (V)		Radical	$E_{1/2\ red}$ (V)
$^{\bullet}CH(COOH)_2$	-	1.30		$SO_4^{\bullet -}$	3.10
$^{\bullet}CH_2Ph$	0.73	-1.45		$^{\bullet}OH$	2.63
$^{\bullet}CHPh_2$	0.35	-1.14		$^{\bullet}CN$	2.56
$^{\bullet}CHPh_3$	0.20	-0.95		$^{\bullet}Br$	2.20
$^{\bullet}CH_2O\text{-}H$	-0.95	-		$^{\bullet}SCN$	1.42
$^{\bullet}CH(CH_3)O\text{-}H$	-1.19	-		$^{\bullet}N_3$	1.34
$^{\bullet}C(CH_3)_2OH$	-1.30	-		$^{\bullet}I$	1.09
$^{\bullet}CH_2\text{-}N(CH_3)$	-1.03	-		$^{\bullet}NO_2$	0.79
$^{\bullet}CHPhN(Bz)_2$	-0.92	-		$^{\bullet}H$	-0.33

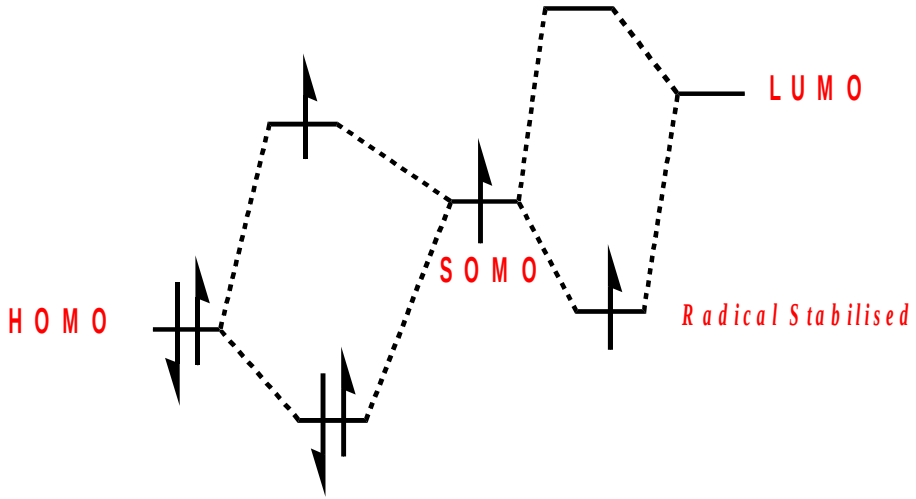
(a) Wayner, D. D. M.; McPhee, D. J.; Griller, D. J. Am. Chem. Soc. 1988, 110, 132. (b) Sim, B. A.; Milne, P. H.; Griller, D.; Wayner, D. D. M. J. Am. Chem. Soc. 1990, 112, 6635.

Captodative Effect

The synergic stabilizing effect on a radical center due to the simultaneous presence on the center of both electron-withdrawing and electron-donating groups. The phenomenon is explained by a succession of orbital interactions; the acceptor stabilizes the unpaired electron, which for this reason interacts more strongly with the donor than in the absence of the acceptor.

	BDE (R-H)
$^{\bullet}CH(CHO)_2$	99
$\bullet CH(NO_2)_2$	99
$\bullet CH(t\text{-}Bu)_2$	98
$^{\bullet}CH(OCH_3)_2$	91
$^{\bullet}CHCH_3(OCH_3)$	91
$^{\bullet}CH(NH_2)CHO$	73
$^{\bullet}CH(NH_2)CO_2H$	76





The Pecking Order of Redox Potentials

Note that the donor antioxidants are found in the middle of the "pecking order".

Redox Couple (one-electron reductions)	E°'/mV
$HO^{\bullet}, H^{+}/H_2O$	+ 2310
$RO^{\bullet}, H^{+}/ROH$ (aliphatic alkoxyl radical)	+ 1600
$ROO^{\bullet}, H^{+}/ROOH$ (alkyl peroxyl radical)	+ 1000
$GS^{\bullet}/GS^{-}$ (glutathione)	+ 920
$PUFA^{\bullet}, H^{+}/PUFA\text{-}H$ (*bis*-allylic-H)	+ 600
$TO^{\bullet}, H^{+}/TOH$ (tocopherol)	**+ 480**
$H_2O_2, H^{+}/H_2O, HO^{\bullet}$	+ 320
$Asc^{\bullet-}, H^{+}/AscH^{-}$ (Ascorbate)	**+ 282**
$CoQ^{\bullet-}, 2H^{+}/CoQH_2$	+ 200
Fe(III) EDTA/Fe(II) EDTA	+ 120
$CoQ/CoQ^{\bullet-}$	- 36
$O_2/O_2^{\bullet-}$	- 160
$Paraquat/Paraquat^{\bullet-}$	- 448
Fe(III)DFO/Fe(II)DFO	- 450
$RSSR/RSSR^{\bullet-}$ (GSH)	- 1500
H_2O/e^{-}_{aq}	- 2870

Buettner GR. (1993) The pecking order of free radicals and antioxidants: Lipid peroxidation, α-tocopherol, and ascorbate. *Arch Biochem Biophys.* **300:**535-543**.** [PDF]