Can Al^{3+} promote the Fenton reaction and oxidative stress?

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and
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Tenth Keele Meeting on Aluminium 2013

Pro-oxidant activity of Al

Pro-Oxidant Acitvity of Aluminium

It is know that Al shows a significant pro-oxidant activity (Kong et al. Free Rad. Biol. Med. 1992, 13, 79) but it is non-redox metal!

Existence of Al-Superoxide (?)

The existence of an Al-superoxide ($O_2^{\cdot -}$) complex has been hypothesized (Exley Free Rad. Biol. Med. 2004, 36, 380) as a key species in the prooxidant activity of Al

Metal-Superoxide Interaction

- Fukuzumi et al. (Chem. Eur. J. 2000, 6, 4532; J. Phys. Org. Chem. 2002, 15, 448; Coord. Chem. Rev. 2002, 226, 71) : linear relationship between oxidant activity of a metal and its interaction strength with superoxide, estimated by the split in π_g levels in metal-superoxides, measured from the ESR g-tensor $g_{zz} = g_e + 2\lambda/\Delta\varepsilon_{\pi_g}$
- $g_{zz} \leftrightarrow \Delta\varepsilon_{\pi_g}$ is a reliable indicator of the pro-oxidant activity

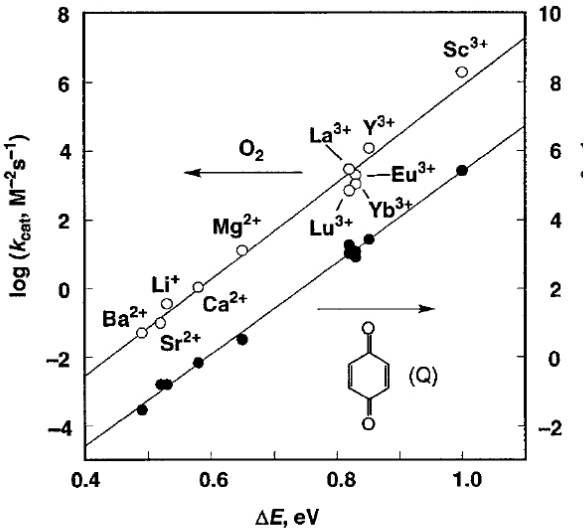
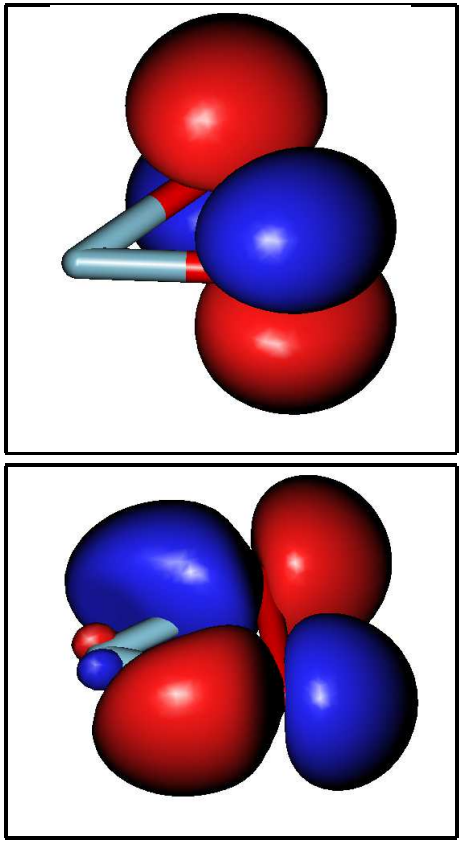


Figure 2. Plots of log k_{cat} vs ΔE in M^{n+}-catalyzed elec transfer from CoTPP to O_2 (○) and *p*-benzoquinone (● acetonitrile at 298 K[8]

Questions to Be Answered

Question 1 (Q1):

Is the Al^{3+}-superoxide interaction strong as compared to biometals?



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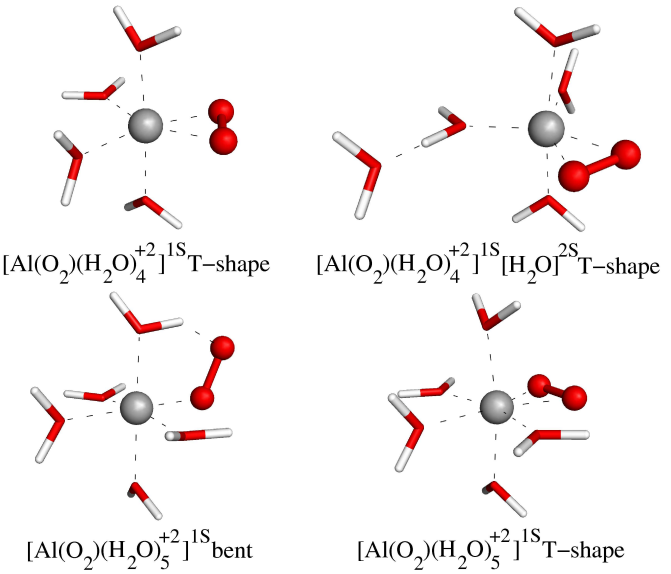
Question 2 (Q2):

Is strong enough as to form Al-superoxide complexes?



Questions to Be Answered

Question 1 (Q1):

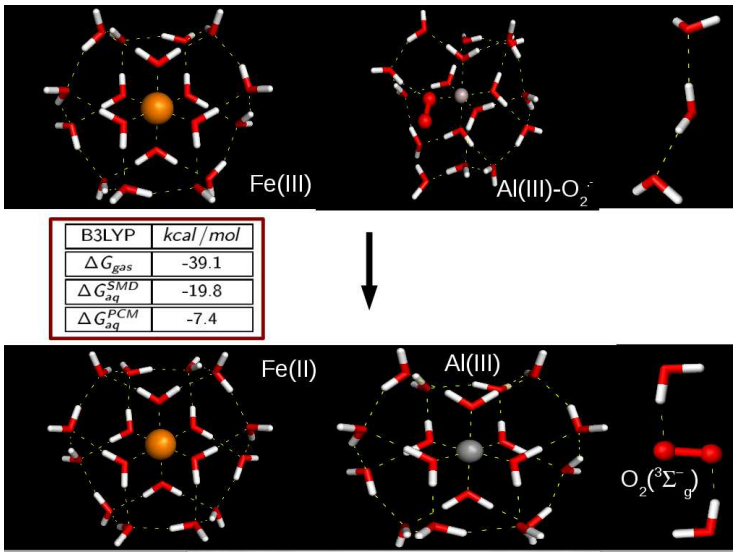
Is the Al^{3+}-superoxide interaction strong as compared to biometals?

Question 2 (Q2):

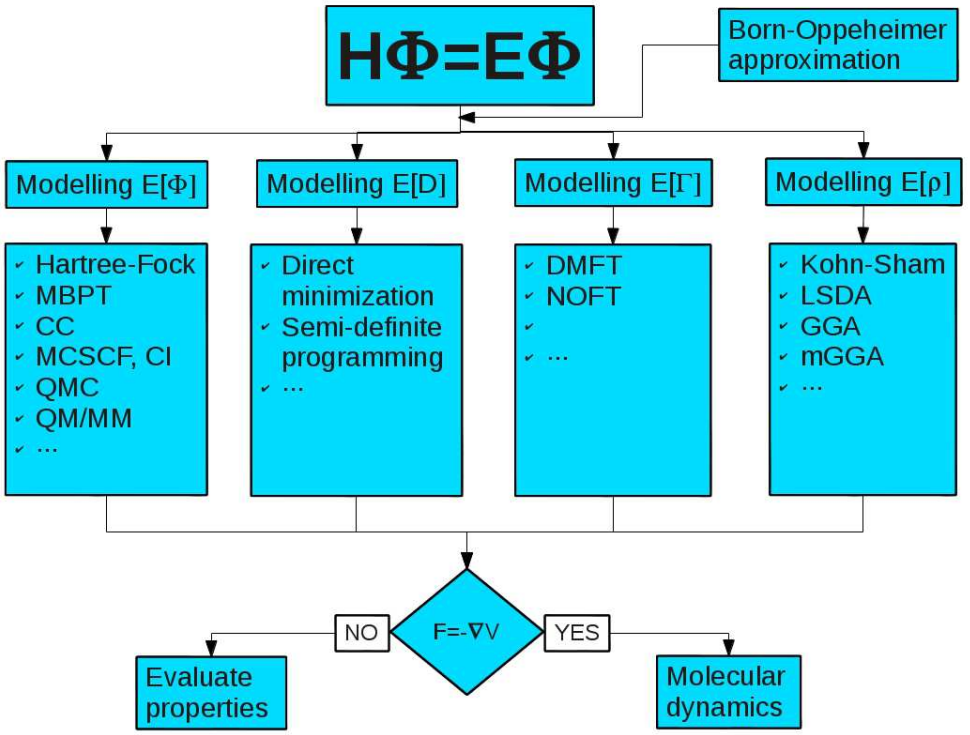
Is strong enough as to form Al-superoxide complexes?

Question 3 (Q3):

Once Al-superoxide is formed how could enhance oxidative stress? Promotion of Fenton Reaction



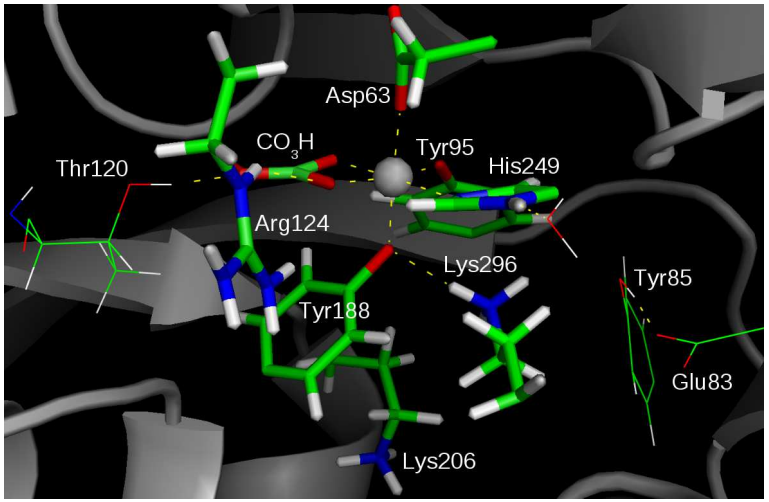
What we can do



- WF: CASSCF, CASPT2
- DFT: B3LYP, PBE, M062X
- NOFT: PNOF5

Explicit versus Implicit Environment

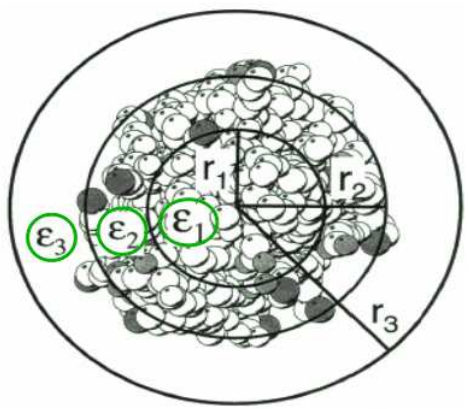
Force Field (Faro et al., J. Chem. Phys., 2010, 132, 114509), QM/MM



Mujika, Escribano, Akhmatskaya, Ugalde and Lopez; Biochemistry, 51, 7017 (2012)
Mujika, Lopez, Rezabal, Castillo, Marti, Moliner and Ugalde; Journal of Inorganic Biochemistry, 105, 1446 (2011)

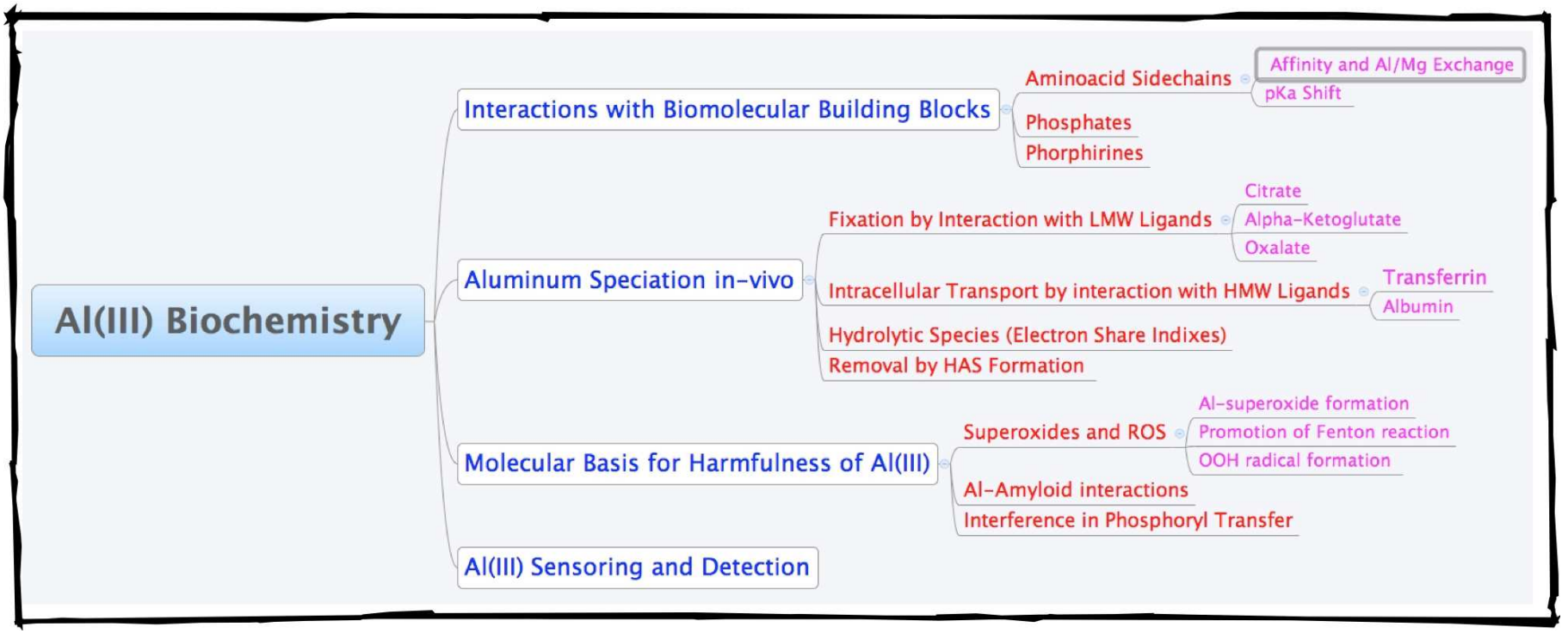
PCM, SMD

Dielectric effects



No environmental effects $\varepsilon=1$
Buried zone of the protein $\varepsilon_1=2-4$
Relatively solvent-exposed area $\varepsilon_2=20$
Fully solvent exposed area $\varepsilon_3=78$

Aluminium Research at the University of the Basque Country



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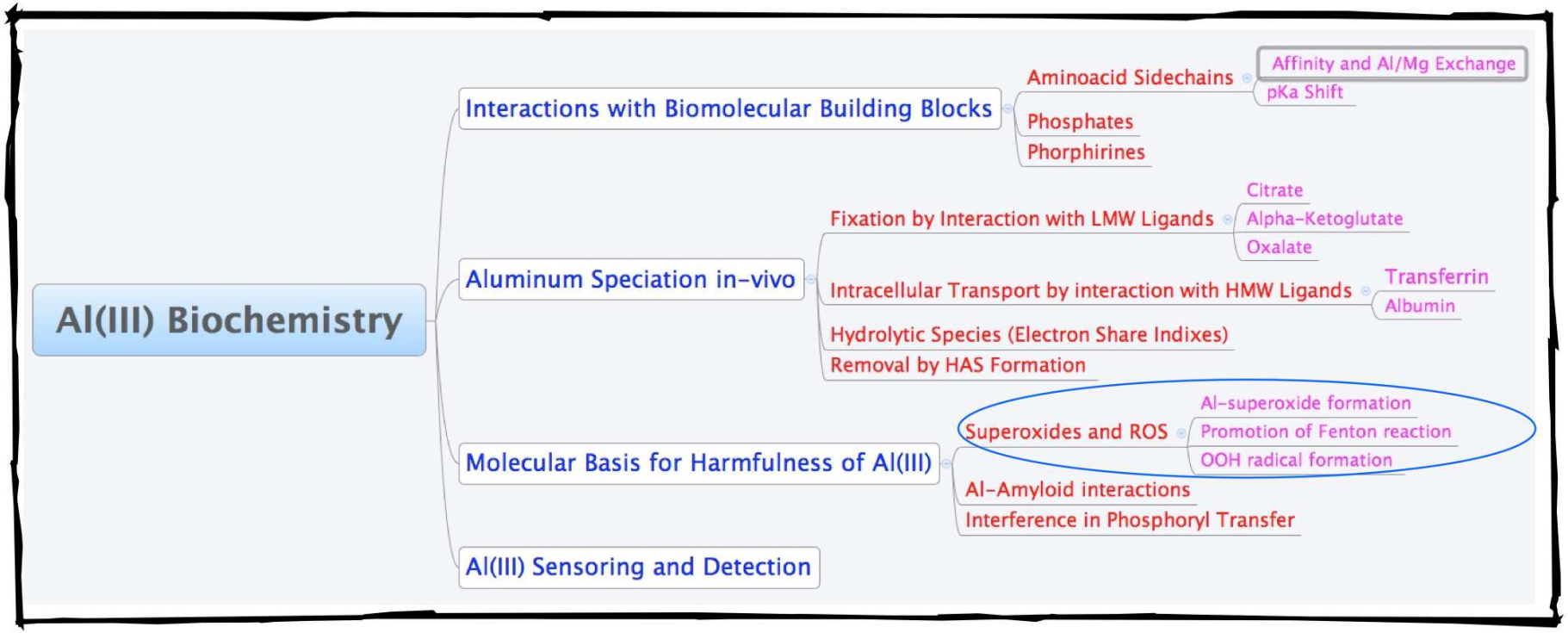
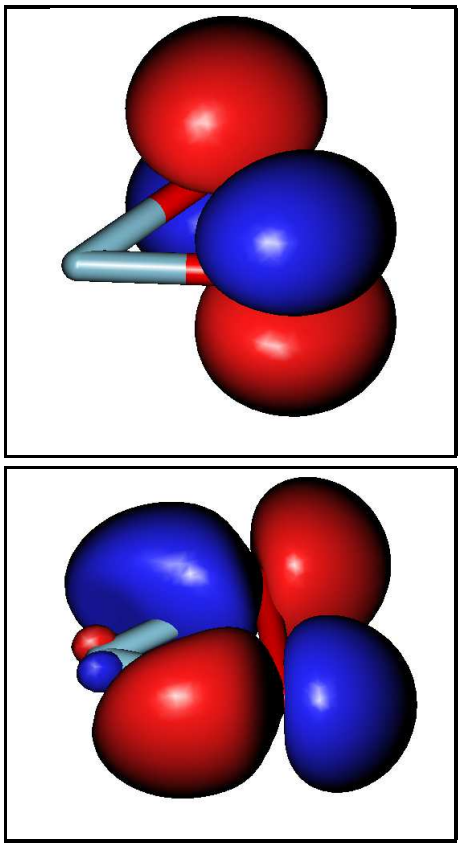


Q1: Strength of Al-superoxide interaction

$\Delta\varepsilon_{\pi_g}$, (estimated from g-tensor value, Vancoille et al. Chem. Phys. Chem. 2007), IP of $M^{n+}O_2^{-}$ and EA of $M^{n+}O_2$ in eV, calculated at CASPT2.

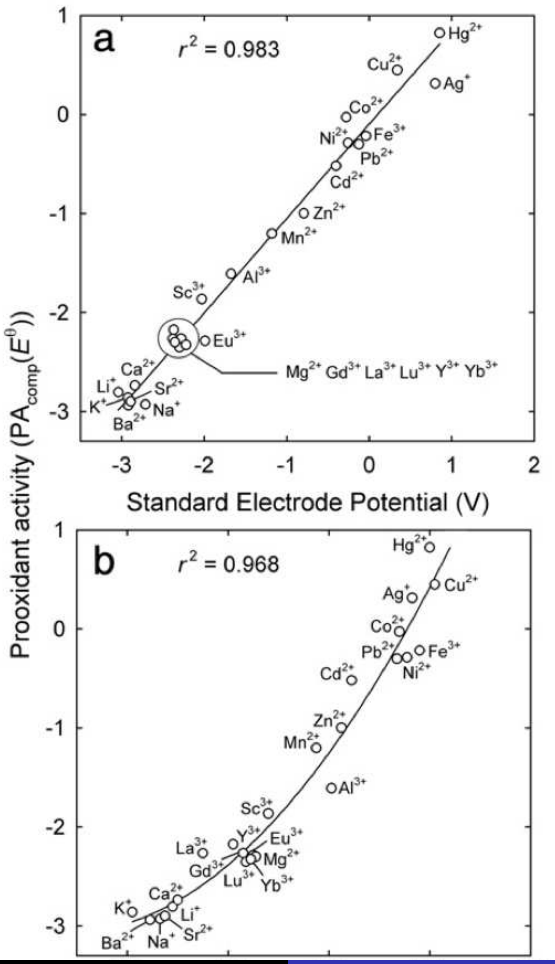
M^{n+}	$\Delta\varepsilon_{\pi_g}$ (eV)		IP (eV)	EA (eV)
	CASPT2	Exp.		
Na^+	0.35	0.34	7.3	4.9
K^+	0.31	—	6.8	4.1
Mg^{2+}	0.65	0.65	15.6	13.5
Ca^{2+}	0.56	0.58	13.9	11.0
Al^{3+}	1.11	—	25.5	25.1



- Charge dominating factor over volume
- Al^{3+}show a very strong interaction as it corresponds to a +3 charge and small

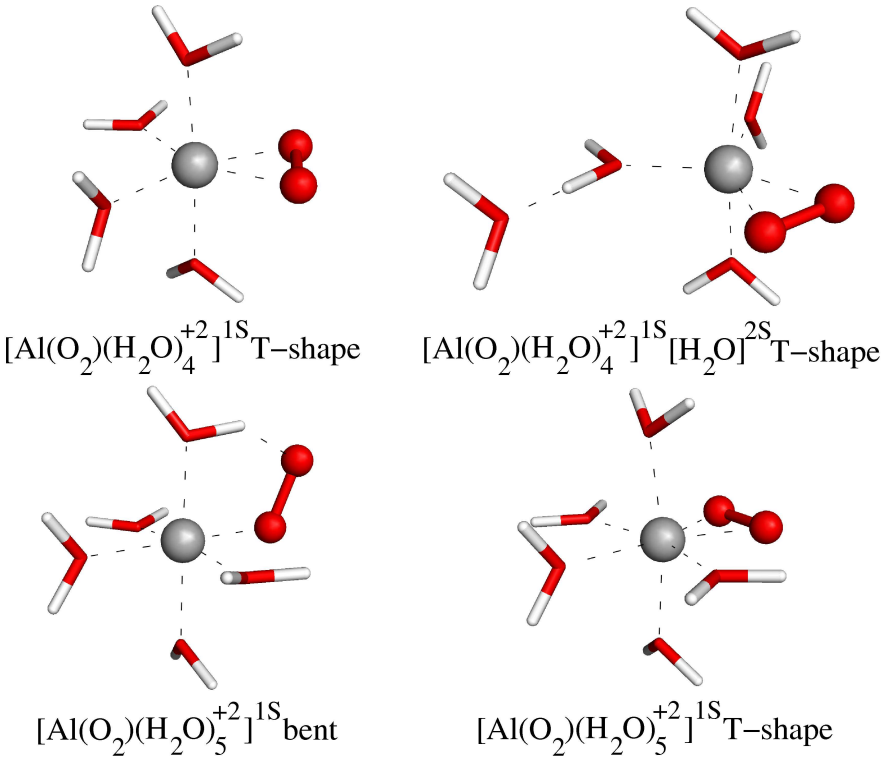
Q1: Strength of Al-superoxide interaction

Kinraide et al. J. Inorganic Biochem., 2011, 105, 1438



Q1: Strength of Al-superoxide Interaction

- Upon solvation and charge transfer from water, do we have the same differential strength in the interaction?
- How is the coordination shell?
  - T-shape bidentate or Bent momodentate
  - 4 or 5 water molecules in 1S



Q1: Strength of Al-superoxide Interaction

CASPT2 level of theory	$\Delta\varepsilon_{\pi_g}$	ΔE
	eV	kcal/mol
T-$[Al^{3+}O_2^{\cdot-}](H_2O)_4^{1S}$	0.86	
T-$[Al^{3+}O_2^{\cdot-}](H_2O)_4^{1S}(H_2O)^{2S}$	0.80	0.0
Bent-$[Al^{3+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.73	3.5
T-$[Al^{3+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.62	7.9
T-$[Mg^{2+}O_2^{\cdot-}](H_2O)_4^{1S}$	0.42	
Bent-$[Mg^{2+}O_2](H_2O)_4^{1S}(H_2O)^{2S}$	0.37	0.0
T-$[Mg^{2+}O_2^{\cdot-}](H_2O)_4^{1S}(H_2O)^{2S}$	0.42	7.0
Bent-$[Mg^{2+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.42	8.9
T-$[Mg^{2+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.32	12.1

- $\downarrow \Delta\varepsilon_{\pi_g}$

Q1: Strength of Al-superoxide Interaction

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T-$[Al^{3+}O_2^{\cdot-}](H_2O)_4^{1S}(H_2O)^{2S}$	0.80	0.0
Bent-$[Al^{3+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.73	3.5
T-$[Al^{3+}O_2^{\cdot-}](H_2O)_5^{1S}$	0.62	7.9
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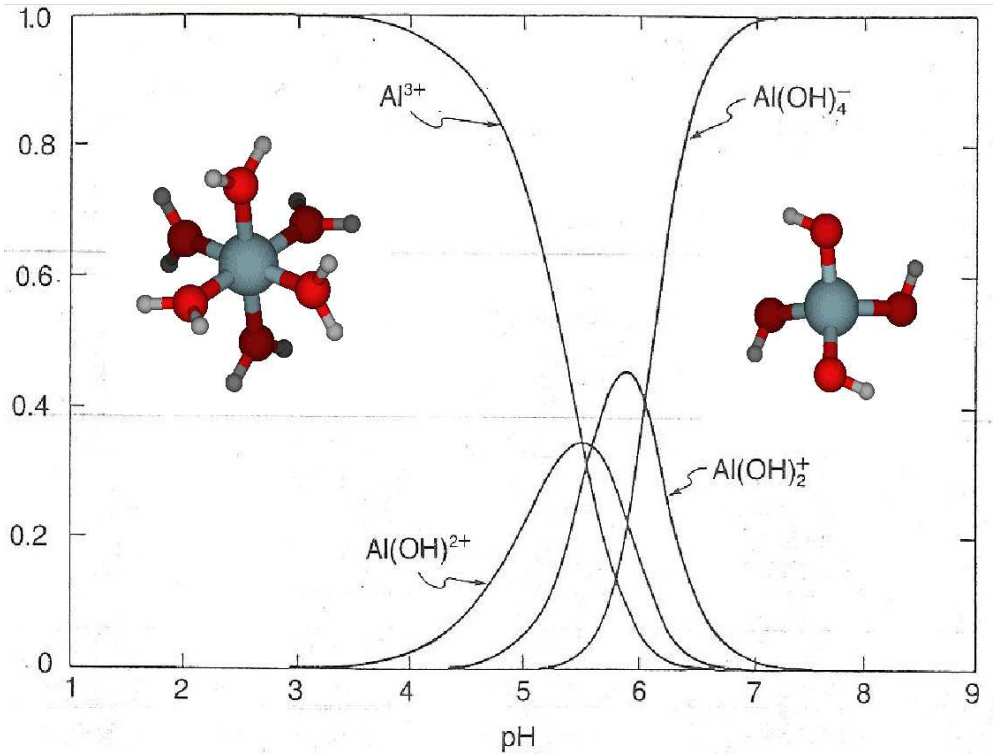
- $\Delta\varepsilon_{\pi_g}$ (Al) $\sim 2\times\Delta\varepsilon_{\pi_g}$ (Mg)

Q2: Formation of Al-superoxide

Hydrolytic Species

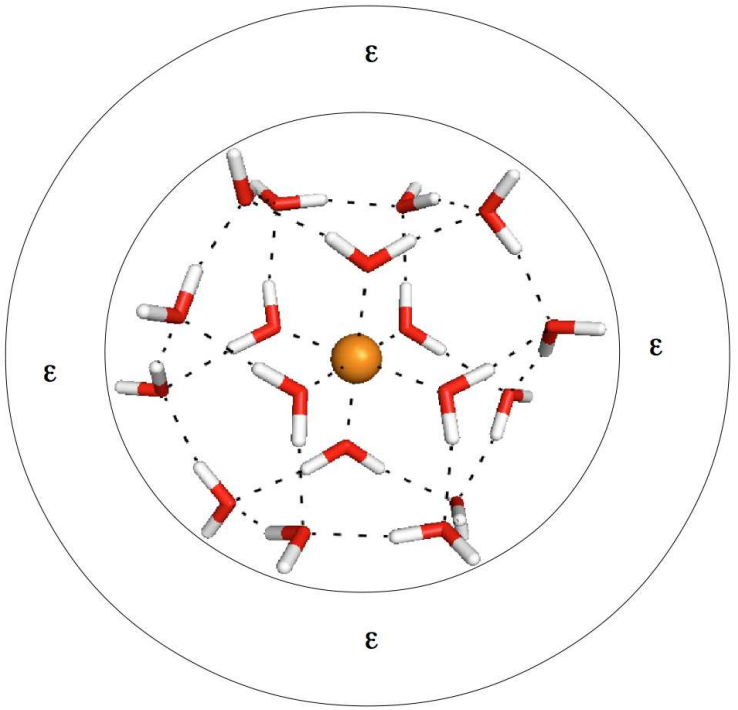
- Is thermodynamically favorable for a $O_2^{\cdot -}$ to displace a H_2O/OH^- from the 1^{st} coord. shell of an Al(III) Hyd. species?



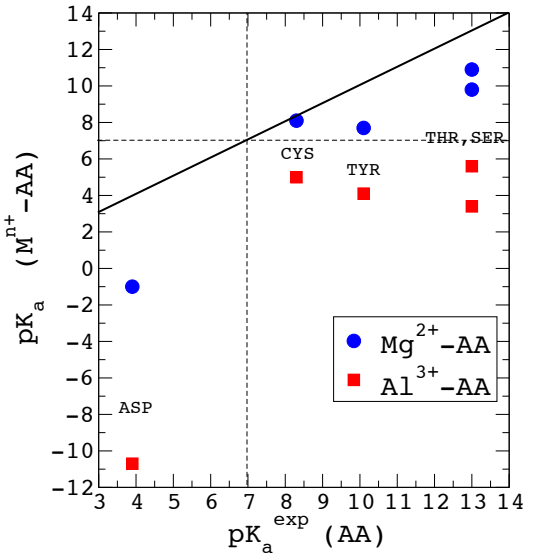
Q2: Formation of Al-superoxide

Calibration: Cluster-Continuum Approach and pK_a's

Pliego, et al. J. Phys. Chem. A 2002, 106, 7434.



Mujika, Ugalde, Lopez, Theoretical Chemistry Accounts, 2011, 128, 477



Q2: Formation of Al-superoxide

Model's Calibration: Relative acidity of $OOH^{\cdot}$ with respect to H_2O

- Methods:
  - Gas Phase: B3LYP, M06X and PBE0 with 6-311++G(3df,2p) basis set
  - Bulk Solvent:
    - PCM HF/6-31G* UAHF
    - SMD at B3LYP/6-311++G(3df,2p)
- Calibration:

$\Delta G_{aq}^{exp}(298K) = -14.9\, kcal/mol$	$\triangle G_{aq}^{SMD}$	$\triangle G_{aq}^{PCM/HF}$
$OOH^{\cdot} + OH^{-} \rightarrow O_2^{-\cdot} + H_2O$	-24.5	-6.5
$OOH^{\cdot}(H_2O)_2 + OH^{-}(H_2O)_2 \rightarrow O_2^{-\cdot}(H_2O)_2 + H_2O(H_2O)_2$	-17.6	-12.6

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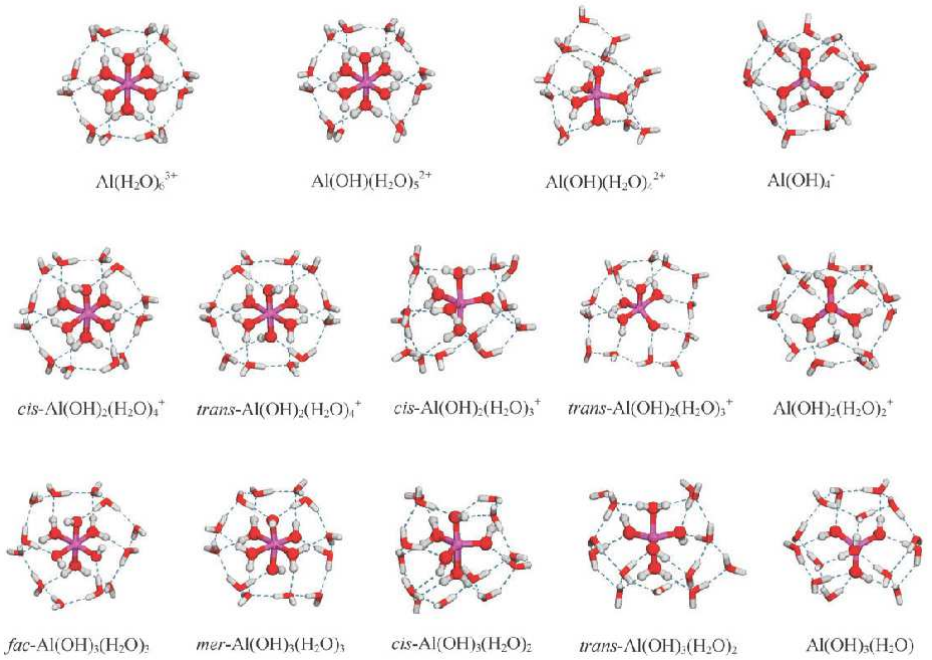
- For $H_2O/OH^{-}/O_2^{\cdot -}$, two explicit water molecules are added in the calculations to reduce errors associated to solvation.

Q2: Formation of Al-superoxide

Al Models

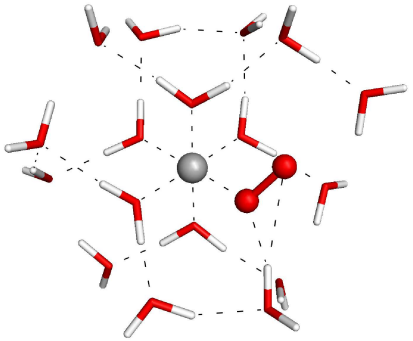
- Is thermodynamically favorable for a $O_2^{\cdot -}$ to displace a H_2O/OH^- from the 1^{st} coord. shell of an Al(III) Hyd. species? Species?



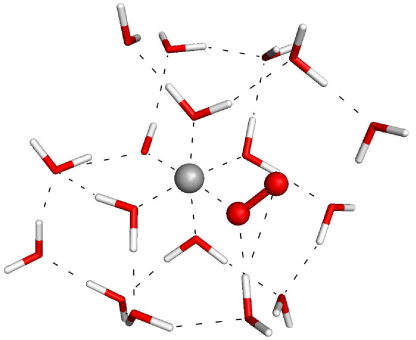
Yang et al. Phys. Chem. Chem. Phys. 2009

Q2: Formation of Al-superoxide

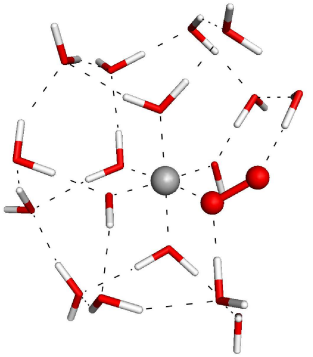
Al-superoxide compounds 1S2S models



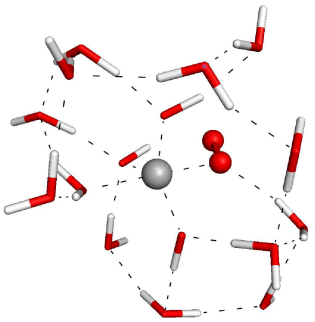
$Al(O_2)(H_2O)_5^{+2}$



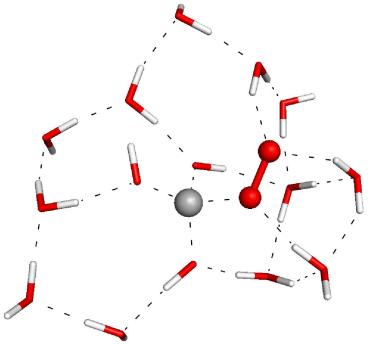
$Al(O_2)(OH)(H_2O)_4^{+1}$



$Al(O_2)(OH)_2(H_2O)_3$



$Al(O_2)(OH)_3(H_2O)^{-1}$



$Al(O_2)(OH)_3^{-1}$

Q2: Formation of Al-superoxide

B3LYP Thermodynamics of Substitution Reactions in kcal/mol			$1^{st}+2^{nd}$ coord. shell	
			$\triangle G_{aq}^{SMD}$	$\triangle G_{aq}^{PCM}$
$Al(H_2O)_6^{+3}+O_2^{\cdot-}$	$\rightarrow$	$Al(O_2^{\cdot})(H_2O)_5^{+2}+H_2O$	-8.3	-15.2
$Al(OH)(H_2O)_5^{+2}+O_2^{\cdot-}$	$\rightarrow$	$Al(O_2^{\cdot})(OH)(H_2O)_4^{+1}+H_2O$	-8.7	-13.5
	$\rightarrow$	$Al(O_2^{\cdot})(H_2O)_5^{+2}+OH^-$	13.5*	11.6*
$Al(OH)_2(H_2O)_4^{+1}+O_2^{\cdot-}$	$\rightarrow$	$Al(O)(OH)_2(H_2O)_3+H_2O$	-1.7	-2.8
	$\rightarrow$	$Al(O_2^{\cdot})(OH)(H_2O)_4^{+1}+OH^-$	11.8*	7.8*
$Al(OH)_3(H_2O)_2+O_2^{\cdot-}$	$\rightarrow$	$Al(O_2^{\cdot})(OH)_3(H_2O)+H_2O$	-2.0	-1.8
	$\rightarrow$	$Al(O_2^{\cdot})(OH)_2(H_2O)_3+OH^-$	12.3*	6.8*
$Al(OH)_4^{-1}+O_2^{\cdot-}$	$\rightarrow$	$Al(O_2^{\cdot})(OH)_3^{-1}+OH^-$	15.8	11.2

*only 1S

- Substitution of OH^- endoergonic while substitution of H_2O exoergonic
- The main source of Al-superoxide formation is Al^{+3}, and $Al(OH)^{+2}$

Summary for Q1 and Q2

Question 1: Al-superoxide Interaction Strength?

- There is a strong intrinsic interaction of Al^{+3} with superoxide
- The strength of this interaction is larger than for common biometals
- Microsolvation does not alter the relative stregnth of the interaction

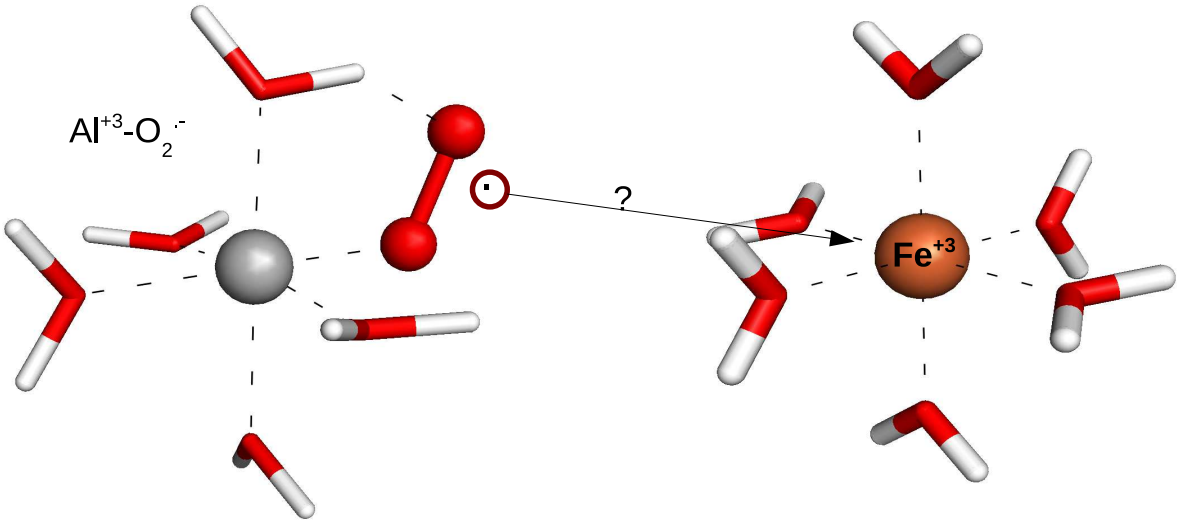
Question 2: Formation of Al-superoxide from Al Hydrolytic Species

- The formation of a complex between Al^{3+} and $Al(OH)^{2+}$ with a superoxide in aqueous solvent highly favored
- Displacement of H_2O , not OH^-

Q3: Promotion of Fenton Reaction

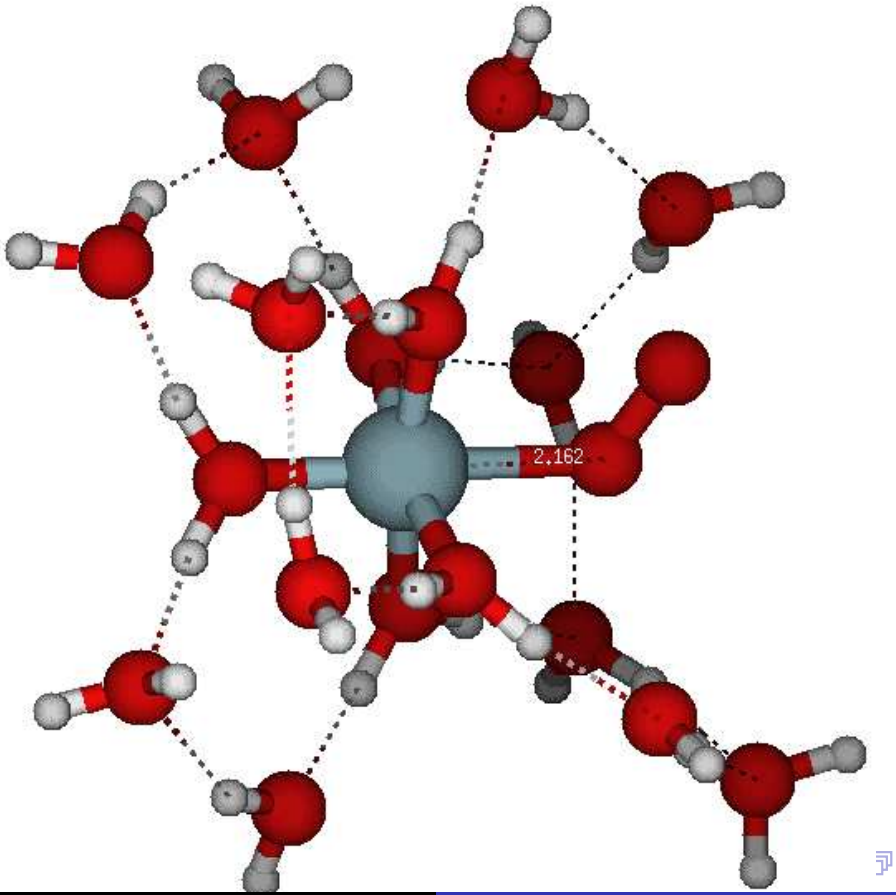
Question 3 (Q3): Al-superoxide could enhance oxidative stress by promotion of Fenton Reaction?

Could Al-superoxide reduce Fe^{3+} to Fe^{2+}?



Q3: Promotion of Fenton Reaction

Spontaneous O_2 Departure from Al(III)



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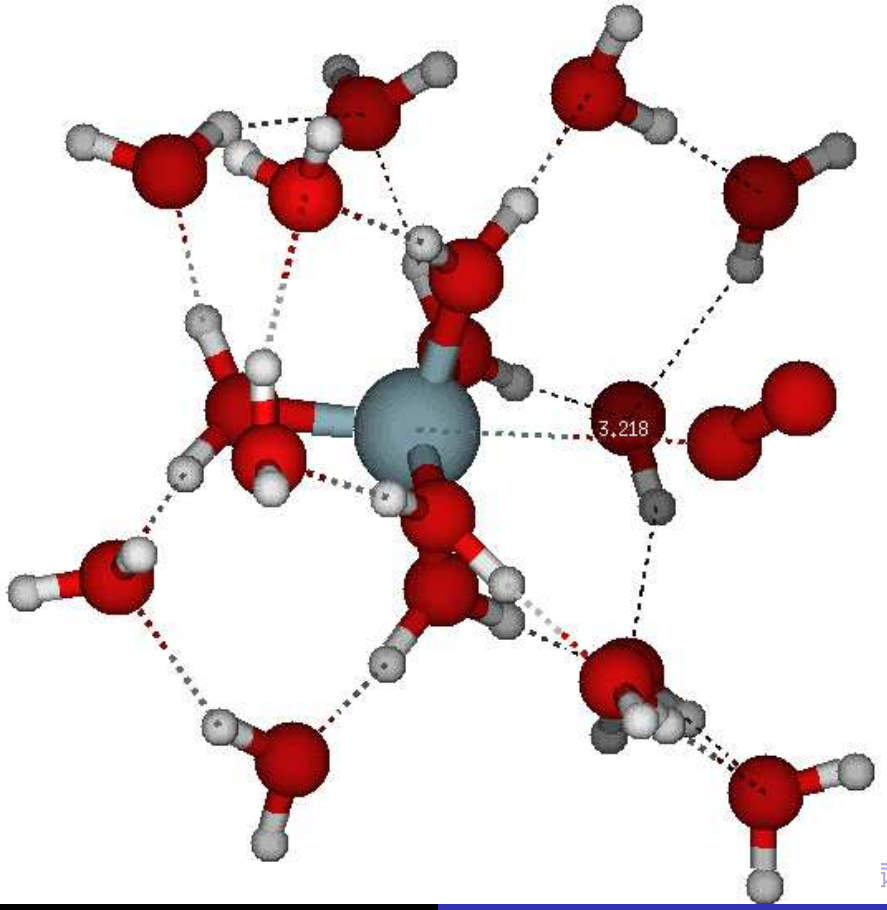


Q3: Promotion of Fenton Reaction

Delocalization Indexes explains the low affinity for neutral O_2

- Delocalization index: Measure of electron sharing (Bader et al. JACS 1975; Fradera et al. JPCA 1999, Matito et al. FD 2007))

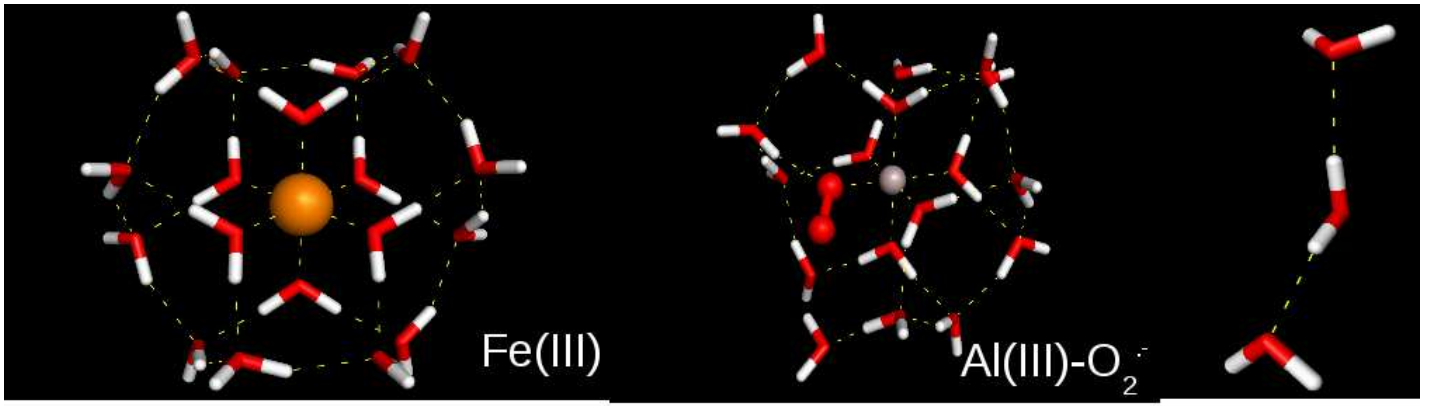
$$\delta_{AB} = -2\int_A\int_B (2\Gamma(\mathbf{r_1},\mathbf{r_2}) - \rho(\mathbf{r_1})\rho(\mathbf{r_2}))\, d\mathbf{r_1} d\mathbf{r_2} \quad (1)$$

Ligand Affinity

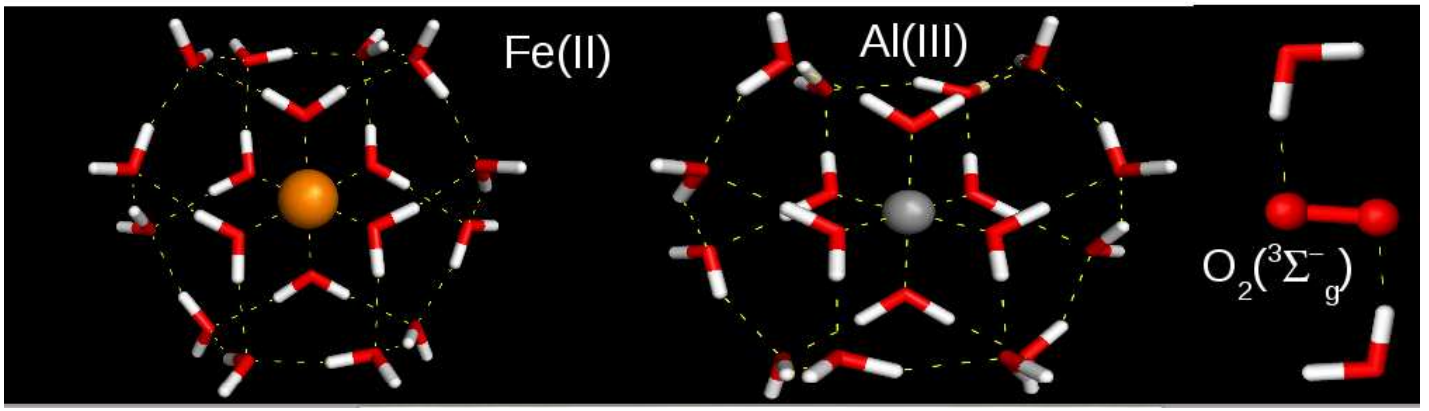
$OH- > O_2^{\cdot -}(^2\Pi_g) > H_2O > O_2(^3\Sigma_g^-)$

Ligand	$< \delta_{OAl} >$
OH^-	0.27±0.03
H_2O	0.13±0.03
$O_2^{\cdot -}(^2\Pi_g)$	0.15/0.20±0.01
$O_2(^3\Sigma_g)$	0.06±0.01

Q3: Promotion of Fenton Reaction



B3LYP	*kcal/mol*
ΔG_{gas}	-39.1
ΔG_{aq}^{SMD}	-19.8
ΔG_{aq}^{PCM}	-7.4



Q3: Promotion of Fenton Reaction

Results for other Hydrolytic Species

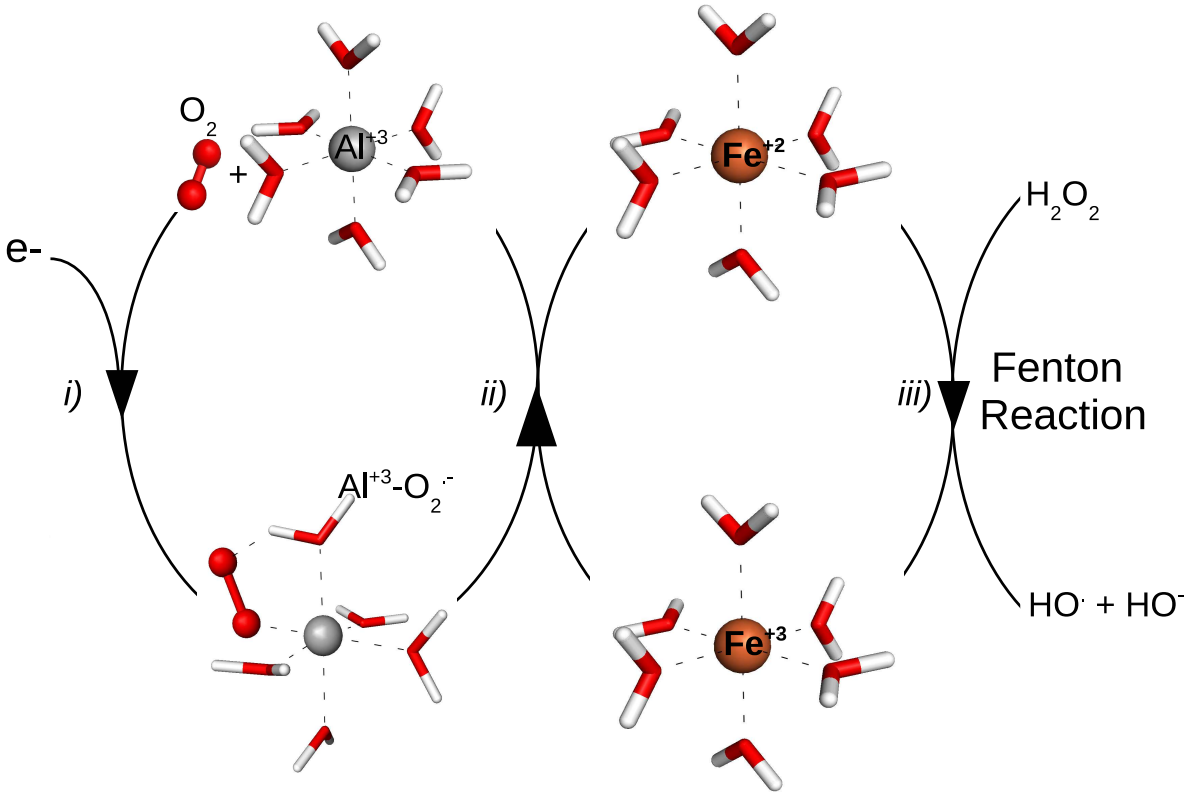
ΔE			ΔG		
B3LYP	PBE	M062X	ΔG_g	ΔG_{aq}^{SMD}	ΔG_{aq}^{PCM}
$Fe^{3+} + AlO_2^{\cdot 2+} \rightarrow Fe^{2+} + Al^{3+} + O_2$					
-42.0	-41.3	-39.6	-39.1	-19.8	-7.4
$Fe^{3+} + Al(OH)O_2^{\cdot +} \rightarrow Fe^{2+} + Al(OH)^{2+} + O_2$					
-101.4	-100.0	-97.5	-104.9	-19.2	-9.2
$Fe^{3+} + Al(OH)_2O_2^{\cdot} \rightarrow Fe^{2+} + Al(OH)_2^{+} + O_2$					
-171.9	-172.8	-176.7	-171.2	-18.9	-12.1

Q3: Promotion of Fenton Reaction

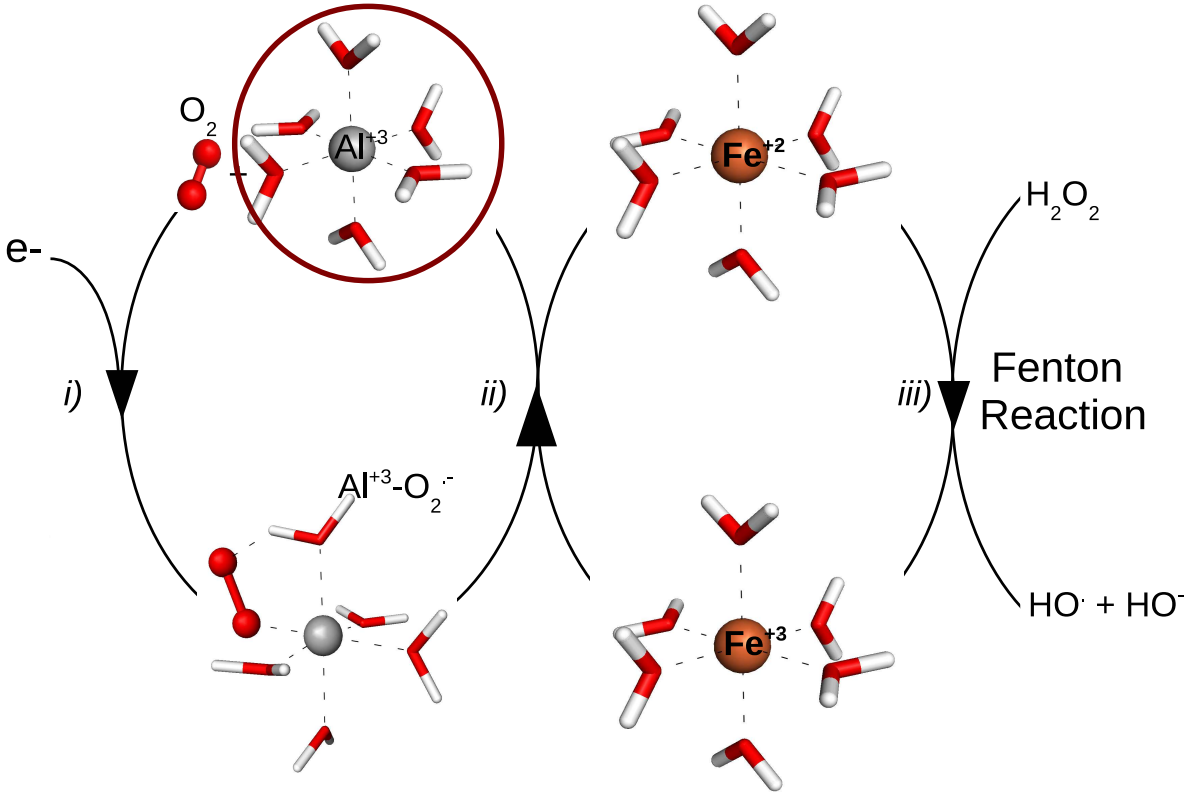
Question 3 (Q3): Al-superoxide could enhance oxidative stress by promotion of Fenton Reaction?

Al-superoxide complexes could reduce Fe^{3+} to Fe^{2+}, provoking the spontaneous departure of O_2 from Al, and therefore, recovering an Al Hydrolytic Species

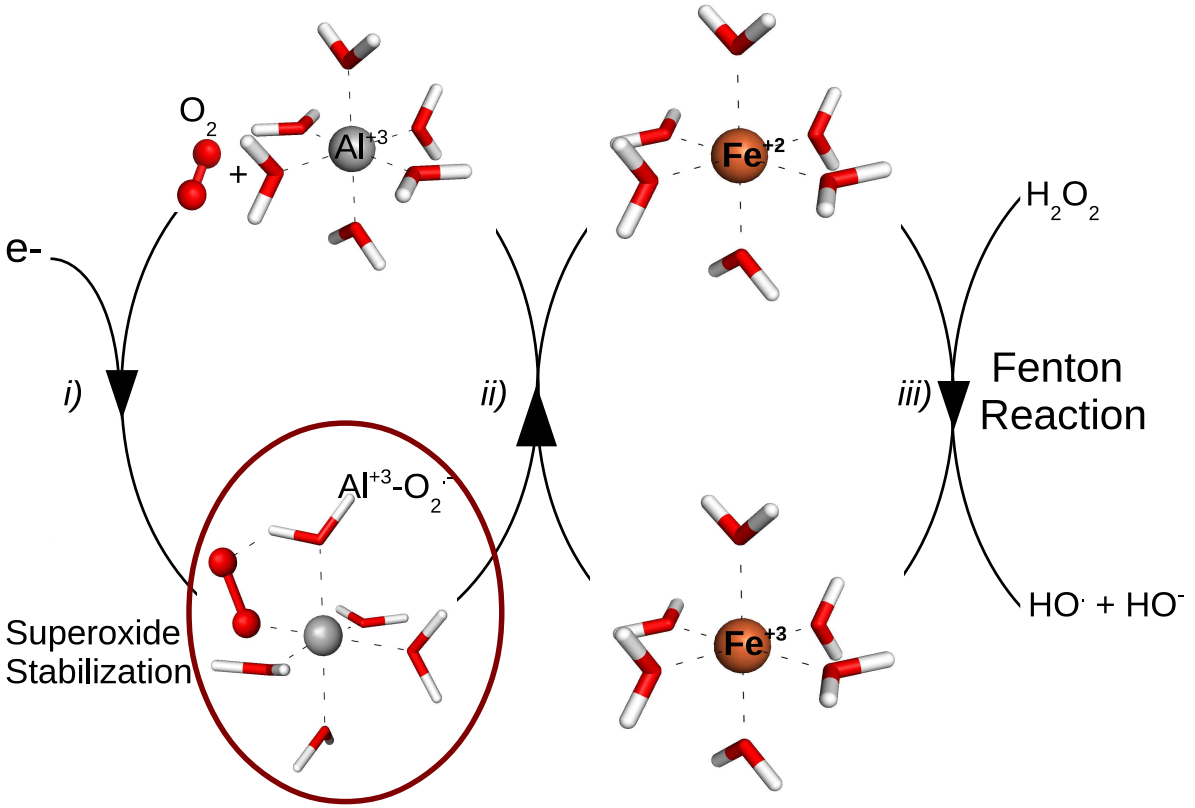
Al(III) Fenton Reaction Promotion Cycle



Al(III) Fenton Reaction Promotion Cycle



Al(III) Fenton Reaction Promotion Cycle



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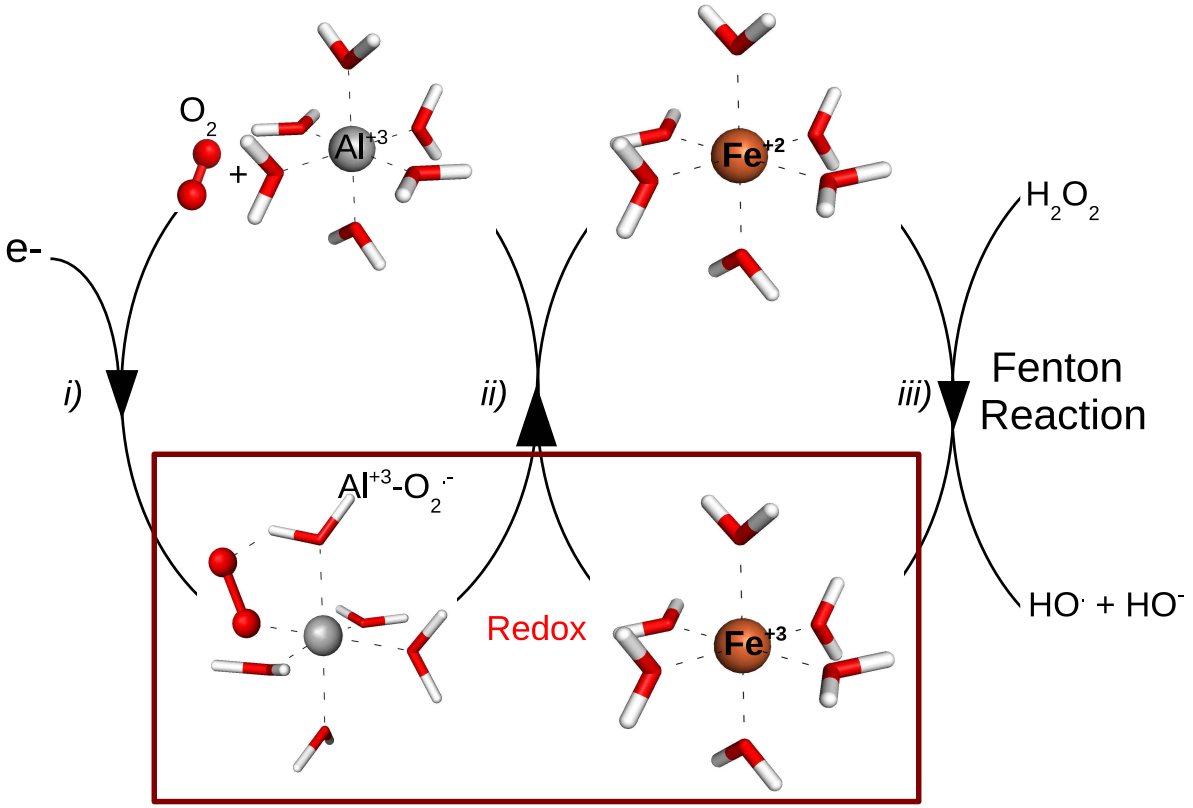
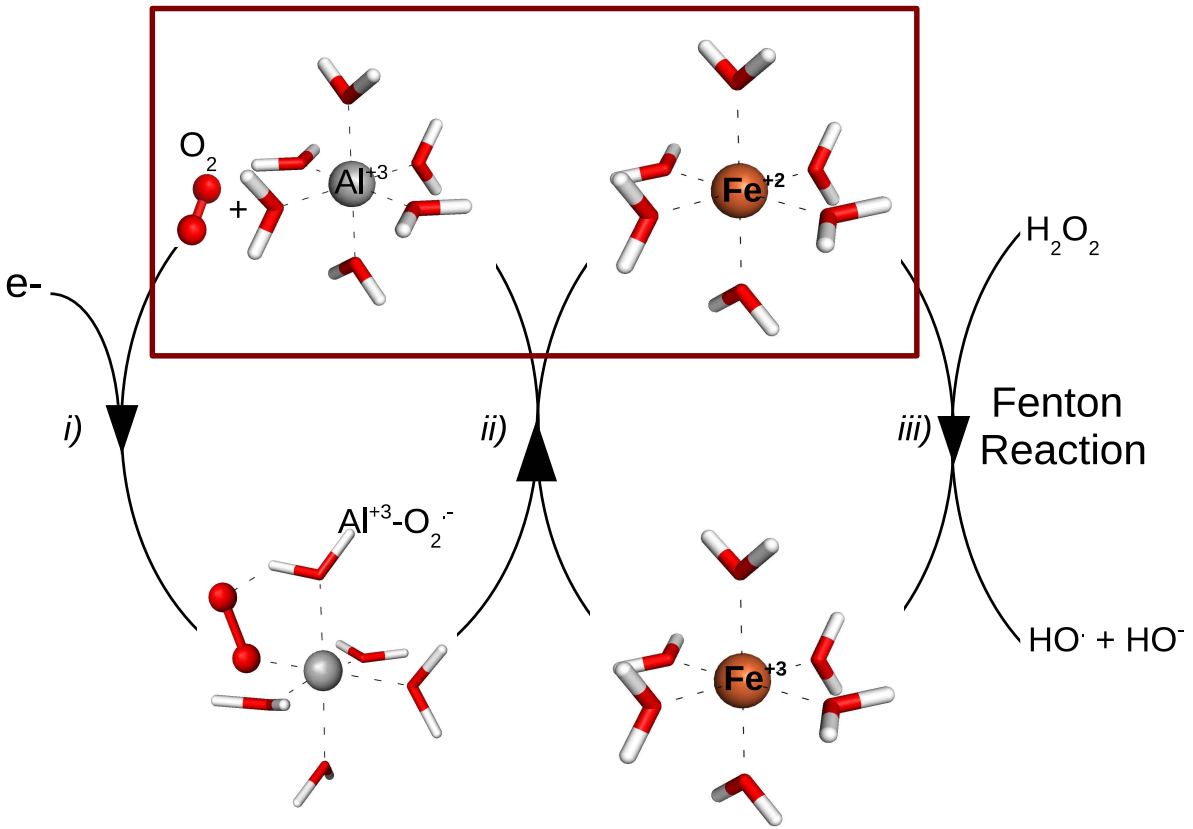
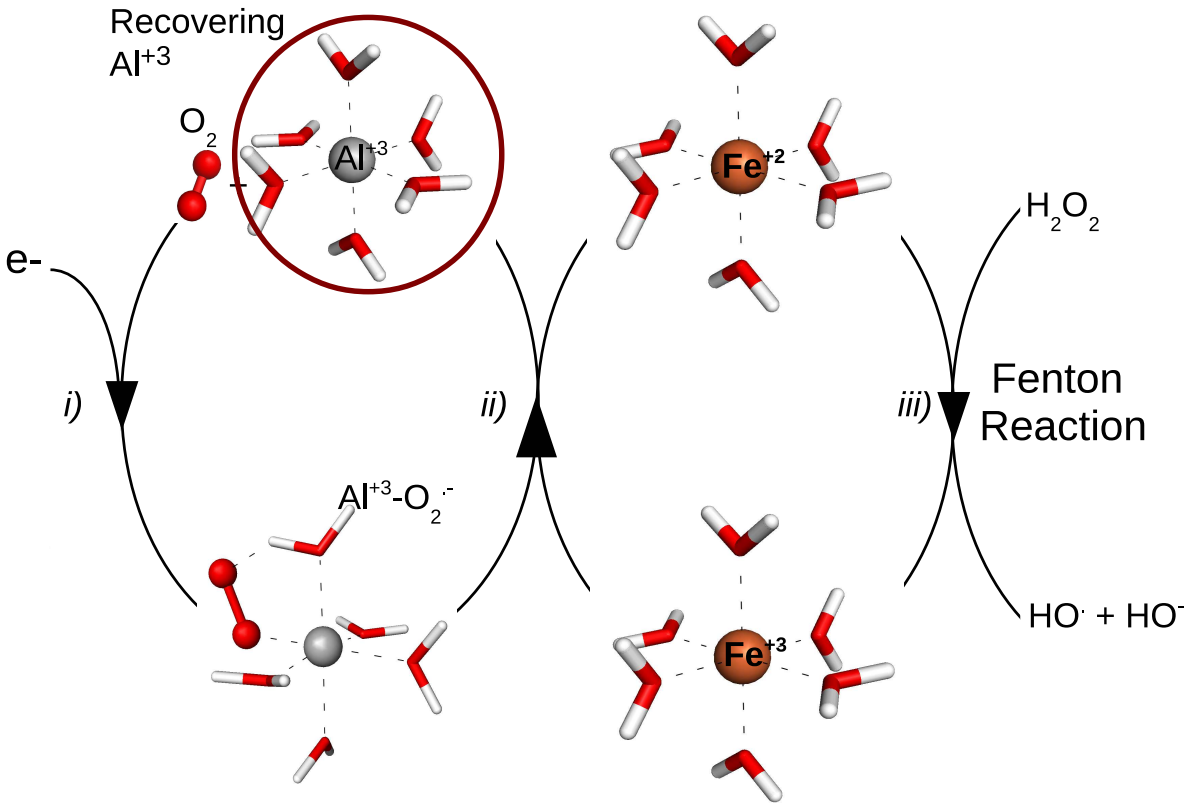


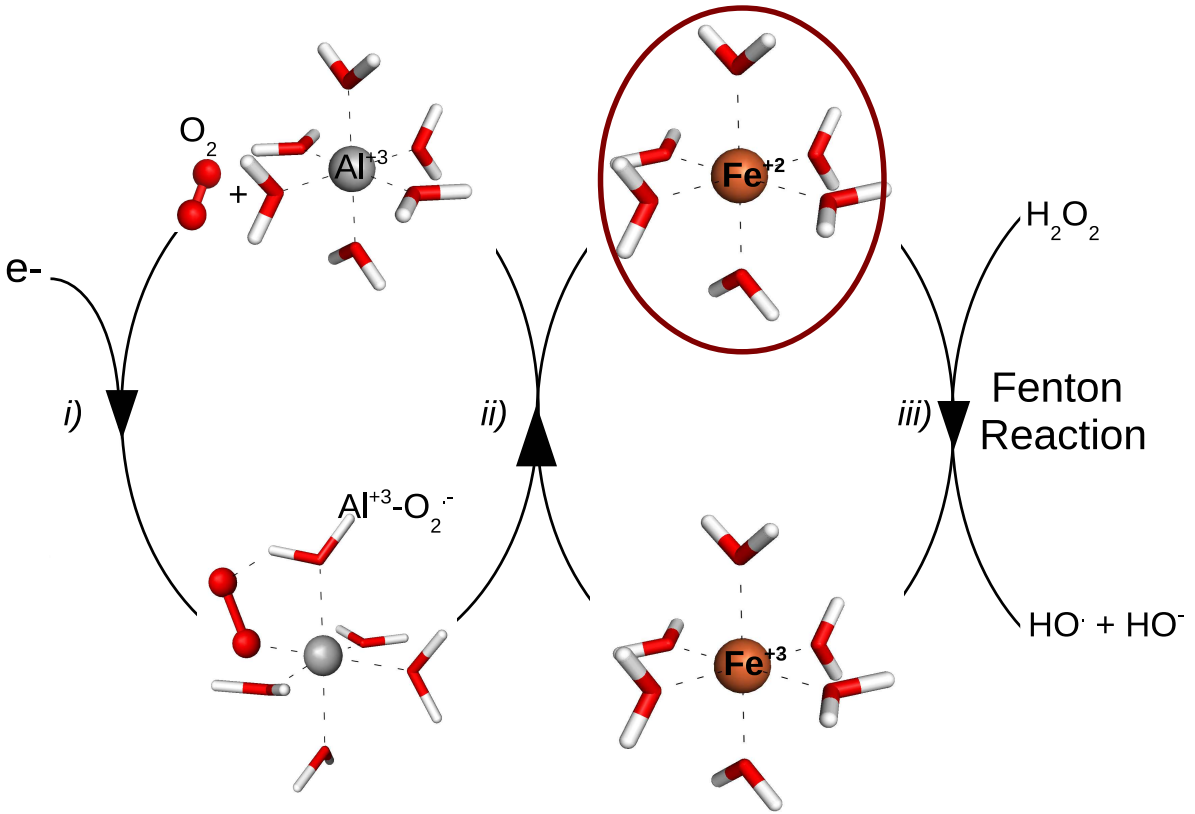
Al(III) Fenton Reaction Promotion Cycle



Al(III) Fenton Reaction Promotion Cycle



Al(III) Fenton Reaction Promotion Cycle



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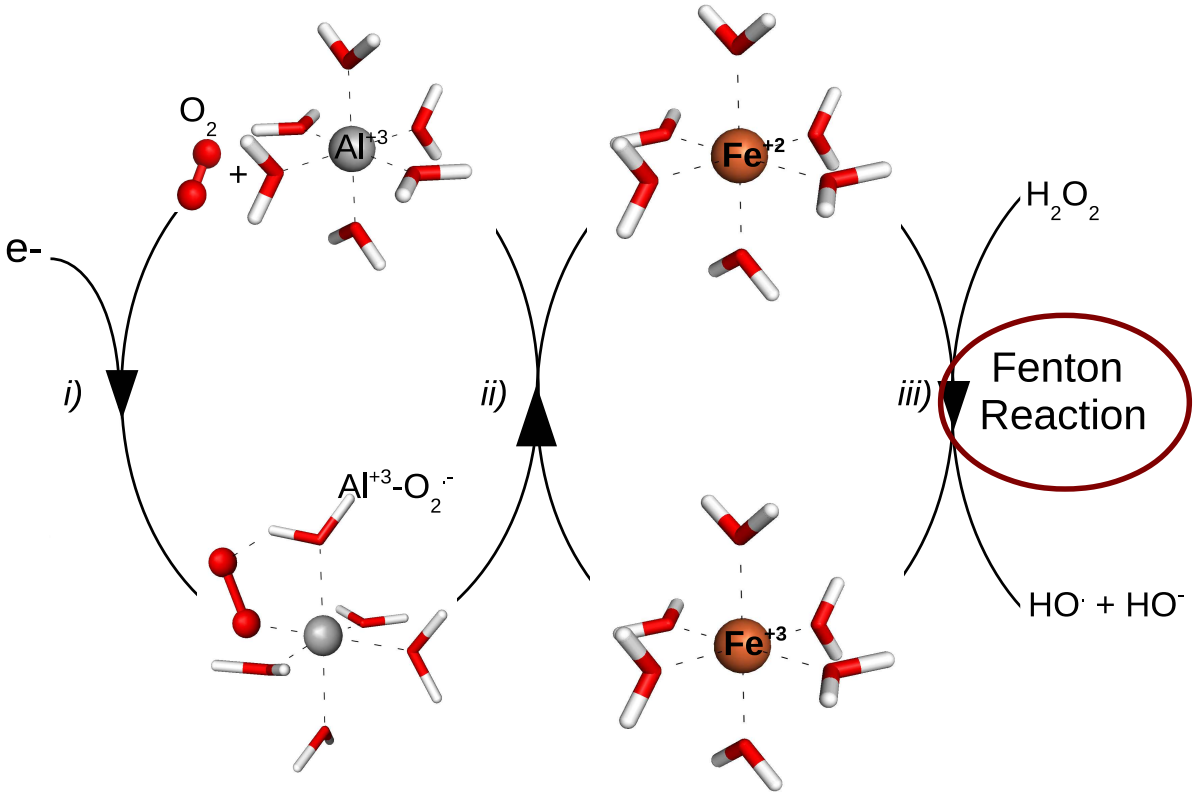

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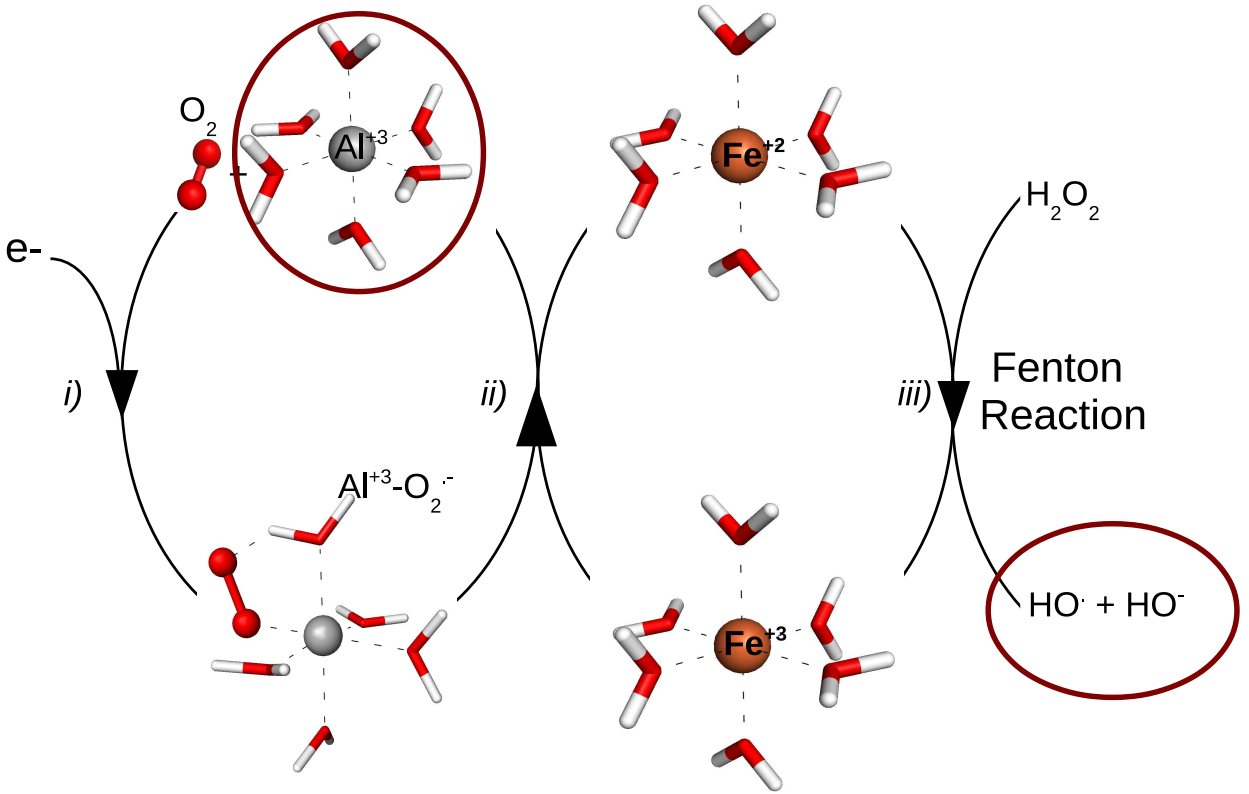

Conclusions on Pro-oxidant activity of Al:

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Further Reading

1. F. Ruipérez, J.I. Mujika, J.M. Ugalde, C. Exley, X. Lopez, "Pro-oxidant activity of aluminum: Promoting the Fenton reaction by reducing Fe(III) to Fe(II)", Journal of Inorganic Biochemistry, vol.117, p.118-123, (2012) . DOI: 10.1016/j.jinorgbio.2012.09.008
2. J. I. Mujika, F. Ruipérez, I. Infante, J. M. Ugalde, C. Exley, X. Lopez, "Pro-oxidant Activity of Aluminum: Stabilization of the Aluminum Superoxide Radical Ion", The Journal of Physical Chemistry A, vol.115, iss.24, p.6717-6723, (2011) . DOI: 10.1021/jp203290b

Acknowledgements