Mimicking Cytochrome P450 Compound I by a model high-valent iron(IV)-oxo porphyrin cation radical complex

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Nature has developed heme mono-oxygenase enzymes, named cytochrome P450, as versatile catalysts able to detoxify drugs and xenobiotics in the human liver. Its active form, namely the high valent iron(IV)-oxo porphyrin cation radical species called Compound I (CpdI), generally reacts with a wide range of substrates through oxygen atom transfer.[1] The full details of the mechanism have still to be elucidated and recent insight has been gathered by the joint application of computational chemistry and Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry, combined with electrospray ionization (ESI). Biomimetic analogues of Cpd I intermediates have been prepared in methanol solution using PhIO as oxidant, and characterized as bare ions by ESI FT-ICR MS, in the gas phase, avoiding the complicating effects of solvent, axial ligand or counterion.[2-9]

Herein, the intrinsic reactivity features of $[(TPFPP)^{\bullet+}Fe^{IV}O]^+$ complex, a fleeting intermediates in solution, has been systematically investigated towards substrates that are likely to react via either hydride (1,3,5-cycloheptatriene, CHT) or aliphatic hydrogen (1,3-cyclohexadiene, CHD, and toluene) atom transfer. A detailed joint mass spectrometric and computational study is presented here providing thermal rate constants, product distributions and kinetic isotope effects for the assayed reactions and an accurate thermochemical bond analysis.[10] All these findings point to a a formal hydride transfer (HT) which is actually a hydrogen atom transfer (HAT) followed by a fast electron transfer (ET). This mechanism may bear relevance to enzymatic reactivity where hydride transfer processes are commonly invoked.

Preparation of metal-oxo porphyrin complexes in solution and characterization by high resolution ESI FT-ICR MS

$$[(TPFPP)Fe^{III}]Cl \xrightarrow[CH_3OH,\ -40°C]{PhIO} [(TPFPP)Fe(O)]^+Cl^- \xrightarrow{ESI} [(TPFPP)Fe(O)]^+$$

(soln) ***(gas phase)***

(1)

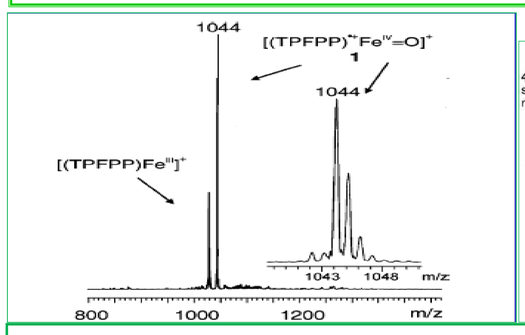
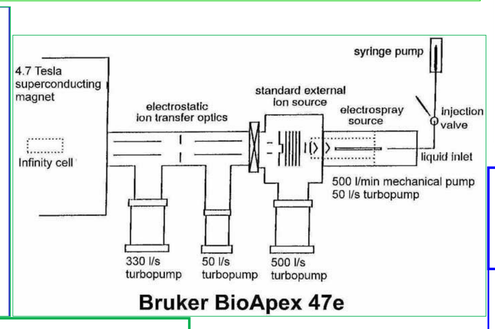


Figure 1. High resolution ESI FT–ICR mass spectrum from a solution of [(TPFPP)Fe]Cl and PhIO in methanol solution.



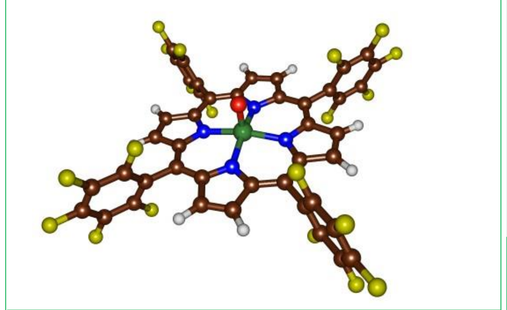


Figure 2. $[(TPFPP^{\bullet+})Fe(O)]^+$: biomimetic model of cytochrome P450 CpdI.

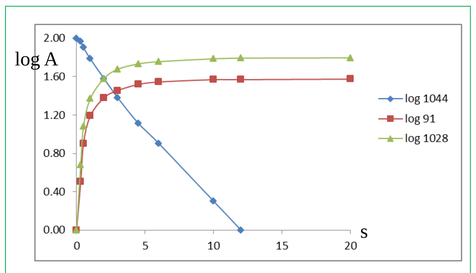


Figure 3. Semi-logarithmic plot of ion abundances (log A) as a function of time (s) for the reaction of $[(TPFPP^{\bullet+})Fe(O)]^+$ with CHT at the stationary pressure of 4×10^{-8} mbar in the FT-ICR cell at 300K.

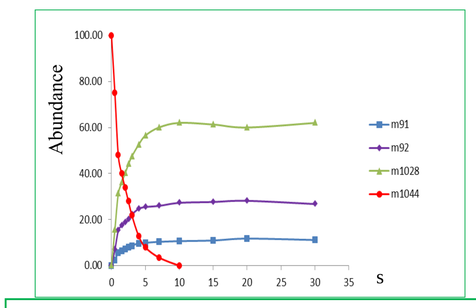


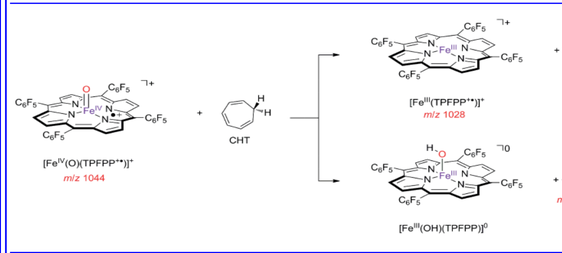
Figure 4. Ion abundances as a function of time after isolation of $[(TPFPP^{\bullet+})Fe(O)]^+$ in the presence of 5×10^{-8} mbar cycloheptatriene-7-$[D_1]$ in the FT-ICR cell at 300K.

Table 1. Thermodynamic and kinetic data and product distributions for the reaction of selected hydrocarbons with $[(TPFPP^{+\bullet})Fe^{IV}(O)]^+$.

Compound	IE[a]	BDE_{CH}[b]	$IE_{radical}$[a]	k_{exp}[c]	Φ [%]	% $[A-H]^+$[d]	%$[Fe^{III}(TPFPP)]^+$	%ADD
Toluene	8.828	87.9	7.242[e]	0.36	3.9[h]	–	80	20
CHT	8.0-8.3	72.9	6.28[f]	2.67	30	40	60	–
CHD	8.25	72.9	6.82[g]	1.58	17[i]	–	100	–

[a] in eV.[b] in kcal mol^{-1}. [c] Second-order rate constants in units of 10^{-10} cm^3 $molecule^{-1}$ s^{-1}, at the temperature of the FT-ICR cell (300K). The estimated error is ±30%; the internal consistency of the data is within ±10%. [d] Product ion at m/z value for substrate minus H^+. [e] Data from http://webbook.nist.gov. [f] The reaction of CHT-7-$[D_1]$ displays a H/D KIE of 2.5. [g] Data from O. Krechkivska, et al. J. Phys. Chem. A 2014, 118, 10252.[h] Data from Ref. 9. [i] Data from Ref. 8.

Gas Phase Ion Chemistry by ESI-FT-ICR Mass Spectrometry



Scheme 1. Reaction products observed from the reaction of $[(TPFPP^{+\bullet})Fe(O)]^+$ with 1,3,5-cycloheptatriene (CHT) in the FT-ICR cell.

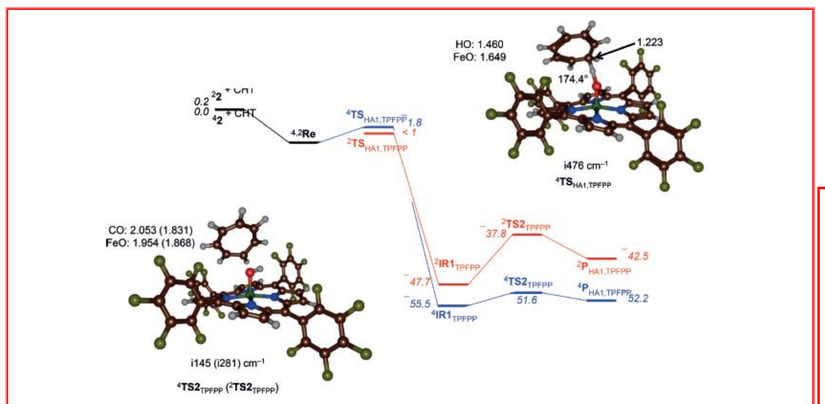


Figure 5. Free energy landscape for oxidation reactions of CHT by $[(TPFPP^{+\bullet})Fe(O)]^+$ ($^{4,2}2$) as calculated at UB3LYP/BS2/UB3LYP/BS1 level in kcal mol^{-1}, at 298 K.

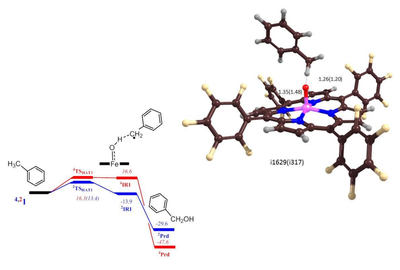


Figure 6. Free energy landscape for hydroxylation reactions of toluene by $^{4,2}2$.

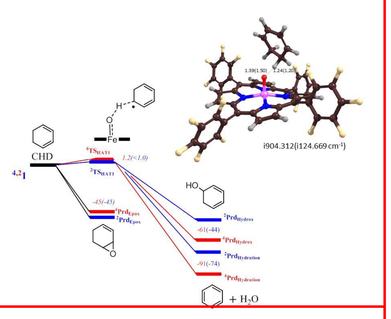


Figure 7. Free energy landscape for OAT reactions of 1,3-cyclohexadiene by $^{4,2}2$.

CONCLUSIONS

The reactivity of 1,3,5-cycloheptatriene, 1,3-cyclohexadiene and toluene with a bare biomimetic model of P450 CpdI, $[Fe^{IV}(O)(TPFPP^{+\bullet})]^+$, has been investigated with a combined approach based on ion-molecule reactions, in a ESI FT-ICR MS, and DFT calculations. Different efficiencies and bifurcation pathways have emerged: whereas CHT reacts through with an initial hydrogen atom abstraction followed by a fast electron transfer in an overall hydride transfer process, toluene undergoes the expected HAT followed by a barrierless OH· rebound and cyclohexadiene gives a mixture of epoxidation and hydroxylation products.

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References. [1] P. R. Ortiz de Montellano, Chem. Rev. 2010, 110, 932-948. [2] M. E. Crestoni, S. Fornarini, *Inorg. Chem*. **2005**, *44*, 5379–5387. [3] M. E. Crestoni, S. Fornarini, *Inorg. Chem*. **2007**, *46*, 9018–9020. [4] B. Chiavarino, R.Cipollini, M. E. Crestoni, S. Fornarini, F. Lanucara, A. Lapi, *J. Am. Chem. Soc.* **2008**, *130*, 3208–3217. [5] M. E. Crestoni, S. Fornarini, F. Lanucara, *Chem. Eur. J.* **2009**, *15*, 7863–7866. [6] M. E. Crestoni, S. Fornarini, F. Lanucara, J. J. Warren, J. M. Mayer, *J. Am. Chem. Soc.* **2010**, *132,* 4336–4343. [7] M. E. Crestoni, F. Lanucara, *Chem. Eur. J*. **2011**, *17*, 12092–12100. [8] M. A. Sainna, S. Kumar, S. Fornarini, M. E. Crestoni, S. P. de Visser, Chem. Sci. **2015**, 6, 1516-1529. [9] F. G. Cantù Reinhard, M. A. Sainna, P. Upadhyay, G. A. Balan, D. Kumar, S. Fornarini, M. E. Crestoni, S. P. de Visser, *Chem. Eur. J*. **2016**, 22, 18608-18619. [10] F. G. Cantù Reinhard, S. Fornarini, M. E. Crestoni, S. P. de Visser, *Eur. J. Inorg. Chem.* 2018, in print (DOI: 10.1002/ejic.201800273).

The First European Network of Fourier-Transform Ion-Cyclotron-Resonance Mass Spectrometry Centers (EU_FT-ICR_MS; ID: 731077-2) offers TransNational Access (TNA) to achieve ion-molecule reactions experiments @ Università La Sapienza - Roma where dedicated, competent expertise will allow to obtain the best achievable data.
All expenses (travel, accomodation and measurements) for TNA are covered .

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