View Article Online View Journal

NJC Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. N. Dhuri, D. Harmalkar, S. G, S. Shetgaonkar and M. Sankaralingam, *New J. Chem.*, 2019, DOI: 10.1039/C9NJ01381D.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the **author guidelines**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/njc

1 2 3 4 5 6 7 8 9 10 11 12 13 14 ₹5 2:52:52 ១8 1070 1070 120 ⊉1 t Unikerstiy 2018, Downloaded by Notkingham Treat 6 10 17 17 17 17 17 38 lbkished 0 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60

New Journal of Chemistry



ARTICLE

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

A putative heme manganese(V)-oxo species in the C-H activation and epoxidation reactions in an aqueous buffer

Dinesh S. Harmalkar,^a G. Santosh,^{a,b} Siddhi B. Shetgaonkar,^a Muniyandi Sankaralingam,^{c*} Sunder N. Dhuri^{a*}

Dedicated to Prof. B. R. Srinivasan on the occasion of his 60th birthday.

A water-soluble manganese(V)-oxo species **1** was generated in the reaction of [Mn(III)(TPPS)Cl] **2** (TPPS = 5,10,15,20-tetrakis(4-sulfonatophenyl)-21H,23H-porphine) and iodosylbenzene (PhIO) in 2:1 aqueous buffer (pH = 10.4): acetonitrile (CH₃CN) mixture. The formula of the EPR silent species **1** is proposed as [Mn(V)(O)(TPPS)Cl] based on the Soret band (422 nm) and Q bands (520, 660 nm) in its UV-vis spectrum and its reaction with thioanisole regenerating **2** and methyl phenyl sulfoxide. The reactivity of **1** was investigated in the C-H activation of alkyl hydrocarbons and epoxidation of cyclohexene. Based on the bond dissociation energy (BDE, kcal mol⁻¹) of alkyl hydrocarbons along with a large kinetic isotope effect (*KIE* = 8.5) for xanthene *vs* xanthene-*d*₂, we propose an H-atom abstraction as the rate determining step in the C-H activation reactions. On the other hand, in contrast to C-H activation reaction cyclohexene which has weak C-H bond (BDE = 82.5 kcal mol⁻¹) undergoes an epoxidation reaction.

Introduction

The high valent metal-oxo short-lived species have been extensively studied and used in the oxidation of the organic substrates into viable products.¹⁻² In iron-heme chemistry, several researchers have investigated two distinct species namely compound I [Fe(IV)(O)(porp^{•+})] and compound II [Fe(IV)(O)(porp)] (porp is porphyrin).¹⁻² Likewise, a large number of reports are available on the biomimetic chemistry of heme and nonheme high valent manganese-oxo species.³⁻⁷ Nam and coworkers reported the first single crystal structure of a nonheme iron compound viz [Fe(IV)(TMC)(O)(CH₃CN)]²⁺ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)⁸, while the first crystal structure of nonheme manganese compound viz [Mn(V)(O)(TAML)]⁻ bearing a tetraamido

Kozhikode, Kerala 673601, India. E-mail: msankaralingam@nitc.ac.in

macrocyclic ligand (TAML) was reported by Collins and coworkers.⁴ Manganese-oxo porphyrin species, [Mn(IV)(O)] and [Mn(V)(O)] have been proposed as key intermediates reactive several oxidative in transformations.⁹ The oxidation of olefins and alkanes by catalytic amounts of Mn(III)-porphyrin compounds in the presence of additional oxidants such as iodosylbenzene (PhIO), hydrogen peroxide $(H_2O_2),$ *tert*-butyl hydroperoxide (t-BuO₂H) and m-chloroperbenzoic acid (*m*-CPBA) has been previously reported.^{10, 11}

The chemistry of Mn(III)-porphyrin compounds is fascinating as these compounds represent a class of new molecular designs that can achieve a redox control while maintaining the low molecular weight and tailored lipophilicity.¹² The high stability of metalloporphyrins compared to nonheme metal macrocycles has led to study Mn(III)-porphyrins in superoxide dismutase (SOD) mimics.¹³ The synthetic water-soluble Mn(III)-porphyrins pyridinium, sulfonate or carboxylato containing substituents are known to be effective radiosensitizers.¹⁴ It has been reported that these water-soluble porphyrins cells.15 The water-soluble accumulate in tumor [Fe(III)(TPPS)Cl] (where TPPS = 5,10,15,20-tetrakis(4sulfonatophenyl)-21H,23H-porphine) is known to catalyze *N*-dealkylation reaction.¹⁶ The compounds such as [Mn(III)-o-TMPyP] (where o-TMPyP = 5,10,15,20- tetra-

^{a.} School of Chemical Sciences, Goa University, Taleigao Plateau, Panaji, Goa 403206, India. E-mail: sndhuri@unigoa.ac.in

^{b.}Divison of Chemistry, School of Advanced Sciences, Vellore Institute of Technology, Chennai, Tamilnadu, 600127, India.

^c Department of Chemistry, National Institute of Technology Calicut,

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

ARTICLE

1 2

3

4

5

6

7

8

9

10

11

12

13

14

₹35

5<u>7</u>57 7

១8

1070 1070 120

∄1

t Unicerstay

Nottingfunding 2

And the management of the second seco

38

lbkished 0

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56 57

58

59 60 (N-methylpyridinium-2-yl)porphyrin) and [Mn(III)(TPPS)Cl] are reported to form high valent manganese(V)-oxo species on addition of external oxidants.¹⁷ [Mn(III)(TPPS)Cl] was used in the dye degradation process and other reactions using H₂O₂ as an oxidant¹⁷ Several other stable water-soluble Mn(III) porphyrins are known in the literature (Scheme 1).9,18,19 Although the [Mn(IV)(O)] and [Mn(V)(O)] species are now well known, only a handful of reports are available the reactivity of water-soluble on [Mn(V)(O)] species.^{9,11,17,20} Nam and coworkers have reported the rate determining H-atom abstraction in the C-H activation reactions of alkyl hydrocarbons by $[Mn(V)(tf_4tmap)(O)_2]^{3+}$ meso-tetrakis(2,3,5,6-tetrafluoro-N,N,N-(tf₄tmap = trimethyl-4-aniliniumyl)porphyrinato dianion) species in aqueous basic buffer solution.9 The resulting species [Mn(IV)(OH)] was reported to be sluggish in the H-atom abstraction as compared to [Mn(V)(O)₂] species. Herein, we report on the characterization and the reactivity of a water-soluble high valent [Mn(V)(O)] species (namely [Mn(V)(O)(TPPS)Cl] 1 in the C-H activation of alkyl hydrocarbons. This reaction is compared with the reactivity of cyclohexene and styrene.



Scheme 1. Water-soluble porphyrins reported in the 5,10,15,20-tetra-(N-methylpyridinium-4literature. (i) yl)porphyrin (p-TMPyP); (ii) 5,10,15,20-tetra-(Nmethylpyridinium-3-yl) porphyrin (m-TMPyP); (iii) 5,10,15,20-tetra-(N-methyl pyridinium-2-yl)porphyrin (o-TMPyP); (iv) 5,10,15,20-tetra-(4-carboxyphenyl)porphyrin 5,10,15,20-tetra-(4-N-(TCPP); (v) trimethylanilinium)porphyrin (TAPPH₂); (vi) 5,10,15,20tetra-(2,3,5,6-tetrafluro-4-N-trimethylanilinium)-porphyrin (TAFPP); 5-(4-amino phenyl)-10,15,20-tri-(4-(vii) sulfophenyl)porphyrin (TAPPS); (viii) 5-(2,6diaminophenyl)-10,15,20-tri-(4-sulfophenyl)porphyrin (TDAPPS); (ix) 5,10,15,20-tetrakis(4-sulfonatophenyl)-21H,23H-porphine (TPPS).

Materials and Methods

The chemicals used in this study were purchased from commercial sources and used without any further purification $% \left({{\left[{{{\rm{s}}_{\rm{s}}} \right]}} \right)$

unless required. The aqueous carbonate-bicarbonate-buffer $(pH \sim 10.4)$ was prepared by mixing 0.1 DM Na₂CO₂(2715 ml) and 0.1 M NaHCO₃ (22.5 mL) and dilution with distilled water in a 100 mL standard flask. pH measurements were performed using Chemi Line Digital pH meter CL-110. PhIO was prepared using a literature procedure (see in ESI⁺).²¹ TPPH, TPPS and [Mn(III)(TPPS)Cl] 2 were prepared as per the literature methods²²⁻²⁴ (Scheme S1 in ESI⁺). The deuterated xanthene was prepared by a procedure described in ESI⁺. ¹H NMR spectra were recorded on a Bruker Avance-III 400 MHz NMR spectrometer. UV-vis spectra were measured on Agilent 8453 UV-vis spectrophotometer attached with a water circulator and thermostatic control (Morya Scientific make). Infrared (IR) spectra in the region of 4000-400 cm⁻¹ were recorded on a Shimadzu (IR-Prestige-21) FTIR spectrometer by diluting the powdered samples in KBr. Elemental analyses were performed on Elementar Variomicro Cube CHNS analyzer. EPR spectra were measured at 77 K on a JEOL X-band spectrometer (JESFA100). The g value was calibrated using the Mn(II) marker. The organic product analysis was performed on Shimadzu GC 2014 equipped with HP capillary column and FID detector. The retention time and peak areas of the products were compared with authentic samples using *n*-decane as an internal standard.

Synthesis of TPPH, TPPS and [Mn(III)(TPPS)Cl] 22-24

TPPH: A round bottom flask containing 100 mL CHCl₃ and freshly distilled benzaldehyde (1.0 mL, 9.84 mmol) was stirred under N_2 atmosphere for about 5 min. To this solution a freshly distilled pyrrole (0.683 mL, 9.84 mmol) was added followed by addition of boron trifluoride-diethyl ether (BF₃.OEt₂) (0.1 mL, 2.5 M). After two hours, 2,3-dichloro-5,6dicyano-p-benzoquinone (DDQ) (0.975 mL, 7.30 mmol) was added to the mixture and kept under stirring for a day. The progress of the reaction was monitored by thin layer chromatography (TLC). At the end of the reaction, the solvent was evaporated to obtain a solid compound that was purified on a silica gel column using 30 % CH_2Cl_2 -petether eluent. Yield: 540 mg. The elemental analyses, calculated (found) are as follows: C 85.96 (85.19), H 4.93 (5.37) and N 9.11 (9.38) %. UV-vis spectrum in CHCl₃ showed Soret band at 421 nm and Q bands at 515, 550, 590, and 646 nm (see Fig. S1 in ESI⁺).

TPPS: 10 mL of conc. H_2SO_4 (36 N) was added to the TPPH (0.099 g, 0.162 mmol) and the reaction mixture was stirred at 60 °C for a day.²² The cooled mixture was then neutralized with sodium hydroxide (1.0 M) and TPPH was then extracted using CHCl₃ (20 mL). The solid product obtained after evaporation of CHCl₃ on rotary evaporator was dissolved in dimethylformamide (DMF). The solution was filtered to remove traces of insoluble impurities and DMF was then removed to give TPPS in good yields (90 mg). The elemental analyses, calculated (found) are as follows: C 51.66 (51.02), H 2.56 (2.83), N 5.47 (5.68) and S 12.53 (12.01) %. UV-vis spectrum in water showed Soret band at 410 nm and the Q bands at 516, 552, 581 and 635 nm (see Fig. S2 in ESI⁺). ¹H NMR spectrum of TPPS is shown in Fig. S3 in ESI⁺.

[Mn(III)(TPPS)Cl] **2**: TPPS (0.06 g, 0.058 mmol) and MnCl₂.4H₂O (0.9 g, 4.55 mmol) were taken in 10 mL DMF in a round bottom flask and heated for two days under N_2

atmosphere at 110 °C. The progress of the reaction was monitored by TLC (20 % CH₃OH in CHCl₃). After the completion of the reaction, the mixture was cooled to room temperature and the unreacted solid was removed by filtration. The filtrate was evaporated to obtain [Mn(III)(TPPS)Cl] in good yields (52 mg, 80.0 %). The elemental analyses, calculated (found) are as follows: C 47.59 (46.93), H 2.18 (2.55), N 5.04 (5.12) and S 11.55(11.98) %. UV-vis spectrum in water showed Soret band at 466 nm and the Q bands at 564 and 599 nm (see Fig. 1). IR spectra of TPPH, TPPS and [Mn(III)(TPPS)Cl] 2 are overlaid and shown in Fig. S4 in ESI⁺ for comparison. EPR spectrum of 2 was silent and discussed in the reactivity section (vide infra).

Results and Discussion

Generation and characterization of [Mn(V)(O)TPPS)Cl] (1)

On addition of 1 equivalent of PhIO to **2** in 1:2 CH₃CNaqueous buffer (pH = 10.4) solution at 298 K, a new Soret (422 nm) and the Q bands (520, 660 nm) appeared in the UVvis spectrum corresponding to species **1** (Fig. 1). The observed Soret and Q bands assigned to **1** were also reported earlier.^{17b,17c} The X-band EPR spectrum of **1** was silent suggesting low-spin state (S = 0) of Mn(V) in **1** (Fig. S5 in ESI⁺).²⁵ The species **1** was quite stable with $t_{\frac{1}{2}} \sim 30$ minutes and decayed slowly to give the starting compound **2**. The species **1** was also generated using 1.5 equivalent of *m*-CPBA. However, the lifetime of **1** formed using *m*-CPBA was quite less ($t_{\frac{1}{2}} = \sim 5$ minutes) and decayed ultimately to regenerate **2**.



Fig. 1. UV-Vis spectra of **1** (blue line) and **2** (red line) in (1:2) CH₃CN-aqueous basic buffer solution (pH = 10.4). Inset shows the Q bands of **1** and **2**. **1** was formed by adding PhIO (1 equiv, CH₃OH) to 1:2 CH₃CN-buffer solution of **2** at 298 K.

The reaction of high valent metal(IV)-oxo species with thioanisole and triphenylphosphine affording quantitative yields of methyl phenyl sulfoxide and triphenylphosphine oxide with formation of starting metal(II) species is well documented.¹ Such transformations are referred to as oxygen atom transfer reactions and conclusively prove that high valent metal(IV)-oxo species has undergone two-electron reduction. We therefore, chose this method for the characterization of species **1**. We investigated the reaction of **1** with thioanisole and analyzed the products after the

ARTICLE

Accepted Manuscr

Chemisti

New Journal of

reaction. On addition of thioanisole (25 equiv) to a solution of 1, the Soret band at 422 nm and the Q bands at 3520 and 3660 nm decayed resulting in the simultaneous formation of a new Soret band at 466 nm and Q bands at 564 and 599 nm corresponding to 2 in the UV-vis spectrum (Fig. S6a in ESI⁺). The appearance of Soret band and Q bands with the same absorbance as that of starting [Mn(III)(TPPS₄)Cl] **2** suggested that the species **1** has undergone an oxygen atom transfer to the thioanisole which is a two-electron process, in turn, converting the [Mn(V)(O)(TPPS)Cl] **1** to the starting [Mn(III)(TPPS)Cl] 2. Further, to confirm that the reaction between 1 and thioanisole has really occurred we subjected the reaction mixture to a gas chromatographic (GC) analysis. This revealed the quantitative formation of methyl phenyl sulfoxide (85 (±5)%) in the above reaction of **1** with thioanisole. Similarly, a reaction of $\mathbf{1}$ with PPh₃ was performed. This reaction was very fast as evidenced by an instant disappearance of Soret band at 422 nm and fast appearance of a band at 466 nm due to Mn(III) species (Fig. S6b in ESI⁺). This reaction also gave a nearly quantitative oxygen atom transferred product i.e. triphenylphosphine oxide $(O=PPh_3)$ and the starting Mn(III) compound **2**. Thus, based on the quantitative regeneration of 2 and the formation of methyl phenyl sulfoxide or $O=PPh_3$ it was confirmed that the intermediate species 1 has Mn(V)(O) active core which is electrophilic in nature and thus able to transfer an oxygen atom to the substrate (Scheme 2).



Scheme 2. Oxygen atom transfer reaction between **1** and thioanisole or PPh₃ to regenerate the Mn(III) species **2**.

C-H activiation reactions by [Mn(V)(O)TPPS)Cl] (1)

The species **1** generated using PhIO was quite stable compared to the species generated by *m*-CPBA. Hence, we decided to explore the reactivity of **1** in C-H bond activation reactions of few alkyl hydrocarbons which were selected based on their C-H bond dissociation energies (BDE). In this investigation, xanthene, 1,10-dihydroanthracene (DHA), 1,4-cyclohexadiene (CHD) and fluorene with BDE values of 75.5, 77.0, 78.0 and 80.0 kcal mol⁻¹ respectively were chosen as the substrates (Scheme 3).²⁶



60

ARTICLE

1 2

3

4

5

6

7

8

9

10

11

12

13

14

₹5

57.55 7

ៗ8

1079 120

21

2018 Downloaded by Nottingham Treat

10¹101

lbkished 20 86

₫1 42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59 60 Scheme 3. Alkyl hydrocarbons, cyclohexene and styrene used in the reactivity studies with ${\bf 1}.$



Fig. 2.a) UV-Vis spectral changes on addition of 10 equiv CHD to the 2 mL 1:2 CH₃CN-aquous buffer solution (pH = 10.4) of **1** (0.1 mM, 2.0 mL) at 298 K. (b) Plot of pseudo-first order rate constants vs concentration of xanthene and xanthene- d_2 . To obtain KIE. (c) Plot of log k_2 vs BDE of xanthene, DHA, CHD and fluorene.

On addition of CHD (10 equiv) to an aqueous buffer (pH = 10.4) : CH₃CN (2:1) solution of **1**, the Soret band at 422 nm of **1** slowly decays forming a new band at 466 nm corresponding to starting compound **2** with distinct isosbestic points at 390, 485, 535 and 610 nm (Fig. 2a). The absorbance of the resulting solution after the reaction with **1** was same as that of starting [Mn(III)(TPPS)CI] (0.1 mM, 2.0 mL) suggesting that the quantitative formation of Mn(III) via two electron reduction of Mn(V) to Mn(III) has occurred. The reaction of **1** and CHD followed pseudo-first-order kinetics as evidenced from the time trace of the reaction at 422 and 466 nm (Fig. 2a). Similarly, the reactions of xanthene, DHA and

pseudo-first-order rate constants increased 10 linearly 01 with increase in the concentration of xanthene and other substrates. The pseudo-first-order rate constants (k_{obs}) thus obtained were plotted against the concentration of xanthene to obtain a second order rate constant, $k_2 = 15.3 (\pm 2) \text{ M}^{-1}\text{s}^{-1}$ (Fig. 2b). The k_2 values for DHA, CHD, and fluorene were 7.9 (± 5) , 4.1 (± 3) and 6.6 x 10⁻¹ (± 2) M⁻¹ s⁻¹, respectively (Fig. S7 in ESI⁺). Further, we determine the kinetic isotope effect (KIE) value using xanthene- d_2 as the substrate. The addition of xanthene- d_2 to a solution of **1** gave $k_2 = 1.8 (\pm 4) \text{ M}^{-1} \text{ s}^{-1}$. Based on this, we determined a KIE = 8.5 for the reaction of xanthene- h_2 vs xanthene- d_2 (Fig. 2b). A linear correlation was observed between the log k_2' and C-H bond dissociation energies (BDE) of the four hydrocarbons thus suggesting that the H-atom abstraction is the rate-determining step in their reactions with $\mathbf{1}$ (the k_2 values were divided by the number of equivalent target C-H bonds of substrates to obtain the k_2' values) (Fig. 2c). When the reaction solutions of xanthene, DHA and CHD were subjected to GC analysis, only xanthone $(42 \pm 5\%)$, anthracene $(84 \pm 5\%)$ and benzene $(90 \pm 4\%)$ were obtained as the products. Since the final solution gave same UV-vis bands corresponding to 2, it was subjected to the X-band EPR measurement which gave an EPR silent signal of Mn(III) (Fig. S8 in ESI⁺).²⁵ Based on the yields of organic products and formation of 2 in the reaction of alkyl hydrocarbons and 1, we conclude that in the C-H activation reaction, a rate determining H-atom abstraction could be similar to the oxygen rebound pathway as proposed in the reactions of several high valent heme metal-oxo compounds and alkanes (Scheme 4).27 Unlike present work, Nam and coworkers have shown an alternate pathway i.e. oxygen nonrebound in the C-H activation by a trans-dioxo Mn(V) porphyrin species, [Mn(V)(tf₄tmap)(O)₂]^{3+.28}

fluorene were performed under identical conditions. The

Scheme 4. Proposed mechanism in the C-H bond activation of DHA by $\mathbf{1}$ to form anthracene. H-atom abstraction is r.d.s in this reaction.

Epoxidation of cyclohexene by [Mn(V)(O)TPPS)Cl] (1)

Cyclohexene has been used as the substrate to test the paradigm of C-H activation *via* an H-atom abstraction forming 2-cyclohexen-1-ol or epoxidation *via* insertion of an oxygen atom to C=C double bond forming cyclohexene oxide.²⁶ It has been reported that the water present in the reaction micture can enhance the rate of epoxidation reaction.²⁹ To validate such an observation we performed the reaction of cyclohexene with **1** under the identical conditions used for the

1 2

3

4

5

6

7

8

9

10

11

12

13

14

₹15

57.55 7

ៗ8

1079 120 120

21

2018, Downloaded by Notkingham Treat

10¹

lbkished 20 86

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59 60

Journal Name

C-H activation of hydrocarbons. Upon addition of cyclohexene (25 equiv) to the solution of **1**, we observed the formation of a new Soret band at 466 nm (Fig. 3a) accompanied by a decay of the 422 nm peak. The band at 466 nm was identical to that observed in the reaction of alkyl hydrocarbons with **1**. The intensity and the absorbance of 466 nm peak were matching with those of starting compound **2**. Based on these evidences we speculated that the reaction of cyclohexene with **1** could be similar to the reaction of alkyl hydrocarbons with **1** giving a two electron manganese(III) compound **2**. Looking at the spectral data, a question arose at this point in our mind was: Does cyclohexene

Fig. 3. (a) UV-Vis spectral changes observed in the reaction of **1** (0.1 mM, red line) and cyclohexene (2.5 mM) in 1:2 CH₃CN: buffer (pH = 10.4) at 25 °C. Inset shows the time course monitored at 422 and 466 nm due to the decay of **2** and formation of **1**. (b) Plot of the pseudo-first-order rate constants, k_{obs} , against cyclohexene- h_{10} and cyclohexene- d_{10} concentrations to determine second-order rate constants, k_2 (M⁻¹s⁻¹) and the determination of the kinetic isotope effect (KIE) value.

undergo an α -allylic C-H bond activation in aqueous buffer like alkyl hydrocarbons or does it undergo an O-atom transfer like thioanisole and triphenylphosphine? To address this dilemma in the reactivity pattern, we performed the reaction of **1** with varying concentrations of cyclohexene- h_{10} and cyclohexene d_{10} . The pseudo-first-order rate constants were obtained by fitting the kinetic data for the decay of 422 nm band with the increasing concentrations of cyclohexene- h_{10} and cyclohexene d_{10} . By plotting the k_{obs} values with the concentrations of cyclohexene- h_{10} , we determine a second-order rate constant, $k_{2H} = 7.2 \times 10^{-1} (\pm 3) \text{ M}^{-1}\text{s}^{-1}$ (Fig. 3b). On addition of cyclohexene- d_{10} to the aqueous solution of **1**, we observed the

ARTICLE

spectral changes similar to the that occurred in the reaction of cyclohexene with 1 (Fig. 3a). The second order rate constant, $k_{2D} = 7.1 \times 10^{-1} (\pm 3) \text{ M}^{-1} \text{s}^{-1}$ was obtained by plotting the k_{obs} values for the reaction of cyclohexene- d_{10} and **1**. On comparing k_{2H} and k_{2D} values, a kinetic isotope effect, KIE = 1.0 was obtained. Such a KIE of 1 in these reactions suggest that, the epoxidation is a likely occurence here instead of C-H bond activation via an H-atom abstraction. The epoxidation reaction was further supported by the product analysis using GC which revealed 85 % (±3) yield of cyclohexene oxide under argon atmosphere and a EPR silent behavior of the resulting Mn(III) solution (EPR spectrum similar to shown in Fig. S6 in ESI⁺). Finally to confirm the nature of **1** which undergoes epoxidation and not an H-atom abstraction in cyclochexene, we performed the reaction of styrene with 1 under identical conditions. On addition of styrene to the 1:2 CH₃CN: buffer (pH = 10.4) solution of $\mathbf{1}$, the Soret band at 422 nm decayed with concomitant formation of a new Soret band at 466 nm (Fig. S9a in ESI⁺). The pseudo-first-order rate constants (k_{obs}) increased linearly with increase in the styrene concentration affording a second order rate constant, $k_2 = 5.5$ x 10^{-1} (±2) M⁻¹ s⁻¹) (Fig. S9b in ESI⁺). When the reaction was carried out using styrene- d_{δ_t} we observed KIE = 1.0 (Fig. S9b in ESI[†]). The KIE value of unity suggests that the reaction of styrene and **1** does not occur via H-atom abstraction and instead follows an oxygen atom transfer pathway forming styrene oxide.²⁶ The product analysis by GC gave styrene oxide as the sole product with yield of 90 (±2). EPR spetcrum of the resulting solution showed no signal suggesting that the inorganic product formed is Mn(III) ion. Thus, the results obtained from this study suggest that the use of [Mn(V)(O)(TPPS)Cl] 1 species in aqueous buffer will result in epoxidation of cyclohexene and styrene over C-H activation reaction (Scheme S2 in ESI⁺).

Conclusions

The present study is on the paradigm reactivity of [Mn(V)(O)(TPPS)Cl] **1** with alkyl hydrocarbons and cyclohexene. A reaction of [Mn(III)(TPPS)Cl] 2 and PhIO in a 1:2 CH₃CN-Buffer solution (pH = 10.4) resulted in the formation of a new species 1 which is formulated as [Mn(V)(O)(TPPS)Cl] based on the appearance of new Soret and Q bands in its UV-vis spectrum and its reaction with thioanisole forming methy phenyl oxide and 2. The reactions of **1** with alkyl hydrocarbons, cyclohexene and styrene were investigated. A large KIE value and a linear correlation of $\log k_{2'}$ with the bond dissociation energies of alkyl hydrocarbons suggested a H-atom abstraction as the rate determining step in the C-H activation reactions. The formation of starting Mn(III) compound 2 and the yields of products suggested that the mechanism subsequent to a H-atom abstraction could be similar to oxygen rebound pathway. Based on the KIE value of 1 for the reaction of cyclohexene as well as styrene with 1 and the quantitive yields of cyclohexene oxide and styrene oxide, an H-atom abstraction step is ruled out in the reaction of cyclohexene and styrene. Efforts are currently

Chemistry Accepted Manusc

ew Journa

Journal Name

58

59

60

underway in our laboratory to stabilize species **1** in different solvent systems and then investigate its reactions with biologically relevant substrates.

Conflicts of interest There are no conflicts of interest to declare.

Acknowledgements

ARTICLE

1

SND thanks Council of Scientific and Industrial Research (CSIR) New Delhi, India for financial assistance (01(2923)/18/EMR-II). DH thanks Goa University for his Research Studentship. SND acknowledges the support from DST-FIST (DST, New Delhi) and UGC-SAP (UGC, New Delhi) to the Department of Chemistry, Goa University. GS (IFA-12-CH-71) and MS (IFA17-CH286) acknowledges the Department of Science and Technology (DST), New Delhi, India for financial support through DST-INSPIRE Faculty Award.

References

- 1. (a) S. Hong, Y.-M. Lee, K. Ray and W. Nam, Coord. *Chem. Rev.*, 2017, **334**, 25-42; (b) S. Fukuzumi, T. Kojima, Y.-M. Lee and W. Nam, *Coord. Chem. Rev.,* 2017, **333**, 44-56; (c) K. Ray, F. Heims, M. Schwalbe and W. Nam, Curr. Opin. Chem. Bio., 2015, 25, 159-171; (d) M. Mitra, H. Nimir, D. A. Hrovat, A. A. Shteinman, M. G. Richmond, M. Costas and E. Nordlander, *J. of Mol. Catal. A: Chem.,* 2017, **426** (Part-B), 350-356. (e) M. Mitra, H. Nimir, S. Demeshko, S. S. Bhat, S. O. Malinkin, M. Haukka, J. Lloret-Fillol, G. C. Lisensky, F. Meyer, A. A. Shteinman, W. R. Browne, D. A. Hrovat, M. G. Richmond, M. Costas and E. Nordlander, *Inorg. Chem.*, 2015, **54**, 7152-7164. (f) W. Nam, Y.-M. Lee and S. Fukuzumi, *Acc. Chem. Res.*, 2014, 47, 1146-1154; (g) Y. Nishida, Y. Morimoto, Y.-M. Lee, W. Nam and S. Fukuzumi, Inorg. Chem., 2013, 52, 3094-3101; (h) W. Ye, D. M. Ho, S. Friedle, T. D. Palluccio and E. V. Rybak-Akimova, *Inorg. Chem.*, 2012, **51**, 5006-5021; (i) J. P. Bigi, W. H. Harman, B. Lassalle-Kaiser, D. M. Robles, T. A. Stich, J. Yano, R. D. Britt and C. J. Chang, J. Am. Chem. Soc., 2012, 134, 1536-1542; (j) S. Fukuzumi, Coord. Chem. Rev., 2013, **257**, 1564-1575; (k) Y.-M. Lee, S. N. Dhuri, S. C. Sawant, J. Cho, M. Kubo, T. Ogura, S. Fukuzumi and W. Nam, Angew. Chem. Int. Ed., 2009, 48, 1803-1806; (I) I. V. Korendovych, S. V. Kryatov and E. V. Rybak-Akimova, *Acc. Chem. Res.*, 2007, **40**, 510-521; (m) M. Newcomb, R. Zhang, R. E. P. Chandrasena, J. A. Halgrimson, J. H. Horner, T. M. Makris and S. G. Sligar, J. Am. Chem. Soc., 2006, **128**, 4580-4581; (n) E. A. Hill, A. C. Weitz, E. Onderko, A. Romero-Rivera, Y. Guo, M. Swart, E. L. Bominaar, M. T. Green, M. P. Hendrich, D. C. Lacy and A. S. Borovik, *J. Am. Chem. Soc.*, 2016, 138, 13143-13146; (o) M. Sankaralingam, Y.-M. Lee, W. Nam and S. Fukuzumi, Coord. Chem. Rev., 2018, **365**, 41-59; (p) C.-M. Lee, M. Sankaralingam, C.-H. Chuo, T.-H. Tseng, P. P.-Y. Chen, M.-H. Chiang, X.-X. Li, Y.-M. Lee and W. Nam, Dalton Trans., 2019, 48, 5203-5213.
- (a) S. Kundu, J. V. K. Thompson, A. D. Ryabov and T. J. Collins, *J. Am. Chem. Soc.*, 2011, **133**, 18546-18549;

(b) H. Chen, W. Lai, J. Yao, and S. Shaik, *J. Chem. Theory Comput.*, 2011, **7**, 3049₁₃053; C9(G)13916 Sankaralingam, Y.-M. Lee, W. Nam and S. Fukuzumi, *Inorg. Chem.*, 2017, **56**, 5096-5104; (d) M. R. Mills, A. C. Weitz, M. P. Hendrich, A. D. Ryabov and T. J. Collins, *J. Am. Chem. Soc.*, 2016, **138**, 13866-13869; (e) S. Kundu, J. V. K. Thompson, L. Q. Shen, M. R. Mills, E. L. Bominaar, A. D. Ryabov and T. J. Collins, *Chem. Eur. J.*, 2015, **21**, 1803-1810; (f) E. Kwon, K.-B. Cho, S. Hong, and W. Nam, *Chem. Commun.*, 2014, **50**, 5572-5575; (g) M. Sankaralingam, Y.-M. Lee, X. Lu, A. K. Vardhaman, W. Nam and S. Fukuzumi, *Chem Commun.*, 2017, **53**, 8348-8351.

- (a) S. Hong, Y.-M. Lee, M. Sankaralingam, A. K. Vardhaman, Y. J. Park, K.-B. Cho, T. Ogura, R. Sarangi, S. Fukuzumi and W. Nam, *J. Am. Chem. Soc.*, 2016, **138**, 8523-8532; (b) H. M. Neu, R. A. Baglia and D. P. Goldberg, *Acc. Chem. Res.*, 2015, **48**, 2754-2764; (c) W. Liu and J. T. Groves, *Acc. Chem. Res.*, 2015, **48**, 1727-1735; (d) Z. Chen and G. Yin, *Chem. Soc. Rev.*, 2015, **44**, 1083-1100.
- 2015, 44, 1083-1100.
 4. (a) D.-L. Popescu, A. Chanda, M. Stadler, F. T. de Oliveira, A. D. Ryabov, E. Munck, E. L. Bominaar and T. J. Collins, *Coord. Chem. Rev.*, 2008, 252, 2050-2071; (b) C. G. Miller, S. W. G.-Wylie, C. P. Horwitz, S. A. Strazisar, D. K. Peraino, G. R. Clark, S. T. Weintraub and T. J. Collins, *J. Am. Chem. Soc.*, 1998, 120, 11540-11541.
- (a) T. Kurahashi, A. Kikuchi, Y. Shiro, M. Hada and H. Fujii, *Inorg. Chem.*, 2010, 49, 6664-6672; (b) X. Wu, M. S. Seo, K. M. Davis, Y.-M. Lee, J. Chen, K.-B. Cho, Y. N. Pushkar and W. Nam, *J. Am. Chem. Soc.*, 2011, **133**, 20088-20091; (c) I. Garcia-Bosch, A. Company, C. W. Cady, S. Styring, W. R. Browne, X. Ribas and M. Costas, *Angew. Chem. Int. Ed.*, 2011, **50**, 5648-5653.
- (a) T. Taguchi, R. Gupta, B. Lassalle-Kaiser, D. W. Boyce, V. K. Yachandra, W. B. Tolman, J. Yano, M. P. Hendrich and A. S. Borovik, *J. Am. Chem. Soc.*, 2012, **134**, 1996-1999; (b) D. F. Leto, R. Ingram, V. W. Day and T. A. Jackson, *Chem. Commun.*, 2013, **49**, 5378-5380; (c) R. Gupta, T. Taguchib, B. Lassalle-Kaiserc, E. L. Bominaara, J. Yanoc, M. P. Hendricha and A. S. Borovik, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 5319-5324; (d) M. Sankaralingam, Y.-M. Lee, Y. Pineda-Galvan, D. G. Karmalkar, M. S. Seo, S. H. Jeon, Y. Pushkar, S. Fukuzumi, and W. Nam, *J. Am. Chem. Soc.*, 2019, **141**, 1324-1336; (e) M. Sankaralingam and M. Palaniandavar, *Dalton Trans.*, 2014, **43**, 538-550; (e) N. Saravanan, M. Sankaralingam and M. Palaniandavar, *RSCAdv.*, 2014, **2**, 12000-12011.
- (a) K. A. Prokop and D. P. Goldberg, *J. Am. Chem. Soc.*, 2012, **134**, 8014-8017; (b) J. Jung, K. Ohkubo, K. A. Prokop-Prigge, H. M. Neu, D. P. Goldberg and S. Fukuzumi, *Inorg. Chem.*, 2013, **52**, 13594-13604.
 J.-U. Rohde, J.-H. In, M. H. Lim, W. W. Brennessel, M.
- J.-U. Rohde, J.-H. In, M. H. Lim, W. W. Brennessel, M. R. Bukowski, A. Stubna, E. Münck, W. Nam and L. Que Jr. *Science*, 2003, **299**, 1037-1039.
- (a) C. Arunkumar, Y.-M. Lee, J. Yoon Lee, S. Fukuzumi and W. Nam, *Chem. Eur. J.* 2009, *15*, 11482-11489; (b)
 W. Nam, I. Kim, M. H. Lim, H. J. Choi, J. S. Lee and H. G. Jang, *Chem. Eur. J.* 2002, *8*, 2067-2071.
- (a) S. Fukuzumi, N. Fujioka, H. Kotani, K. Ohkubo, Y.-M. Lee and W. Nam, *J. Am. Chem. Soc.*, 2009, *131*, 17127-17134; (b) M. E. Crestoni, S. Fornarini and F. Lanucara, *Chem. Eur. J.*, 2009, *15*, 7863-7866.
- W. J. Song, M. S. Seo, S. D. George, T. Ohta, R. Song, M.-J. Kang, T. Tosha, T. Kitagawa, E. I. Solomon, W. Nam and *J. Am. Chem. Soc.*, 2007, **129**, 1268-1277.

7086.

12. D. Lahaye, K. Muthukumaran, Chen-H. Hung, D. Gryko,

13. P. J. F. Gauuan, M. P. Trova, L. Gregor-Boros, S. B. Bocckino, J. D. Crapoc and B. J. Dayc, *Bioorg. Med.*

14. J. A. O'Hara, E. B. Douple, M. J. Abrams, D. J. Picker,

15. S.P.S. Tita and J.R. Perussi, Braz. J. Med. Biol. Res.,

16. Z. Dong and P. J. Scammells, J. Org. Chem., 2007, 72,

17. (a) N. Jin and J. T. Groves, J. Am. Chem. Soc., 1999,

121, 2923-2924. (b) M. Procner, Ł. Orzeł, G. Stochel

and R. van Eldik, *Eur. J. Inorg. Chem.*, 2018, 3462-3471. (c) M. Procner, Ł. Orzeł, G. Stochel and R. van Eldik, *Chem. Commun.*, 2016, **52**, 5297-5300.
18. I. Batinic-Haberle, I. Spasojevic, H. M. Tse, A. Taumagua, Z. Batila, D. K. Chen, K. Tsumagua, J. Batila, J. Sumagua, J. Sumagua,

Tovmasya, Z. Rajic, D. K. St. Clair, Z. Vujaskovic, M. W. Dewhirst and J. D. Piganelli, *Amino Acids*, 2012, **42**,

 (a) K. Kalyanasundaram and M. Gratzel, *Helv. Chimi. Acta* 1980, **63**, 478-485; (b) R. F. Pasternack, *Mol. Chirality*, 2003, **15**, 329-332; (c) X. Zhang, K. S. Lovejoy, A. Jasanoff and S. J. Lippard, *Proc. Natl. Acad. Sci. U.S.*, 2007, **104**, 10780-10785; (d) D. Praseuth, A. Gaudemer, Jean-B. Verlhac, I. Kraljic, I. Sissoeff and E. Guille, *Photochem and Photobiol*, 1986, **44**, 717-724; (e) J. Chen, and C. P. Collier, *J. Phys. Chem. B* 2005,

 (a) N. Jin, M. Ibrahim, T. G. Spiro and J. T. Groves, J. Am. Chem. Soc., 2007, **129**, 12416-12417; (b) J. T. Groves, J. Lee and S. S. Marla, J. Am. Chem. Soc.,

21. H. Saltzman and J. G. Sharefkin, Org. Syntheses, 1963,

22. Y.-H. Zhang, D.-M. Chen, T. He, F.-C. Spectrochimica

23. B. Gao, Y. Chen and Q. Lei, J. Incl. Phenom. Macrocycl.

24. G. Santosh and M. Ravikanth, Tetrahedron, 2007, 63,

25. M. Guo, Y.-M. Lee, R. Gupta, M.S. Seo, T. Ohta, H.-H. Wang, H.-Y. Liu, S. N. Dhuri, R. Sarangi, S. Fukuzumi,

26. S. N. Dhuri, K.-Bin Cho, Y.-Min Lee, S. Y. Shin, J. H.

27. K.-B. Cho, H. Hirao, S Shaik and W. Nam, Chem. Soc.

28. K.-B. Cho and W. Nam, Chem. Commun., 2016, 52,

29. L. Mahmoudi, D. Mohajer, R. Kissnerb and W. H.

Koppenol, Dalton Trans., 2011, 40, 8695-8700.

W. Nam, J. Am. Chem. Soc. 2017, 139, 15858-15867,

Kim, D. Mandal, S. Shaik and W. Nam, *J. Am. Chem. Soc.*, 2015, **137**, 8623-8632.

C. M. Giandomenico and J. F. Vollano, Int. J. Radiat.

Chem., 2002, 10, 3013-3021.

2001, **34**, 1331-1336.

9881-9885.

95-113.

43, 60.

7833-7844.

904-907.

109. 7605-7609.

1997, **119**, 6269-6273.

Acta Part A, 2003, **59**, 87-101.

Chem., 2012, 74, 455-465.

and references therein.

Rev., 2016, **45**, 1197-1210.

Oncol. Biol. Phys., 1989, 16, 1049-1052.

J. S. Reboucas, I. Spasojevic['], I. Batinic[']-Haberleb and J. S. Lindsey, Bioorg. *Med. Chem.*, 2007, **15**, 7066-

New Journal of Chemistry Accepted Manuscript

View Article Online DOI: 10.1039/C9NJ01381D

- 1 2 3 4 5 6 7 8 9 10 11 12 13 14 ₹15 5<u>7</u>57 7 ១8 1020 120 120 ∄1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 5 1 2 3 4 5 10¹101 38 lbkihed 0 41 42 43 44 45 46 47 48 49
- 52 53 54 55

50 51

- 56 57 58
- 59 60
- This journal is © The Royal Society of Chemistry 20xx

A putative heme manganese(V)-oxo species in the 10.10 Control 1001381D activation and epoxidation reactions in an aqueous buffer

Dinesh S. Harmalkar,^a G. Santosh,^{a,b} Siddhi B. Shetgaonkar,^a Muniyandi Sankaralingam,^{c*} Sunder N. Dhuri^{a*}

^aSchool of Chemical Sciences, Goa University, Taleigao Plateau, Panaji, Goa 403206, India. ^bDivison of Chemistry, School of Advanced Sciences, Vellore Institute of Technology, Chennai, Tamilnadu, 600127, India.

^cDepartment of Chemistry, National Institute of Technology Calicut, Kozhikode 673601, Kerala, India.

*corresponding author email: sndhuri@unigoa.ac.in; msankaralingam@nitc.ac.in

Table of Content (TOC)

Synthesis and reactivity studies of manganese(V)-oxo species in the C-H activation of alkyl hydrocarbons and epoxidation of cyclohexene in aqueous conditions are investigated.

