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Synthesis and characterization of a novel manganese–carbene metalloporphyrin: a model for cytochrome P-450

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Abstract

The reaction of [Mn(TPP)Cl], where TPP = 5, 10, 15, 20-tetraphenylporphyrinato dianion, and CCl_4 in CH_2Cl_2 with excess iron powder or sodium borohydride ($NaBH_4$), resulted in the formation of the new complex, [Mn(TPP)(CCl_2)]. The manganese–carbene metalloporphyrin displayed a broad ^{13}C NMR resonance at 264.5 ppm, attributable to the carbene carbon. All skeletal porphyrin carbons resonated between 120 and 150 ppm in the ^{13}C NMR spectrum. Confirmation of the 264.5 ppm ^{13}C NMR resonance as due to the carbene carbon was made by synthesizing the metalloporphyrin carbene in 95% enriched $^{13}CCl_4$. The ^{13}C NMR spectrum of the enriched carbene showed an enhanced signal, centered at 264 ppm. Elemental analysis (C, H, N, Cl, Mn and Fe) of the Mn–carbene porphyrin agreed to within ±0.30% of theoretical values. The five-coordinate Mn–carbene could bind axial ligands, such as H_2O and n-butanethiol, as demonstrated by ^{13}C NMR and UV–Vis absorption studies.

It has been well established that the anaerobic reaction of the heme enzyme, cytochrome P-450, with polyhalogenated hydrocarbons results in the formation of iron–carbene metalloporphyrin complexes [1]. These iron–carbene complexes cause eventual cell destruction and tissue damage [2]. The reactions of cytochrome P-450 with halogenated hydrocarbons such as CCl_4, CH_2Cl_2 and various halogenated pesticides have been studied in detail both *in vivo* and *in vitro* [3]. One of the model compounds used to study the organometallic chemistry of cytochrome P-450 was the first metalloporphyrin carbene to be synthesized, [Fe(TPP)(CCl_2)], where TPP = 5, 10, 15, 20-tetraphenylporphyrinato dianion [4].

The first carbene complex of a metalloporhyrin was formed by the reaction of 5, 10, 15, 20-tetraphenylporphyrinato–iron(III) chloride with carbon tetrachloride in the presence of a reducing agent, resulting in the formation of [Fe(TPP)(CCl_2)] [4]. An X-ray diffraction study of this iron–carbene metalloporphyrin by Mansuy *et al.* found the iron–carbene (Fe=C) bond distance to be 1.83(3) Å [5]. Mansuy *et al.* examined the difference spectra when a thiolate ligand (the fifth ligand to the heme iron in cytochrome P-450) was reacted with an Fe(TPP)–carbene complex and observed that the spectral properties of the model porphyrin were very similar to those observed for cytochrome P-450 [6].

It has been demonstrated by others that some manganese metalloporphyrins serve as excellent model compounds for the catalytic activity of cytochrome P-450 [7]. It is for this reason that we wish to report the synthesis and characterization of a novel manganese metalloporphyrin, [Mn(TPP)(CCl_2)], and compare the properties of the manganese–carbene bond with the iron–carbene bond in [Fe(TPP)(CCl_2)]. Since the iron–carbene bond in the metalloporphyrin complex was found to be robust, our eventual goal was to synthesize a metallo–carbene porphyrin with properties amenable to the determination of a metal–carbene bond dissociation energy in a metalloporphyrin complex.

The manganese–carbene metalloporphyrin was synthesized by reacting [Mn(TPP)Cl] and CCl_4 in CH_2Cl_2 with excess iron powder under a nitrogen atmosphere for 12 h. Isolation and purification of the carbene complex was as for the iron–carbene metalloporphyrin, except that the manganese analogue was not heated under pressure, but was recrystallized from $CHCl_3$ and CH_3OH (3:1 vol./vol.). The recrystallized porphyrin was dried *in vacuo* and gave the following elemental analysis (Atlantic Microlab, Norcross, GA U.S.A.). *Anal.* Calc. for $C_{45}H_{28}N_4Cl_2Mn$: C, 68.35; H, 3.57; N, 12.14; Cl, 9.46; Mn, 7.32. Found: C, 68.51; H, 3.78; N, 12.33; Cl, 9.20; Mn, 7.48; Fe, 0.12%. The 360 MHz ^{13}C NMR spectrum of the purified Mn porphyrin (in $CDCl_3$,

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$Si(CH_3)_4$) exhibited resonances due to the carbons in the porphyrin skeleton (in ppm) at 152.1, 148.1, 142.3, 132.2, 130.6, 128.5 and 123.9. A second method of preparation, without the use of iron powder as reductant, was used to synthesize the complex. It has been demonstrated previously that the use of other reducing agents such as zinc or sodium amalgam reduce tetraphenylporphyrins to chlorins, so these reductants could not be used. Instead, [Mn(TPP)Cl] was reacted with CCl_4 in CH_2Cl_2 with excess $NaBH_4$ (dissolved in a minimum volume of methanol) under a nitrogen atmosphere. The reaction was stirred at room temperature for 6 h. The reaction was quenched by pouring it into 10 ml of deoxygenated water, and the porphyrin was filtered under a nitrogen atmosphere, recrystallized from $CH_3OH/CHCl_3$, and dried *in vacuo*. Yield was 82%. The most interesting aspect of the spectrum of the manganese metalloporphyrin was the broad signal seen at 264.5 ppm (see Fig. 1), in the region of other observed metal–carbene carbon resonances. In order to confirm the assignment of the 264.5 ppm resonance as the carbene carbon, the synthesis of the carbene complex was performed in the presence of 95% ^{13}C-enriched CCl_4 (MSD Isotopes). The isolated product displayed an enhanced signal centered at 264 ppm, confirming our assignment of this resonance as the carbene carbon. In comparison, the ^{13}C NMR spectrum of [Fe(TPP)($^{13}CCl_2$)], showed that the carbene resonated at 224.7 ppm in the same solvent system as was used for dissolving the manganese–carbene metalloporphyrin in this study [5]. The 500 MHz ^1H NMR spectrum ($CDCl_3$, $Si(CH_3)_4$) of the manganese–carbene showed broadened signals assignable to the protons on the porphyrin ring. The broadness of the proton resonances indicated that the porphyrin was a low-spin Mn(II) porphyrin complex. The chemical shifts observed were (in ppm): 7.27 (br, 12H); 8.00 (br, 8H); 8.92 (s, 8H). The unenriched carbene in [Mn(TPP)(CCl_2)] exhibited a strong ν(C–Cl) stretch (KBr disk) in the IR at 805 cm^{-1}, while the ^{13}C-enriched sample showed a doublet centered at 777 cm^{-1}. In addition, when only one equivalent of iron powder was added as a reducing agent in the presence of ^{13}C-enriched CCl_4 in the synthesis, a new product with a greatly enhanced ^{13}C NMR signal at 105.0 ppm was seen. This resonance was found to be in the region of metal σ-bonded trihalocarbon resonances (the enriched $^{13}CCl_4$ displayed a ^{13}C resonance at 95.00 ppm), and we assigned this resonance to the [Mn(TPP)($^{13}CCl_3$)] complex, since only one equivalent of reducing agent was added in the synthesis. It has been established previously that the polyhalogenated compound (CCl_4) must be reduced twice in order to form a carbene [8]. If the polyhalogenated compound is reduced only once, a metal–CCl_3 complex can be formed.

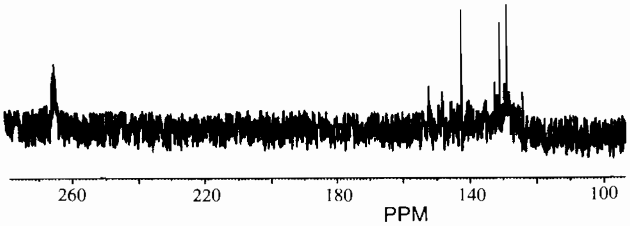

Fig. 1. The 360 MHz ^{13}C NMR spectrum at ambient temperature (in $CDCl_3$, $Si(CH_3)_4$) of the isolated Mn–carbene metalloporphyrin, [Mn(TPP)(CCl_2)], where TPP = 5,10,15,20-tetraphenylporphyrinato dianion. The broad resonance at 264.5 ppm is attributed to the carbene carbon.

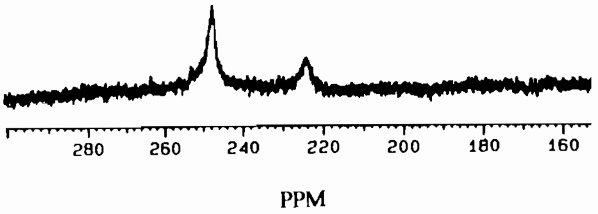

Fig. 2. The 360 MHz ^{13}C NMR spectrum (at ambient temperature) of [Mn(TPP)(CCl_2)] in the presence of 1 μl n-butanethiol in $CDCl_3/Si(CH_3)_4$ solvent. Only the carbene resonance region is depicted. Note the presence of the new peak at 224 ppm, assigned to the six-coordinate [Mn(TPP)(CCl_2)(n-butanethiol)] complex.

The electronic absorption spectrum of [Mn(TPP)(CCl_2)] displayed a λ_{max} at 378 (shoulder), 478, 586 and 619 nm in benzene with an $\epsilon = 3.1 \times 10^5$ M^{-1} cm^{-1} for the 478 nm band. Like the iron–carbene analogue, the manganese–carbene metalloporphyrin was found to bind axial ligands, such as water and n-butanethiol. The addition of exactly one equivalent of n-butanethiol to [Mn(TPP)(CCl_2)] in benzene resulted in the formation of a 'split-Soret' spectrum, characteristic of sulfur ligand binding to the metalloporphyrin*. We confirmed that the carbene was still bound to the manganese in the presence of added thiol by first recording the ^{13}C NMR spectrum of the [Mn(TPP)(CCl_2)] complex in $CDCl_3/Si(CH_3)_4$. Following this, 1 μl of n-butanethiol was added to the NMR sample under nitrogen. As seen in Fig. 2, two carbene resonances were seen, one centered at 247.7 ppm (the five-coordinate Mn–carbene), and another broad resonance of lower intensity at 224.0 ppm, that can be assigned to the six-coordinate thiol-bound Mn–carbene. High resolution mass spectral analysis (Midwest Center for Mass Spectrometry, University of Nebraska) of the [Mn(TPP)(CCl_2)] and [Fe(TPP)(CCl_2)] complexes showed a molecular ion at 667.61 for $[Mn(TPP)]^+$ and 668.52 for $[Fe(TPP)]^+$, due to the loss of carbene, with concomittant production of an ion at *m/e* 166 for the

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*UV–Vis of [Mn(TPP)(CCl_2)(n-butanethiol)] in benzene: λ_{max} = 380, 432, 654 and 729 nm. A 'split Soret' spectrum for metallo–carbene porphyrins has been predicted [9].

TABLE 1. A comparison of spectral properties of [Mn(TPP)(CCl_2)] and [Fe(TPP)(CCl_2)]

Complex	Mass spectroscopy *m*/*e*	^{13}C NMR (ppm)	UV–Vis (nm) (benzene)
Fe(TPP)(CCl_2)	668.52[a]	224.7 (carbene) 148.3, 143.7, 134.5, 133.8, 128.1, 126.8, 122.3[b]	412 ($\epsilon=2\times10^5$ M^{-1} cm^{-1}) 516 ($\epsilon=4.8\times10^3$ M^{-1} cm^{-1})
Mn(TPP)(CCl_2)	667.61[a]	264.5 (carbene) 152.1, 148.1, 142.3 132.2, 130.6, 128.5, 123.9[b]	378 (shoulder) 478 ($\epsilon=3.1\times10^5$ M^{-1} cm^{-1}) 586 619

[a] High resolution mass spectra (FAB–MS) were run in a 3-norbornyl acetate (3-NBA) matrix at the Midwest Center for Mass Spectrometry, Lincoln, NE. [b] NMR spectra were recorded both in C_6D_6/TMS and $CDCl_3$/TMS at ambient temperature.

dimer (C_2Cl_4) produced from the coupling of the dihalocarbene radical. A summary of the spectral results for the [Mn(TPP)(CCl_2)] compound and the iron analogue, [Fe(TPP)(CCl_2)] can be seen in Table 1.

Since the iron–carbene metalloporphyrins were initially found to be resistant to thermal decomposition at temperatures exceeding 200 °C, it has thus far not been possible to study the kinetics of iron–carbene bond cleavage in [Fe(TPP)(CCl_2)]. The fact that the Mn–carbene metalloporphyrin could be isolated and could bind axial ligands has initiated an investigation of the determination of the mechanism of the Mn–carbene bond dissociation energies in these porphyrin complexes.

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