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Nitrones are suitable ligands for heme models: X-ray crystal structure of the first metalloporphyrin nitrone complex

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The metalloporphyrin nitrone complexes [M(oep)(CO)(DMPO)] (M = Ru, Os; oep = octaethylporphyrinato dianion; DMPO = 5,5-dimethyl-1-pyrroline *N*-oxide) have been prepared: the crystal structure of the Ru complex reveals a sole η^1-O binding mode of the nitrone ligand to the metal center.

Nitrones belong to the general class of RN(O)=X compounds, where X is a carbon-linked group (Fig. 1).[1] They are frequently used as spin traps in physiological media.[2] Some nitrone-based spin traps protect against oxidative damage to the central nervous system: studies on α-phenyl-*tert*-butylnitrone (PBN; Fig. 1)† show that it is an antioxidant, it exhibits protective activity in septic shock, and it is neuroprotective (PBN has also been identified intact in the brain).[3] Some nitrones also protect against cerebral ischemia-reperfusion injury (stroke), and some have potent anti-inflammatory properties.[4] The successful use of nitrones in research on aging suggests that they may mitigate mitochondrial efflux of reactive oxygen species.[4]

Interestingly, nitrones are now known to be produced during the oxidation of some amines by cytochrome P450. Excellent work by Lindeke and coworkers has shown that the *in vitro* metabolism of norbenzphetamine by cytochrome P450 gives the hydroxylamine and the nitrone metabolites.[5] Guengerich and coworkers also showed that cytochrome P450 catalyzes the oxidation of cycloalkylamines to nitrones.[6] Importantly, however, it has been proposed that some nitrones are capable of serving as ligands for cytochrome P450[7]and hemoglobin.[8] PBN has also been shown to decompose photolytically to NO, which was trapped by heme and non-heme proteins to give metal-NO products.[9] Despite the obvious importance in heme-dependent biochemistry and relevance to amine oxidation chemistry, no nitrone complexes of synthetic heme models had been reported prior to this study.‡ We now report our successful syntheses and crystallographic characterization of the first thermally stable metalloporphyrin nitrone complexes.

Excess DMPO (0.1 g, 0.9 mmol) was added to a toluene (10 mL) solution of [Ru(oep)(CO)(H_2O)] (0.030 g, 0.044 mmol) under a nitrogen atmosphere, and the solution was heated to reflux for 15 min. The solvent was removed *in vacuo*, and the residue was redissolved in CH_2Cl_2/hexane (1 : 1, 10 mL). Slow evaporation of the solution under a nitrogen atmosphere resulted in the generation of red crystals which were washed with hexane (10 mL) and dried *in vacuo* to give the product [Ru(oep)(CO)(DMPO)] as a solvate in 77% yield.§ ¶ The IR spectrum of the product (as a KBr pellet) revealed a ν_{CO} of 1914 cm^{-1}, which is 16 cm^{-1} lower in energy than the ν_{CO} of the starting [Ru(oep)(CO)(H_2O)] at 1930 cm^{-1}. The lowering of the ν_{CO} is *opposite* to that seen for [Ru(oep)(CO)($ONC_6H_4NMe_2$)][19] which contains an N-bound nitrosoarene ligand that behaves as a net π-acid in this complex, but is similar to that seen for [Ru(oep)(CO)($ONNEt_2$)] (ν_{CO} 1910 cm^{-1})[20] which contains an O-bound axial nitrosamine ligand.

The solid-state X-ray crystal structure of [Ru(oep)(CO)(DMPO)] is shown in Fig. 2.‖ The Ru–C(O) and C–O bond lengths are 1.816(6) and 1.167(7) Å, respectively, and the Ru–C–O bond angle is 178.5(6)°. The Ru–N(por) bond lengths lie in the range 2.051(9)–2.069(10) Å, and the Ru atom is displaced by 0.11 Å from the 24-atom mean porphyrin plane toward the π-acid CO ligand. The porphyrin macrocycle exhibits a *dome* distortion. The most chemically interesting feature of the structure of [Ru(oep)(CO)(DMPO)] is that the nitrone ligand is

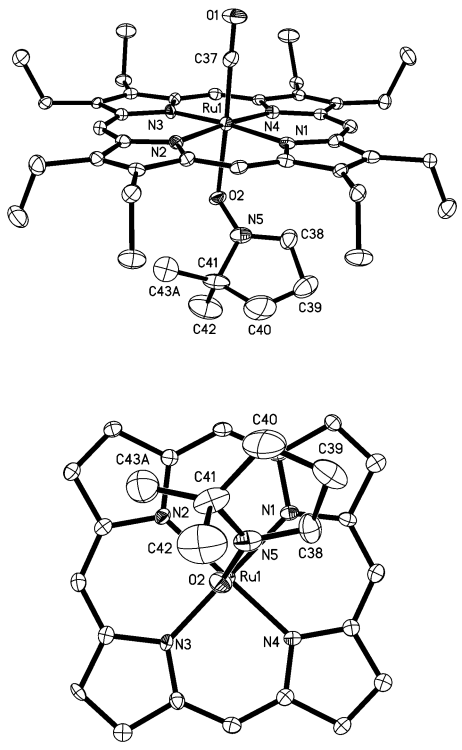

Fig. 2 (a) Molecular structure of [Ru(oep)(CO)(DMPO)]. The C43 atom is disordered at two positions (C43a 69%/C43b 31%), and only one of these positions is shown. Hydrogen atoms have been omitted for clarity. (b) View of the orientation of the nitrone ligand relative to the porphyrin skeleton. The porphyrin ethyl substituents and the *trans* CO ligand have been omitted for clarity. Selected bond distances (Å) and angles (°): Ru(1)–N(por) 2.051(9)–2.069(10), Ru(1)–C(37) 1.816(6), C(37)–O(1) 1.167(7), Ru(1)–O(2) 2.214(4), O(2)–N(5) 1.299(6), N(5)–C(38) 1.312(9), N(5)–C(41) 1.486(9); Ru(1)–C(37)–O(1) 178.5(6), Ru(1)–O(2)–N(5) 122.2(3).

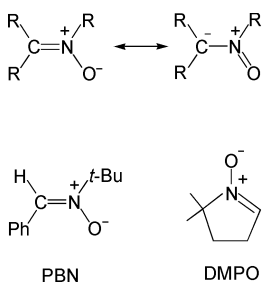

Fig. 1 Resonance forms of the nitrone functional group, and two examples of nitrones.

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bound to the Ru^{II} center in a η^1-O fashion. The axial Ru–O(nitrone) distance is 2.214(4) Å. The nitrone O–N and N=C bond lengths are 1.299(6) and 1.312(9) Å, respectively, and the Ru–O–N bond angle is 122.2(3)°. To the best of our knowledge, the crystal structure of DMPO has not been reported. However, the metrical parameters of the DMPO moiety in [Ru(oep)(CO)(DMPO)] are suggestive of a dominant contribution of the $R_2C{=}N^+(R){-}O^-$ resonance form (Fig. 1, top left) for this ligand. The osmium derivative [Os(oep)(CO)(DMPO)] has also been prepared in 61% yield.§**

In summary, these results show for the first time that nitrones are suitable ligands for the metal centers in heme models, and that the $R_2C{=}N^+(R){-}O^-$ resonance contribution stabilizes the interaction with the metal center. Extensions of this chemistry to heme derivatives, and to reactions designed to investigate the integrity of nitrones in the presence of heme biomolecules are currently in progress.

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Notes and references

† Abbreviations: oep = octaethylporphyrinato dianion, DMPO = 5,5-dimethyl-1-pyrroline *N*-oxide, PBN = α-phenyl-*tert*-butylnitrone.

‡ Only a handful of monometallic coordination compounds containing η^1-O nitrone ligands have been characterized by X-ray crystallography (refs. 10–14). Related complexes containing bridging nitrone ligands (refs. 11 and 15) or metallacyclic nitrones (ref. 11) are known. Other metallacycles in which the metal–O–N=C group occurs (metal = Re, Pt) have been reported (refs. 16–18).

§ The two metalloporphyrin nitrone products obtained in this study give satisfactory (±0.4%) elemental analyses for C, H, N and Cl.

¶ Data for [Ru(oep)(CO)(DMPO)]·0.19CH_2Cl_2·0.5H_2O: IR (KBr, cm^{-1}): ν_{CO} 1914 s; also 2961 m, 2930 w, 2869 w, 1593 w, 1538 vw, 1466 m, 1453 m, 1371 w, 1316 vw, 1304 vw, 1272 m, 1230 m, 1215 vw, 1198 vw, 1148 m, 1111 w, 1056 m, 1019 m, 991 w, 960 m, 840 m, 746 w, 712 vw, 666 vw, 583 vw. ^{1}H NMR ($CDCl_3$, −40 °C): δ 9.81 (s, 4H, *meso*-H of OEP), 5.27 (s, CH_2Cl_2), 3.97 (m, 16H, CH_2CH_3 of OEP), 1.84 (t, *J* 8, 24H, CH_2CH_3 of OEP), 0.65 (br t, 2H of DMPO), 0.18 (m, overlapping 1H and 2H of DMPO), –1.67 (s, 6H, CH_3 of DMPO). High-resolution mass spectrum (ESI) for $[Ru(oep)(CO)(DMPO) + H]^+$ ($C_{43}H_{56}N_5O_2Ru$): *m*/*z* 776.3563. Calc. 776.3477.

‖ Crystal data for [Ru(oep)(CO)(DMPO)] were collected on Bruker (Siemens) SMART/CCD diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using the SHELXTL system and refined by full-matrix least squares on F^2. *Crystal data*: $C_{43}H_{55}N_5O_2Ru$, *M* = 774.99, monoclinic, space group *Pn*, *a* = 8.3720(11), *b* = 10.5284(14), *c* = 22.576(3) Å, β = 92.559(4)°, *V* = 1987.9(5) $Å^3$, *Z* = 2, D_c = 1.295 g cm^{-3}, *T* = 203(2) K, μ = 0.436 mm^{-1}, 4973 independent reflections (R_{int} = 0.0399). Final *R* (*F* obs. data) = 0.0437.

CCDC reference number 175749. See http://www.rsc.org/suppdata/cc/b1/b111057h/ for crystallographic data in CIF or other electronic format.

** *Data* for [Os(oep)(CO)(DMPO)]·0.5CH_2Cl_2: IR (KBr, cm^{-1}):ν_{CO} 1883 s; also 2961 m, 2931 w, 2868 w, 1598 w, 1466 m, 1452 m, 1371 m, 1316 vw, 1304 vw, 1273 m, 1232 m, 1191 w, 1149 m, 1111 w, 1056 m, 1019 m, 992 w, 961 m, 842 m, 742 w, 716 w. ^{1}H NMR ($CDCl_3$): δ 9.66 (s, 4H, *meso*-H of OEP), 5.27 (s, CH_2Cl_2), 3.95 (m, 16H, CH_2CH_3 of OEP), 1.87 (t, *J* 8, 24H, CH_2CH_3 of OEP), 0.68 (br t, 2H of DMPO), 0.30 (br s, 1H of DMPO), 0.22 (t, *J* 7, 2H of DMPO), −1.60 (br s, 6H, CH_3 of DMPO). High-resolution mass spectrum (ESI) for $[Os(oep)(CO)(DMPO)]^+$ ($C_{43}H_{55}N_5O_2Os$): *m*/*z* 865.3893. Calc. 865.3971.

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