Formal addition of *S*- and *O*-nitroso compounds to metalloporphyrins

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S- and O-nitroso compounds undergo unprecedented formal *trans*-addition to the metal centre in [Ru(por)(CO)] complexes to give nitrosyl thiolates and alkoxides, respectively.

The chemistry of *S*-nitroso compounds (RSNO, thionitrites)[1] is receiving renewed attention due to the fact that these compounds have been found to play key roles in the biological actions of nitric oxide.[2] For example, *S*-nitrosohaemoglobin forms naturally during oxygenation of red blood cells in the lung,[3] and the *S*-nitroso adduct of glutathione has been detected in the airways of humans.[4] In general, *S*-nitroso compounds such as *S*-nitrosocysteine and *S*-nitroso-*N*-acetylpenicillamine possess vasodilator action, leading a few authors to suggest that EDRF is actually an RSNO compound rather than NO itself.[5] Importantly, the vasodilator action of many organic nitroso compounds and nitroprusside can be attributed, in part, to the formation of intermediate *S*-nitroso compounds.[6] Nitrosation of thiol groups (RSH) in proteins occurs under a variety of conditions,[7,8] and reactions of RSNO compounds include (*i*) transnitrosation, (*ii*) NO release with concomitant disulfide (RSSR) formation, and (*iii*) nitrosylation of metal centres.[8–11]

Various metal ions are also known to catalyse the decomposition of RSNO,[1a,12] and we have been intrigued by a recent suggestion that RSNO may be able to bind directly to the haem of guanylyl cyclase.[13] Indeed, we have previously shown that organic nitroso compounds such as nitrosamines[14,15] and nitrosoarenes[16] bind *intact* to metalloporphyrins, and we proceeded to investigate the possibility that RSNO may interact directly with haem models. We now communicate our unexpected results in this area: namely, the *unprecedented* formal addition of RSNO and RONO *across* the metal centre in metalloporphyrins to give nitrosyl thiolates and alkoxides, respectively.†

Reaction of [Ru(oep)(CO)] with 1 equiv. of *N*-acetyl-*S*-nitroso-L-cysteine methyl ester in CH_2Cl_2 under a prepurified nitrogen atmosphere is instantaneous, and produces the [Ru(oep)(NO)(*S*-NACysMe)]·0.4CH_2Cl_2 (NACysMe = L-*N*-acetylcysteinate methyl ester) addition product as analytically pure crystals in 78% isolated yield {^{1}H NMR ($CDCl_3$): δ 10.29 (s, 4H, *meta*-H of oep), 5.28 (s, 0.8H, CH_2Cl_2), 4.17 (m, 16H, CH_2CH_3 of oep), 2.88 (s, 3H, OCH_3 of NACysMe), 2.39 (br d, J_{HH} 7 Hz, 1H, NHCH of NACysMe), 1.99 (t, J_{HH} 7 Hz, 24H, CH_2CH_3 of oep), 1.48 [m (app. q), 1H, CHNH of NACysMe], 1.19 [s, 3H, C(O)CH_3 of NACysMe], −2.61 (dd, J_{HH} 7/13 Hz, 1H, $CH_\alpha H_\beta$ of NACysMe), −3.16 (dd, J_{HH} 5/13 Hz, 1H, $CH_\alpha H_\beta$ of NACysMe)}. The reaction is virtually quantitative (>99%) in CD_2Cl_2 by ^{1}H NMR spectroscopy. The IR spectrum of the complex as a KBr pellet reveals the υ_{NO} at 1791 cm^{-1}, and bands at 1755 and 1683 cm^{-1} due to the carbonyl groups of the cysteinate ligand. The low-resolution FAB mass spectrum reveals peaks at *m/z* 810 (18) and 664 (100%) due to [Ru(oep)(*S*-NACysMe)]$^+$ and [Ru(oep)(NO)]$^+$, respectively. Due to the multi-heteroatom nature of the cysteinate ligand, we proceeded to unambiguously determine its *S*-attachment to the ruthenium centre by subjecting suitable crystals to a single-crystal X-ray diffraction study.‡ The molecular structure of the complex is shown together with selected bond lengths and angles in Fig. 1. The most chemically interesting feature of the structure is the essentially linear Ru–N–O bond angle of 174.8(6)°. Although compounds of the form [M(por)(NO)(Cys)] (CysO = cysteinate) are models for the interaction of NO with cytochrome P450 and NO synthase, this is the first isolation and X-ray structural report of such a *nitrosyl cysteinate* metalloporphyrin.§ The known [Ru(oep)(NO)(SCH_2CF_3)][15] compound is also prepared in quantitative yield by a similar reaction of [Ru(oep)(CO)] with CF_3CH_2SNO in CH_2Cl_2.

We propose a mechanism (Scheme 1) in which RSNO binds through the sulfur atom to [Ru(oep)(CO)] to form a 1 : 1 adduct (*S*-bound adducts have been proposed previously as intermediates during the metal-catalysed decomposition of RSNO).[19] This then activates the bound RSNO towards S–N homolytic cleavage. The NO released then reacts very rapidly (inter- or intra-molecularly) with the formally Ru^{III}–thiolate intermediate to give [Ru(oep)(NO)(SR)]. An alternate mechanism could involve *N*-binding of the RSNO, which could result in ·SR release.¶ We do not favour this alternate pathway, since we do not detect any subsequent (or partial) RSSR formation in the reaction mixture.

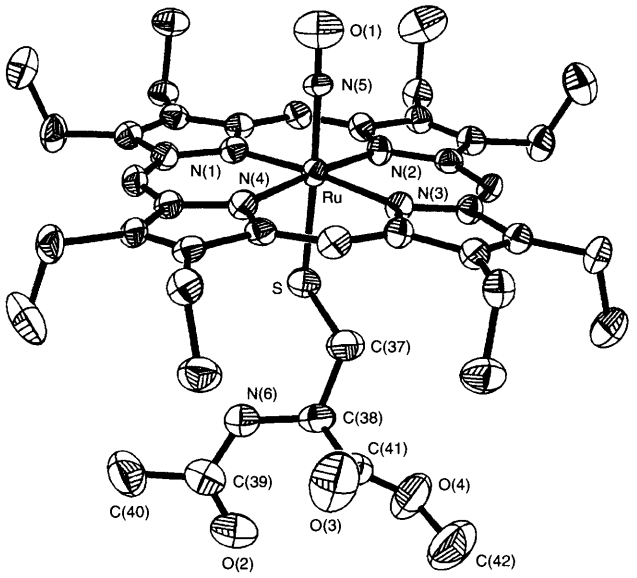
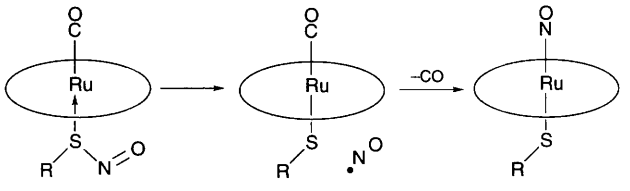


Fig. 1 Molecular structure of [Ru(oep)(NO)(*S*-NACysMe)]. Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (°): Ru–N(1) 2.057(5), Ru–N(2) 2.043(4), Ru–N(3) 2.045(6), Ru–N(4) 2.068(4), Ru–N(5) 1.790(5), N(5)–O(1) 1.123(8), Ru–S 2.362(2), S–C(37) 1.814(8); O(1)–N(5)–Ru 174.8(6), N(5)–Ru–S 177.0(2), Ru–S–C(37) 107.1(3).



Scheme 1

We then investigated the related addition chemistry of the *O*-nitrovasodilator, isoamyl nitrite. Reaction of [Ru(ttp)(CO)] with isoamyl nitrite produces the corresponding nitrosyl alkoxide, [Ru(ttp)(NO)(*O*-isoamyl)]·0.5CH_2Cl_2, as analytically pure crystals in 58% isolated yield. {^{1}H NMR ($CDCl_3$): δ 8.92 (s, 8H, pyrrole-H, ttp), 8.12 (m, 8H, *meta*-H of ttp), 7.56 (d, *J* 8 Hz, 8H, *o*-H of ttp), 5.28 (s, 1H, CH_2Cl_2), 2.70 (s, 12H, CH_3 of ttp), −0.59 [d, *J* 7 Hz, 6H, $(CH_3)_2CHCH_2CH_2O$], −1.02 [m, 1H, $(CH_3)_2CHCH_2CH_2O$], −2.34 [t, *J* 7 Hz, 2H, $(CH_3)_2CHCH_2CH_2O$], −2.78 [dt, *J* 7/7 Hz, 2H, $(CH_3)_2CHCH_2CH_2O$]}. The low-resolution FAB mass spectrum of the complex reveals peaks at *m/z* 887 (8) and 800 (100%) due to the parent [Ru(ttp)(NO)(*O*-isoamyl)]$^+$ and [Ru(ttp)(NO)]$^+$, respectively; υ_{NO} of this compound occurs at 1809 cm^{-1}.

We note that although the formal release of NO from RSNO is generally considered necessary for its pharmacological activity, the mechanisms of this release are not well understood. Our results show, for the first time, that RSNO and RONO can add to metalloporphyrins in a net *trans* fashion.

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Footnotes

† The addition products give satisfactory elemental analyses (±0.4%) for C, H, N, Cl and S. Abbreviations: oep = octaethylporphyrinato dianion; ttp = tetratolylporphyrinato dianion; por = porphyrinato dianion.

‡ Crystal data were collected on a Siemens P4 diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The structure was solved using the SHELXTL (Siemens) system and refined by full-matrix least squares on F^2 using all reflections (SHELXL-93). The data were corrected for Lorentz and polarization effects. No absorption correction was applied since it was judged to be insignificant. *Crystal data*: $C_{42}H_{54}N_6O_4RuS$, *M* = 840.04, monoclinic, space group $P2_1$, *a* = 8.281(1), *b* = 19.455(3), *c* = 12.670(2), β = 90.71(1)°, *U* = 2041.1(5) Å^3, *Z* = 2, D_c = 1.367 g cm^{-3}, *T* = 203(2) K. Final *R*1 = 0.0465 (*wR*2 = 0.1047, GOF = 1.079) for 4127 'observed' reflections with $I > 2\sigma(I)$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/176.

§ We have also demonstrated that thiolate anions react with [Ru(oep)(NO)(H_2O)]$^+$ to give nitrosyl thiolate complexes (ref. 15). Related [Ru(por)(NO)X] (X = alkoxide, alkyl/aryl) complexes have been prepared (refs. 17 and 18).

¶ Nitroprusside reacts with thiols and thiolate anions to produce unstable metal–RSNO intermediates in which the RSNO ligands are believed to be *N*-bound (ref. 20).

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