



ELSEVIER

Journal of Inorganic Biochemistry 84 (2001) 297–299

JOURNAL OF
**Inorganic
Biochemistry**

www.elsevier.nl/locate/jinorgbio

Short Communication

Spontaneous nucleophilic addition of hydroxide ions to the *meso*-position of high-valent antimony-oxo porphyrin complexes

Günther Knör*

Universität Regensburg, Institut für Anorganische Chemie, 93040 Regensburg, Germany

Received 12 October 2000; received in revised form 20 November 2000; accepted 29 November 2000

Abstract

Bimolecular reactions of the antimony(V) porphyrin complexes $\text{SbO}(\text{tpp})\text{OH}$, **1** and $\text{SbO}(\text{oep})\text{OH}$, **2** with tetra-*n*-butylammonium hydroxide were investigated at 298 K in acetonitrile solution (tpp, dianion of 5,10,15,20-tetraphenylporphyrin and oep, dianion of 2,3,7,8,12,13,17,18-octaethylporphyrin). Spontaneous nucleophilic addition of hydroxide ions to the non-oxidized porphyrin macrocycle leads to novel hydroxyphlorin derivatives, which contain a saturated *meso*-carbon bridge. While this process is a reversible equilibrium reaction for the TPP derivative, the OEP complex undergoes subsequent demetallation and oxidative ring cleavage in the presence of dioxygen. Possible implications for the competitive inhibition of heme-oxygenase by high-valent metalloporphyrin therapeutics are discussed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Porphyrins; Metal oxo complexes; Enzyme inhibitors; Redox mechanisms; Heme model compounds

Regioselective functionalization of the porphyrin periphery at the methine bridges (α - or *meso*-positions) of the macrocycle has attracted considerable attention [1–3]. The impetus for many of these studies arises from the occurrence of porphyrin derivatives with a saturated *meso*-carbon as byproducts of heme catabolism [4–6] and as putative intermediates in the biosynthesis of tetrapyrrole ligands [7–10]. Besides the main body of known electrophilic substitutions on the porphyrin periphery, only a few nucleophilic functionalizations have been reported so far. For reactions of a conjugated molecule with nucleophiles the lowest unoccupied molecular orbital (LUMO) is the frontier orbital. Activation of the porphyrin π -system toward nucleophilic attack can be achieved by oxidation of the macrocyclic ligand or by insertion of a central metal of high electronegativity, which reduces the frontier orbital electron density at the ring periphery [1]. However, direct nucleophilic addition to the non-oxidized porphyrin ring is still a very rare phenomenon in porphyrin chemistry [11–14], and only one previous report on a *meso*-hydroxylation reaction has appeared in the literature [15]. In this latter case, gold(III) porphyrins had been investigated and the study resulted in the first observation of hydroxyphlorin derivatives (Chart 1).

Due to their high-valent central metal, antimony(V) porphyrin complexes, quite similar to gold(III) porphyrins, are also expected to be very strong electrophiles. To explore this possibility, the reactions of the compounds $\text{SbO}(\text{tpp})\text{OH}$, **1** and $\text{SbO}(\text{oep})\text{OH}$, **2** with tetra-*n*-butylam-

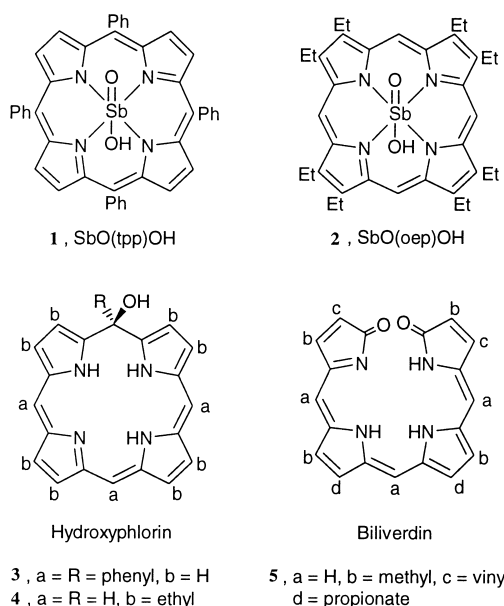
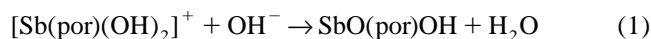


Chart 1.

*Fax: +49-941-943-4488.

E-mail address: guenther.knoer@chemie.uni-regensburg.de (G. Knör).

monium hydroxide as a nucleophilic agent were investigated¹ (tpp, dianion of 5,10,15,20-tetraphenylporphyrin; oep, dianion of 2,3,7,8,12,13,17,18-octaethylporphyrin). These neutral antimony(V) oxo complexes [16] were generated in situ by axial deprotonation (Eq. (1)) of the corresponding cationic dihydroxo precursors $[\text{Sb}(\text{por})(\text{OH})_2]^+$ with $\text{por}=\text{tpp}$ or oep , which were synthesized and purified according to the reported procedures [17,18]:



Indeed, a high reactivity toward nucleophilic attack was also observed with the antimony(V) porphyrin compounds. When an excess of $\text{N}(\text{Bu})_4\text{OH}$ was added to a solution of the octaethylporphyrin complex **2** in acetonitrile at room temperature, the color of the mixture continuously changed from red to greenish brown.² At the same time a bleaching of the metalloporphyrin *B*(Soret) and *Q*-band maxima at 397, 530 and 570 nm was observed, while new absorptions occurred with maxima at 302, 353, 439, 667 and 777 nm (Fig. 1).

These spectral changes with a broad new phlorin-type absorption [1,2] arising in the near-IR region are diagnostic for an interruption of the conjugated π -electron system of the porphyrin ligand at one of the *meso*-positions. The occurrence of several isosbestic points (Fig. 1) indicates that a clean and quantitative reaction takes place. In agreement with previous observations [15], the transformation of the absorption spectrum of **2** is ascribed to a

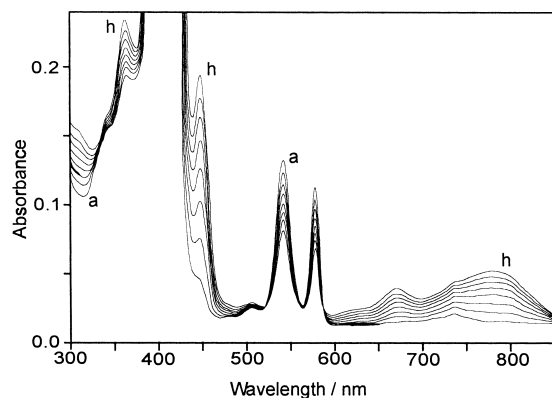


Fig. 1. Spectral variations during the conversion of 1.5×10^{-5} M $\text{SbO}(\text{oep})\text{OH}$, **2** in the presence of 4.0×10^{-2} M $\text{N}(\text{Bu})_4\text{OH}$ at (a) 0, 2, 6, 10, 14, 18, 22 and (h) 30 min reaction times (CH_3CN , 298 K, 1-cm cell).

¹All experiments were carried out at 298 K in the dark in thermostatted and teflon stoppered quartz cuvettes. A 40% aqueous solution of $\text{N}(\text{Bu})_4\text{OH}$ (Fluka) diluted with spectrograde acetonitrile was used as a source of hydroxide ions. Increasing amounts of hydrochloric acid were added to test the reversibility of the reactions. Optical absorption spectra and kinetic data were measured with a Uvikon 860 double-beam spectrophotometer.

²No reaction occurred when $\text{N}(\text{Bu})_4\text{BF}_4$ was added instead of the hydroxide.

nucleophilic addition of hydroxide to the porphyrin *meso*-position, forming an antimony(V) complex of the octaethyl-hydroxyphlorin ligand $\text{H}_3(\text{oepOH})$, **4** (Chart 1) according to the following stoichiometry, (Eq. (2)):



A similar reaction also occurred when $\text{N}(\text{Bu})_4\text{OH}$ was added to the tetraphenylporphyrin derivative **1** in acetonitrile solution. Under pseudo-first-order conditions with large excess amounts of tetra-*n*-butylammonium hydroxide and 7.5×10^{-5} M metalloporphyrin, the second-order rate constant for the reaction of **1** with OH^- ions was estimated as $k = (8.4 \pm 0.1) \times 10^{-1} \text{ M}^{-1} \text{ s}^{-1}$ (CH_3CN , 298 K, $R = 0.995$). The final product (Fig. 2), which in analogy to the nucleophilic adduct of **2** is assigned as the antimony(V) complex of tetraphenyl-hydroxyphlorin $\text{H}_3(\text{tppOH})$, **3** (Chart 1), also displays a phlorin-type absorption spectrum with bands at $\lambda_{\text{max}} = 392 \text{ nm}$ ($\epsilon = 27,500 \text{ M}^{-1} \text{ cm}^{-1}$), 413 (38,600), 449 (57,600), 719 (8900), and 792 nm ($\epsilon = 17,600 \text{ M}^{-1} \text{ cm}^{-1}$). These spectral features are in good agreement with the previously reported properties [15] of the gold(III) complex of **3**, apart from the typical blue-shift generally observed with gold porphyrin derivatives, which display *hypso*-type electronic spectra [19].

It was found that the nucleophilic addition of hydroxide to the *meso*-carbon of the tetraphenylporphyrin ring of **1** is a reversible process, and that the equilibrium between hydroxyphlorin and porphyrin is almost completely driven back to the starting complex in the presence of acid. In contrast, this is not the case with the octaethylporphyrin derivative **2**, which is irreversibly transformed into permanent products upon standing for several hours in the presence of $\text{N}(\text{Bu})_4\text{OH}$ and dioxygen. In a slow dark reaction the primary octaethyl-hydroxyphlorin complex (Fig. 1) is converted into a mixture of several compounds, as indicated by a shift and loss of the initial isosbestic points. Obviously, the nature of the substituents R present at the saturated *meso*-bridges of the hydroxyphlorin lig-

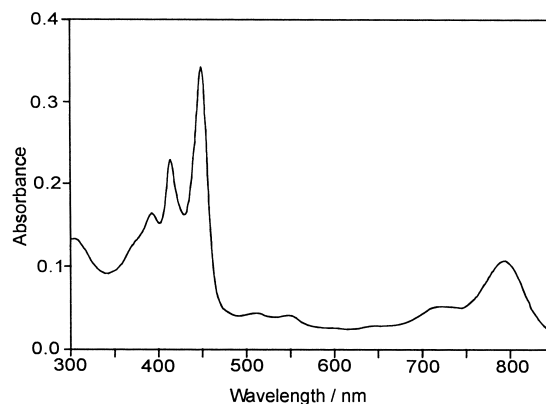


Fig. 2. Electronic absorption spectrum of the nucleophilic adduct obtained from the reaction of 5.8×10^{-6} M $\text{SbO}(\text{tpp})\text{OH}$, **1** and 4.0×10^{-2} M $\text{N}(\text{Bu})_4\text{OH}$ in CH_3CN (1-cm cell).

ands **3** and **4** (Chart 1) is responsible for the different reactivities observed.³ Although a detailed investigation of the secondary processes occurring with **2** was not within the scope of the present work, the open chain tetrapyrrole pigment octaethylbilindione [20,21] with broad absorptions at $\lambda_{\text{max}} = 366 \text{ nm}$ ($\epsilon = 58,000 \text{ M}^{-1} \text{ cm}^{-1}$) and 645 nm ($\epsilon = 15,000 \text{ M}^{-1} \text{ cm}^{-1}$) could be identified as one of the final products. These observations are consistent with a demetallation and oxidative degradation of the octaethylporphyrin ligand of the antimony(V) complex in a sequence of processes that resembles the enzyme-catalyzed formation of biliverdin derivatives, **5** (Chart 1) under physiological conditions [4–6]. It is widely accepted that the first step in biological heme degradation by heme oxygenase results in hydroxylation of the *meso*-position of the porphyrin ligand [22]. In this context it is interesting to note that other high-valent metalloporphyrin complexes such as tin(IV) octaalkylporphyrins have been successfully established as drugs for the competitive inhibition of heme oxygenase [23–26]. Based on the present results, it is very tempting to predict a similar biological activity also for octaalkylporphyrin derivatives of gold(III) and antimony(V), although an isolation and further characterization of the porphyrin degradation products is necessary to confirm these assumptions.

References

- [1] J.-H. Fuhrhop, in: D. Dolphin (Ed.), *The Porphyrins*, Vol. II, Academic Press, New York, 1978, pp. 131–159.
- [2] D. Dolphin, D.J. Halko, E.C. Johnson, K. Rousseau, in: F.R. Longo (Ed.), *Porphyrin Chemistry Advances*, Ann Arbor Science, Ann Arbor, MI, 1979, pp. 119–141.
- [3] K.M. Kadish, K.M. Smith, R. Guilard (Eds.), *Synthesis and Organic Chemistry, The Porphyrin Handbook*, Vol. I, Academic Press, New York, 1999, pp. 176–179, 213–215.
- [4] M.D. Maines, in: *Heme Oxygenase: Clinical Applications and Functions*, CRC Press, Boca Raton, FL, 1992, pp. 71–77.
- [5] P.R. Ortiz de Montellano, *Acc. Chem. Res.* 31 (1998) 543–549.
- [6] T.N. St. Claire, A.L. Balch, *Inorg. Chem.* 38 (1999) 684–691.
- [7] H.A. Dailey, in: *Biosynthesis of Heme and Chlorophylls*, McGraw Hill, New York, 1990, pp. 564–569.
- [8] P.M. Jordan, in: *Biosynthesis of Tetrapyrroles*, Elsevier, Amsterdam, 1991, pp. 116–120.
- [9] S.I. Beale, *Adv. Photosynth.* 2 (1995) 153–177.
- [10] A.R. Battersby, F.J. Leeper, *Top. Curr. Chem.* 195 (1998) 143–193.
- [11] H. Sugimoto, *J. Chem. Soc. Dalton Trans* (1982) 1169–1171.
- [12] R.P. Pandian, T.K. Chandrashekar, V. Chandrasekhar, *Indian J. Chem.* 30A (1991) 579–583.
- [13] W.W. Kalisch, M.O. Senge, *Angew. Chem.* 110 (1998) 1156–1159.
- [14] W.W. Kalisch, M.O. Senge, *Angew. Chem. Int. Ed.* 37 (1998) 1107–1109.
- [15] H. Segawa, R. Azumi, T. Shimidzu, *J. Am. Chem. Soc.* 114 (1992) 7564–7565.
- [16] G. Knör, *Inorg. Chem. Commun.* 3 (2000) 505–507.
- [17] H. Inoue, T. Okamoto, Y. Kameo, M. Sumitani, A. Fujiwara, D. Ishibashi, M. Hida, *J. Chem. Soc. Perkin. Trans. I* (1994) 105–111.
- [18] G. Knör, A. Vogler, *Inorg. Chem.* 33 (1994) 314–318.
- [19] J.W. Buchler, in: D. Dolphin (Ed.), *The Porphyrins*, Vol. I, Academic Press, New York, 1978, p. 416, 471.
- [20] J.A.S. Cavaleiro, K.M. Smith, *J. Chem. Soc. Perkin Trans. I* (1973) 2149–2155.
- [21] R. Bonnett, D.G. Buckley, D.J. Hamzesh, *J. Chem. Soc. Perkin Trans. I* (1981) 322–325.
- [22] A.L. Balch, *Coord. Chem. Rev.* 200–202 (2000) 349–377.
- [23] G.S. Drummond, A. Kappas, *Proc. Natl. Acad. Sci. USA* 78 (1981) 6466–6470.
- [24] A. Kappas, G.S. Drummond, C. Henschke, T. Valaes, *Pediatrics* 95 (1995) 468–474.
- [25] G.S. Drummond, A. Kappas, *Pharmacology* 56 (1998) 158–164.
- [26] T.O. Philippova, B.N. Galkin, N.Ya. Golovenko, S.V. Zhilina, S.V. Vodzinskii, *J. Porph. Phthaloc.* 4 (2000) 243–247.

³Besides the ~300 mV lower oxidation potential of compound **2** compared to **1**, a crucial property should be the driving force for an elimination of the substituent R, allowing the formation of *meso*-hydroxy porphyrin derivatives in an overall nucleophilic aromatic substitution process.