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Reaction chemistry of metallotexaphyrins: the synthesis and characterization of the first meso-oxotexaphlorin†

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Received (in Purdue, IN, USA, UK) 24th September 2001, Accepted 5th February 2002
First published as an Advance Article on the web 4th March 2002

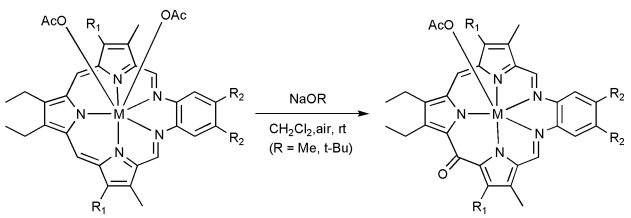
Ring-oxygenation of metallotexaphyrins, promoted by strong bases, produces oxotexaphlorin, the first example of a meso-oxo functionalized texaphyrin derivative.

Texaphyrins are a class of expanded porphyrins with a 22π-electron aromatic periphery.[1] Possessing a central cavity that is *ca.* 20% larger than natural porphyrins, these synthetic pentadentate macrocyclic ligands form near-planar 1 : 1 complexes with large metal cations, such as the trivalent lanthanides [*e.g.*, Gd(III) and Lu(III)].[1] Currently, two texaphyrin complexes, motexafin gadolinium (MGd, **1**, Scheme 1) and motexafin lutetium (MLu, **2**, not shown), are being evaluated in advanced clinical trials as a radiation enhancer and a photodynamic therapeutic agent, respectively.[2]

Since the synthesis of the first metallotexaphyrin in 1988, this class of molecules has been studied extensively with a view to characterizing their spectral, redox, photophysical, and other physicochemical characteristics,[1,3,4] as well as their biological properties.[5] On the other hand, few if any studies involving the chemical reactivity of the texaphyrin macrocycle *per se* have been carried out. Herein, we present the discovery of a unique base-promoted ring-oxygenation reaction of metallotexaphyrin, and the first synthesis of meso-oxotexaphlorin, a novel pentadentate macrocyclic compound.

During ongoing investigations designed to probe the chemical stability of various metallotexaphyrins under forcing conditions, we recently found that under strongly basic conditions, nucleophilic attack at the meso-like positions could occur, as inferred from an increased degree of degradation under such conditions. These observations and inferences prompted us to study in detail the reaction of metallotexaphyrins when exposed to strong bases, such as alkali-metal alkoxides.

In a typical study, MGd (**1**) was treated with sodium methoxide (NaOMe, 2 equiv.) in CH_2Cl_2 at room temperature. Under these conditions, the solution changed from yellowish green (characteristic of MGd solutions) to deep green, and HPLC analysis revealed the presence of a new peak indicating the formation of a new compound. This putative new compound was found to be unstable in weakly acidic aqueous buffer solutions (*e.g.*, 100 mM ammonium acetate, pH 4.3).[6] Nonetheless, it could be purified and isolated using normal phase silica gel chromatography ($MeOH/CH_2Cl_2$ as the eluent). The UV–VIS spectrum of the purified product (**3**) revealed dramatic differences as compared to the MGd starting material: the Soret- and Q-type bands shift from 470 to 434 nm, and from 740 to 672 nm, respectively (see ESI†). This finding is interpreted in terms of the texaphyrin chromophore having undergone significant modification. FAB mass spectrometric analysis of **3** revealed a cluster of peaks around *m*/*z* 1045, which displayed the isotopic distribution characteristic of gadolinium. Further, the peak at *m*/*z* = 1045.3962 obtained by HRMS was found to correspond to $C_{48}H_{65}GdN_5O_{11}^+$, a formula that corresponds to a system wherein one hydrogen atom of the texaphyrin is replaced by an oxygen atom.



M-Tex
1 M = Gd, $R_1 = (CH_2)_3OH$, $R_2 = O(CH_2CH_2O)_3CH_3$
4 M = Lu, $R_1 = (CH_2)_3OH$, $R_2 = H$
6 M = Gd, $R_1 = (CH_2)_3OTBDMS$, $R_2 = O(CH_2CH_2O)_3CH_3$
7 M = Gd, $R_1 = C_2H_5$, $R_2 = OCH_3$

M-OTP
3 M = Gd, $R_1 = (CH_2)_3OH$, $R_2 = O(CH_2CH_2O)_3CH_3$
5 M = Lu, $R_1 = (CH_2)_3OH$, $R_2 = H$

Scheme 1

To obtain further insight into the structure of **3**, we chose to synthesize a Lu(III) analogue starting from the lutetium texaphyrin derivative **4** (Scheme 1). Such an approach, it was thought, would generate a structurally simpler diamagnetic product that could be readily analyzed by NMR spectroscopy. Thus, **4** was reacted with NaOMe to afford **5** in 34% isolated yield. This compound (**5**) was fully characterized by elemental analysis, MS, ^1H and ^{13}C NMR, as well as COSY and HMQC 2D-NMR spectroscopy (see ESI†). Comparing the ^1H NMR spectra of **4** and **5** revealed that most of the protons in **5** are upfield-shifted compared to those in the starting material **4**. Futhermore, in **5**, the molecule has become unsymmetrical: There is only one meso proton (8.18 ppm); the two imine protons (9.91, 9.85 ppm) and most geminal side chain protons exhibit two sets of resonances. In the ^{13}C NMR spectra, a new carbonyl resonance is found at 183.6 ppm in addition to that at 182.8 ppm, which corresponds to the carbonyl of the acetate anion. The IR spectrum of **5** also shows two carbonyl absorption bands at 1650 cm^{-1} and 1576 cm^{-1}, confirming the presence of another keto group besides the acetate carbonyl.[7] Based on these combined data and the HRMS result of **5**, we conclude that **5** is a meso-oxotexaphlorin (OTP)‡ (Scheme 1). Although the cyclic hemiacetal structure (protonated form of **IV**, Scheme 2, *vide infra*) could give the same *m*/*z* value in its MS, it does not account for the two types of keto signals observed in the IR and ^{13}C NMR spectra. By analogy, structure **3** was assigned as being the corresponding gadolinium oxotexaphlorin.

To the best of our knowledge, **3** and **5** are the first examples of meso-oxo functionalized derivatives of metallotexaphyrins. By contrast, their porphyrin counterparts, oxophlorins (or oxyporphyrins), are classics of the early literature,[7,8] and have been studied extensively for their biological relevance because of their interesting structural and physicochemical properties. In fact, iron oxophlorin is known to be a key intermediate in heme catabolism.[10] This fact, coupled with our serendipitous discovery of oxotexaphlorin, led us to consider whether a similar set of transformations could be involved in the metabolic fate, if any, of metallotexaphyrins *in vivo*. This interest, in turn, led us to study in greater detail the mechanism of oxotexaphlorin synthesis.

† Electronic supplementary information (ESI) available: experimental section, UV–VIS spectra of **1** and **3** and NMR spectra. See http://www.rsc.org/suppdata/cc/b1/b108914p/

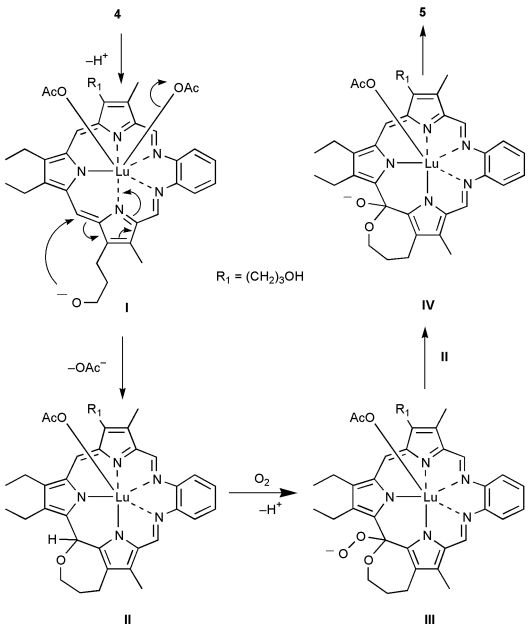
DOI: 10.1039/b108914p

Table 1 Reaction of metallotexaphyrins with sodium alkoxide (NaOR)[a]

Entry	Substrate	Base (R)	Solvent	Product	Yield (%)[b]
1	**1**	Me	CH_2Cl_2	**3**	33
2	**1**	^{t}Bu	MeOH–CH_2Cl_2[c]	**3**[d]	15
3	**1**	^{t}Bu	CH_2Cl_2	**3**	51
4[e]	**1**	^{t}Bu	CH_2Cl_2	**3**	0
5	**4**	Me	CH_2Cl_2	**5**	34
6	**4**	^{t}Bu	^{i}PrOH–CH_2Cl_2[f]	**5**	35
7	**4**	^{t}Bu	CH_2Cl_2	**5**	56
8	**6**	^{t}Bu	CH_2Cl_2	—[g]	0
9	**7**	^{t}Bu	CH_2Cl_2	—[g]	0

[a] *Reaction conditions*: **1** or **4** (0.2 mmol), NaOR (4 equiv.) react in specified solvent at rt under air for 12 h. [b] Isolated yield. [c] MeOH–CH_2Cl_2 = 1/1 (v/v). [d] Another texaphyrin-like byproduct was formed which is currently under investigation. [e] The reaction was conducted under nitrogen. [f] ^{i}PrOH–CH_2Cl_2 = 1/1 (v/v). [g] No oxotexaphlorin product was detected.

A series of varying reaction conditions were employed to study the factors affecting the formation of oxotexaphlorin (Scheme 1). Table 1 summarizes these results. The experiments using different solvents lead to the consideration that an aprotic solvent such as CH_2Cl_2 favors the formation of oxotexaphlorin (entry 2 *vs*. 3, entry 6 *vs*. 7). Using NaO^{t}Bu instead of NaOMe gives higher yield of oxotexaphlorin, leading us to suggest that a key step in the reaction might involve deprotonation. Entry 4 confirms the fact that when MGd (**1**) was treated with NaO^{t}Bu in CH_2Cl_2 under anaerobic conditions, no oxygenation product **3** was formed. This supports the contention that the terminal oxidant of the reaction is O_2 in the air. Another important observation is that metallotexaphyrins without the peripheral OH groups, *e.g*., the silyl-protected MGd (**6**, R_1 = $(CH_2)_3OTBDMS$, R_2 = $O(CH_2CHO)_3CH_3$) and the all-alkyl substituted derivative (**7**, R_1 = C_2H_5, R_2 = OCH_3) , did not afford oxotexaphlorin products under the standard conditions (entries 8 and 9). This suggests that the OH functional group plays an important role in this oxidation reaction. We also tested the effect of other oxidants, and found treating a metallotexaphyrin with H_2O_2 only resulted in demetalation and complex degradation products; no oxotexaphlorin was formed from such conditions.



Scheme 2

A mechanism consistent with the above findings is presented in Scheme 2. In the presence of a strong base (such as NaO^{t}Bu), the hydroxy group of **4** is first deprotonated to give **I**, which undergoes intramolecular nucleophilic addition with elimination of OAc^- to yield intermediate **II**.[11] The allylic C–H of **II** is further deprotonated and reacts with dioxygen to give peroxide anion **III**.[12] Finally, **III** is reduced by another molecule of **II** to afford **IV**,[13] which rearranges to form **5**.

One intriguing facet of oxotexaphlorin is its potential to exist in the form of an enolate structure. Smith and coworkers[14] and Balch *et al*.[10] showed that oxophlorin derivatives can exist in keto, enol, or valence-isomeric π-radical forms depending on the ring substituents, metalation state, and the nature of the central metal. In the oxotexaphlorin case, the similarity of the UV–VIS spectra of complexes derived from different starting metallotexaphyrins led us to suggest that these particular species all exist in their keto forms. Further, attempts to alkylate **3** with Meerwein's salt or methyl iodide gave no meso-alkoxy metallotexaphyrin. Such a finding is most easily rationalized in terms of the negative charge of the ligand anion not being delocalized onto the meso-oxygen. As a consequence, the carbonyl group acts as one in a normal dipyrroketone.[7] The ^{13}C NMR shift at 183.6 ppm observed for this carbon in **5** is consistent with this conclusion.

Currently, we are investigating the coordination chemistry and potential applications of this new ligand system.

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‡ We termed this new structure oxotexaphlorin (OTP) based on its porphyrin counterpart, oxophlorin.

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