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New texaphyrin-type expanded porphyrins

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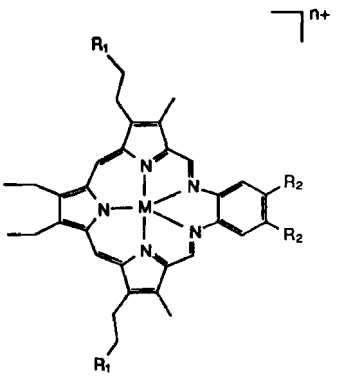
Abstract

This paper presents the synthesis of several new Schiff-base type expanded porphyrins. A dimeric, tetraazacyclododecane-linked texaphyrin system has been prepared. It, as its gadolinium(III) adduct, displays a relaxivity in aqueous solution that is roughly 5 times higher than the benchmark texaphyrin monomer currently undergoing human clinical trials as a potential MRI enhancing and X-ray radiation sensitizing drug. Polymeric gadolinium(III) texaphyrin species, derived from poly-L-lysine and a glycosylated poly-L-lysine, have also been prepared; they too display greatly enhanced relaxivities. In work along different lines, the synthesis of an "expanded" texaphyrin has been effected and the construction of two "three dimensional" texaphyrin-inspired targets accomplished. These latter define a new class of pyrrolic cryptands.

The texaphyrins, (e.g. **1-3**), are among the more interesting of the known expanded porphyrins (1). This reflects the fact that, in marked contrast to many other expanded porphyrins (2), a rich metal coordination chemistry is known for the texaphyrins. Indeed, the texaphyrins are now recognized as being lanthanide-coordinating ligands par excellence; the resulting dicationic, trivalent lanthanide complexes are generally quite stable and are often crystalline in nature (3). This, in turn, has allowed the lanthanide(III) coordination chemistry of the texaphyrins to be studied in considerable detail, both in solution (4) and in the solid state (1, 3-5). It has also allowed the texaphyrins to be explored in terms of several putative biomedical applications. Here, several other intrinsic properties are conspiring to make the texaphyrins of special interest.



1. $R_1 = R_2 = H$
2. $R_1 = CH_2OH$; $R_2 = O(CH_2)_3OH$
3. $R_1 = CH_2OH$; $R_2 = O(CH_2CH_2O)_3CH_3$

One characteristic of metallotexaphyrins is that they, like certain porphyrins (6), localize selectively in neoplastic tissue (1,7). However, unlike the smaller tetrapyrrolic porphyrins, the texaphyrins will ligate gadolinium(III). This nucleus is highly paramagnetic, possessing 7 unpaired spins, and well-known for its MRI enhancing capabilities (8). Thus, the texaphyrins possess two critical attributes that make them of potential interest as possible state-of-the-art tumor selective MRI contrast enhancing agents. For actual *in vivo* use, however, these texaphyrins must also be made water soluble (to facilitate intravenous administration) and demonstrated as being physiologically acceptable. This has been done now for complex **3** (M = Gd; n = 2). Indeed, this species is currently undergoing Phase I human clinical trials in the United States.

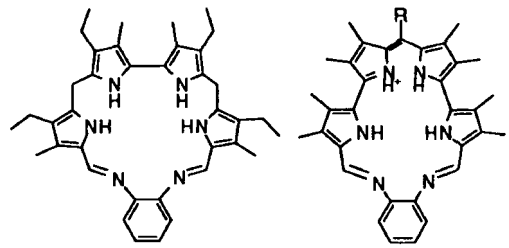
The texaphyrins are also easy to reduce and capable of "capturing" hydrated electrons in aqueous solution. This makes them of potential interest as radiation sensitizers (9); in fact, the above-mentioned clinical study is designed, in part, to explore just this possibility. Here, mechanistically, it is expected that texaphyrin-mediated "trapping" of hydrated electrons under conditions of X-ray therapy should prevent "recombination" of these species with hydroxyl radicals (to give relatively nontoxic hydroxide anion) and thus leave more of the latter present to mediate its known DNA-crosslinking-based cytotoxic effect. What makes this of special interest is that the texaphyrin-based radical, formed as the result of the electron "capture" event, appears itself to be capable of reacting with cytosine; this is leading us to suggest that it too could contribute to an overall cytotoxic effect (9).

A further noteworthy property of the texaphyrins is that they, like many other expanded porphyrins (2), absorb in the red part of the visible spectral region where human tissues are most transparent (10); indeed, λ_{max} values on the order of 740-760 nm are generally recorded for metalated texaphyrins **1-3** (1).

The various diamagnetic texaphyrin derivatives (e.g., the Cd(II) adduct of **1** or the Lu(III) derivative of **3**) also produce singlet oxygen with near-record quantum efficiency when irradiated with red light tuned to match these low energy absorption maxima. Taken together, these properties make the various diamagnetic texaphyrins of special interest as potential photosensitizers for use in photodynamic tumor therapy. Here, it was considered likely that 1) the tumor-localizing features of the texaphyrins would allow high local concentration of the drug to be attained at the neoplastic site of interest, 2) irradiation with red light would generate singlet oxygen efficiently just at these targeted cancerous tissues, and 3) the singlet oxygen, being a known cytotoxin, would then eradicate the tumor. To date, this promise has been realized in animal models involving the water solubilized Lu(III) texaphyrin complex **3** (M = Lu and n = 2); actual cures of transplanted human carcinomas have been effected using this drug in conjunction with irradiation at 732 nm (11).

A final feature of the texaphyrins that is worthy of comment involves the Lewis acidity of the centrally bound metal centers. Lewis acidic centers, especially those derived from lanthanide(III) cations, are known to be effective catalysts for the hydrolysis of simple phosphodiesters and, nonspecifically, RNA. This, in turn, has made this kind of Lewis acidic metal complex of interest in the context of antisense technology (12). In the special case of the texaphyrins, one gets not only a coordinated Lewis acidic lanthanide(III) center but also a stable, easy-to-modify organic structure. This salubrious combination of characteristics, in turn, has allowed for 1) the construction of short oligomeric DNA-texaphyrin conjugates, namely texaphyrin-modified 20mers, and 2) the demonstration that the Eu(III) and Dy(III) derivatives of these conjugates are capable of effecting the site-specific cleavage of appropriate complementary RNA fragments (13). By using the photosensitizing Lu(III) analogues, it has also proved possible to cleave DNA photochemically; this was done in a site-selective manner using excitation at ≥ 700 nm (14). This ability to cleave selected nucleotides via either light- or hydrolysis-based pathways is a special feature of the texaphyrins. It leads us to suggest that these molecules will have an important role to play in the emerging area of antisense technology.

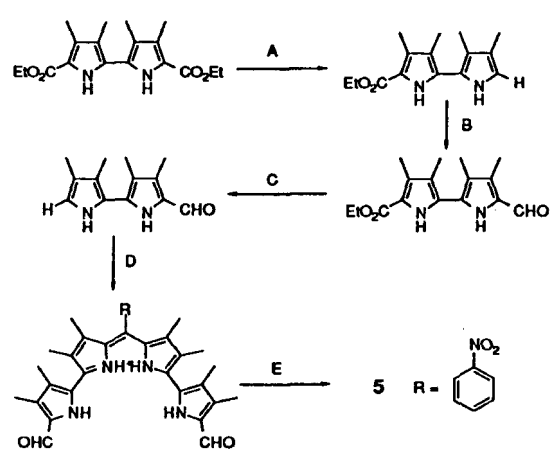
Given the excitement attendant to the above applications, it is not surprising that several approaches are currently being pursued in an effort to extend further the chemistry of the texaphyrins. One such approach involves "expanding" the size of the texaphyrin skeleton *per se*. In previous work, we succeeded in preparing compound **4** (1). Now, we wish to report another "expanded texaphyrin", namely system **5**. In this new texaphyrin-type system, one pyrrole subunit has been added to the macrocyclic "periphery". Also, one *meso*-like position has been removed. Unlike **4**, the expanded texaphyrin **5**, is fully conjugated giving a highly colored solution with a Soret-type absorption at 439 nm. Although **5** can be regarded as being a 22 π-electron conjugated system, it does not show the characteristic proton shifts of an aromatic macrocycle. The reasons for this, however, remain unknown at present.



4 **5**

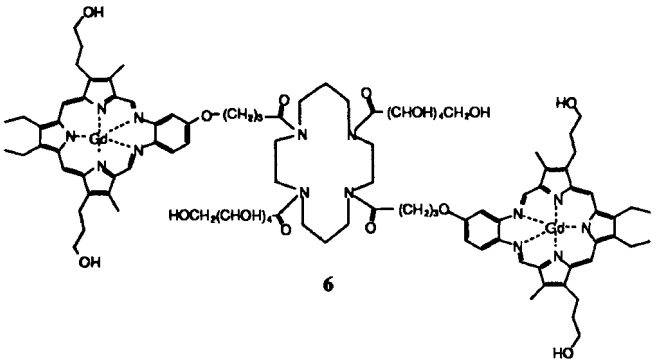
The synthesis of **5**, Scheme 1, starts with the mono-saponification and decarboxylation of the known bipyrrole diester. Vilsmeier formylation followed by a second round of saponification-decarboxylation gives the versatile mono-aldehyde bipyrrole. Reacting two equivalents of the mono-aldehyde bipyrrole with one equivalent of an activated aryl aldehyde then gives the *meso*-substituted tetrapyrrole dialdehyde. Finally, in analogy to what is used to prepare the parent texaphyrins (e.g., **1**-**3**), the resulting tetrapyrrole dialdehyde is cyclized with *ortho*-phenylenediamine in acidic medium to give the expanded texaphyrin **5**.

Scheme 1



A. 1.1 eqv. NaOH, H_2O, EtOH; 2. TFA; B. DMF, $POCl_3$, $C_2H_2Cl_2$; C. NaOH, ethylene glycol, heat; D. 1. *para*-nitrobenzaldehyde, CH_2Cl_2, TFA; 2. DDQ: E. *ortho*-phenylenediamine, MeOH, HCl

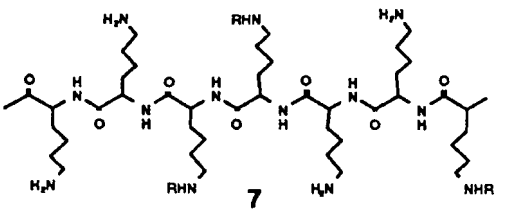
A second way the chemistry of texaphyrins has been modified is via the construction of a water-solubilized dimer **6**. Here, the critical solubility-enhancing spacer is a gluconolated 1,4,8,11-tetraazacyclotetradecane; it not only bridges the two texaphyrin units, but also provides an additional site for metal chelation. This system is thus potentially able to coordinate three separate metal cations.



6

To date, system **6** has been studied only in the form of the bis-Gd(III) adduct (i.e., the complex shown). Interestingly, on a per gadolinium(III) basis, this system was found to have longitudinal (T_1) relaxivity of ca. 40 $mM^{-1}s^{-1}$ at normal temperature, neutral pH and 500 MHz applied field; under these same conditions, the benchmark system **3** (with M = Gd; n = 2) displayed a relaxivity of 8 $mM^{-1}s^{-1}$. While the reason system **6** displays such a high per cation relaxivity is still not completely understood, it could have to do with a reduction in overall molecular freedom. Such reductions, especially when they involve the rates of whole-molecule rotation, are known to increase the longitudinal relaxivity (8). In any event the augmented relaxivity for **6** makes this system of interest as a potentially improved texaphyrin-type MRI contrast enhancing agent.

In order to probe further how augmentations in molecular size (and corresponding decreases in molecule-centered rotation rates), influence the per-Gd(III) based relaxivities of the gadolinium(III) texaphyrins, two water soluble polymeric systems were prepared, namely compounds **7** and **8**. In both cases, the backbone consists of poly-L-lysine. In the case of **7** this backbone is not further modified; in the case of **8**, however, it has been functionalized by reaction with δ-gluconolactone. Importantly, both systems proved water soluble with **8** proving better than **7** in this regard. Further, both displayed per-metal-center relaxivities, of ca. 90 and 315 $mM^{-1}s^{-1}$, respectively, that are substantially enhanced relative to those seen for the Gd(III) adducts of monomers such as **2** or **3**. Thus, as in the case of **6**, one is tempted to suggest that these new systems might emerge as being yet-improved MRI contrast agents.



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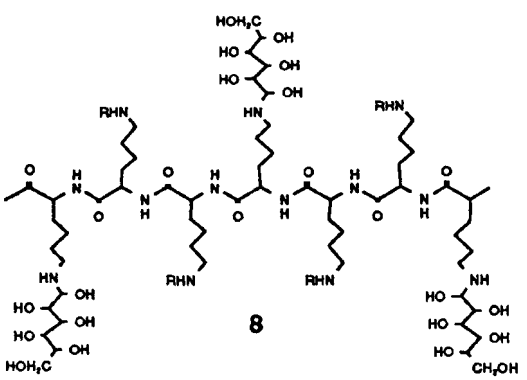

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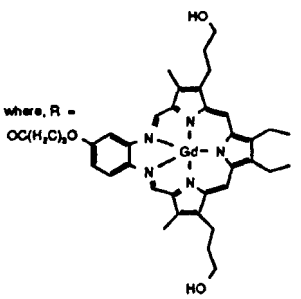
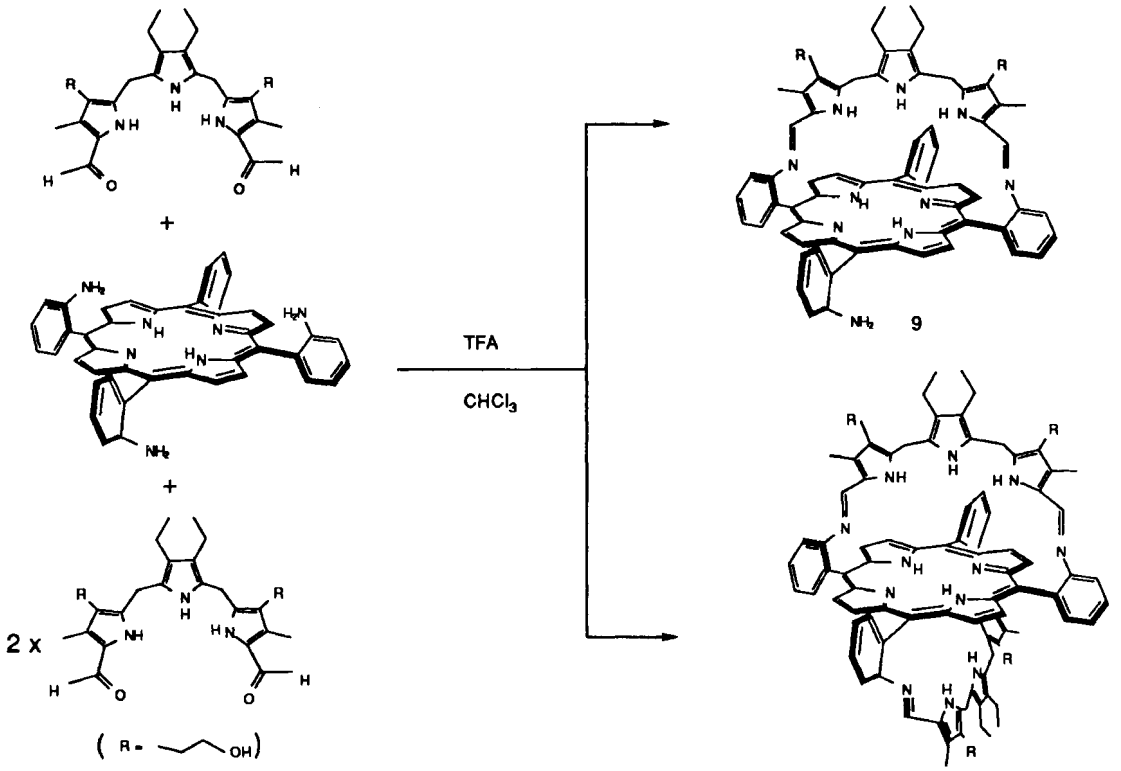


The final direction in which we have been trying to take the chemistry of texaphyrins is towards the development of superstructured systems, i.e., the creation of three-dimensional expanded porphyrins. Such systems, interestingly enough, are currently unknown. Superstructured porphyrins, on the other hand, are common; indeed it is an area that has received considerable attention in recent years with regard to 1) hemoprotein active site modeling (15-19), electron transfer analysis (20), chiral catalyst development (21), and molecular recognition (22-24).



Scheme 2

With the continued development of expanded porphyrins, a number of symmetric tripyrranes have become available as precursors for their synthesis (1). The length of these tripyrrane units is suitable for their use as straps for porphyrin molecules, particularly for those of the tetraphenylporphyrin type. It was an appreciation of this fact that has led us to the design of new three-dimensional expanded porphyrins embodied in the first prototypic systems **9** and **10** (Scheme 2). Compound **9** is an example of a tetrakis(2-aminophenyl)porphyrin with a single tripyrrane strap across the plane of the porphyrin whereas compound **10** represents the corresponding doubly-strapped analog. Together, they define a new class of cryptand-like expanded porphyrins.

The synthesis of these compounds involves the acid catalyzed condensation of bis-(hydroxypropyl) substituted diformyltripyrrane with the α,β,α,β atropisomer of 5,10,15,20-tetrakis(2-aminophenyl)porphyrin under conditions of high dilution. The products are isolated in moderate yields, with the imine products obtained being characterized by high resolution mass spectrometry as well as via ^{1}H and ^{13}C NMR spectroscopy. In the proton NMR spectra, for instance, an upfield shift in the signals corresponding to the tripyrrane subunit(s) is observed. This is an indication that the strap lies above the plane of the porphyrin.

Unfortunately the bridged systems **9** and **10** both appear to be unstable in the presence of acid. Attempts to purify the compounds via column chromatography using both silica gel and basic alumina as the non-mobile phase have, therefore, proved unsuccessful. Nonetheless, it has proved possible to prepare and characterize the porphyrin-centered Ni(II) and Cu(II) complexes of the "three dimensional" system **9**. Preliminary mass spectrometric work has also served to show that this system and its congener **10** is capable of binding small molecules, such as MeOH and CD_3CN, within the cavities defined by the bridging tripyrrane straps. Thus, it is our expectation that these systems will be of interest from the point of view of both coordination chemistry and molecular recognition. This, then, is something we are continuing to explore.

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