# Texaphyrins: Synthesis and Applications

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The porphyrins and related tetrapyrrolic systems are among the most widely studied of all macrocyclic compounds.[1] In fact, in one capacity or another these versatile molecules have influenced nearly all disciplines of chemistry. Not surprisingly, therefore, considerable effort continues to be devoted to porphyrin-related research. Increasingly, a percentage of this effort is being directed toward the synthesis and study of "expanded porphyrins",[2-21] large, porphyrin-like macrocycles that contain an increased number of $\pi$-electrons, additional coordinating heteroatoms (from, e.g., pyrroles), and/or a larger central binding core compared to their smaller, better studied tetrapyrrolic analogues.

Unlike that of the porphyrins,[1] the synthetic chemistry of expanded porphyrins is still in its infancy. Nonetheless, a number of expanded porphyrin macrocycles have been described.[2-21] Some examples include the sapphyrins,[3] first prepared by the groups of R. B. Woodward and A. W. Johnson, the superphthalocyanines of Marks;[4] the vinylogous porphyrins of LeGoff[5] and Franck;[6] the pentaphyrins[7] and hexaphyrins[8] of Gossauer; the stretched porphycenes of Vogel;[9] and most recently the rubyrins[10] and rosarins[11] described by our own group. While all of these macrocycles have individual properties that make them appealing in a number of different ways, they are all to a greater or lesser extent difficult to prepare and difficult to derivatize. In 1988, we discovered a new class of expanded porphyrins that is based on the Schiff base condensation between a diformyltripyrrane and an aromatic 1,2-diamine.[12] This new class of expanded porphyrins, of which compound H-1 (Figure 1) is the prototype, has come to be known as the "texaphyrins".[12b]

The generality of this Schiff base synthetic procedure has enabled the systematic preparation and investigation of a wide range of ostensibly congeneric com-

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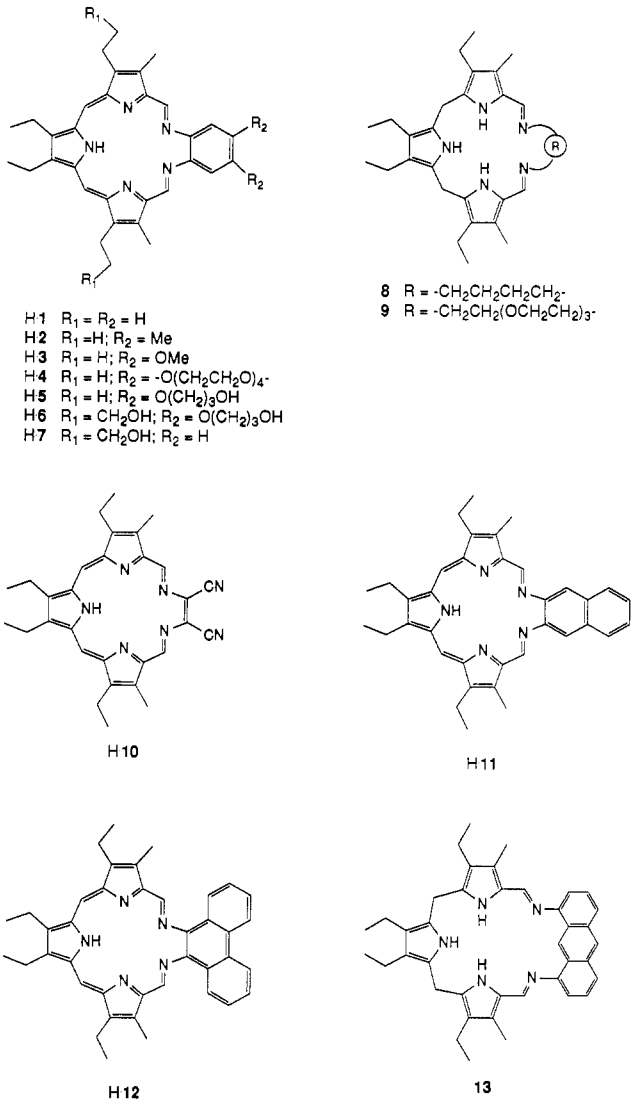


**Figure 1.** Structures of metal-free forms of texaphyrins (H·1–H·7 and H·10–H·12) and reduced, nonaromatic analogues (**8**, **9**, and **13**). The use of the abbreviations H·1, H·2, etc. is meant to highlight the fact that the texaphyrins are monoanionic ligands. Di- and trivalent metal complexes are thus designated as $[M\cdot1]^+$ and $[M\cdot1]^{2+}$, respectively. With the exception of H·1, the aromatic texaphyrins were isolated as metal complexes whereas the nonaromatic species were generally isolated in their metal-free forms.

pounds, including H·2–H·7 (cf. Figure 1),[12] as well as others, such as H·10–H·12 shown in Figure 1 and structures **8**, **9**, **13** (Figure 1), and **14** (Figure 2), that are less closely related.[17–21] These efforts, in turn, have revealed that texaphyrin-type molecules possess a number of unique physical and chemical properties that make them of interest in a variety of biomedical applications including those of photodynamic therapy (PDT) and magnetic resonance imaging (MRI). It is a review of this chemistry and the resultant properties that is the subject of this Account.

Before going on, it is important to note that we were not the first to realize the potential of Schiff base expanded porphyrins. A number of pyrrole-containing Schiff base macrocycles had been investigated previously. However, these compounds, such as the pyrrole-based systems of Fenton (e.g., **15**; Figure 2),[17] the uranyl- and methanol-binding analogues **16** and **17** recently reported by us,[18,19] and the "accordion" porphyrins (e.g., **18**) of Mertes and co-workers,[20] do not have the potential for becoming aromatic. The further stabilization gained, however, when the macrocycle becomes aromatic, as in the case of the texaphyrins H·1–H·7 and H·10–H·12, is great enough to allow a considerable chemistry.

## Synthesis and Initial Characterization

The chemistry of texaphyrins became practical with the advent in 1987 of a simple, high-yielding synthesis of symmetric tripyrranes.[12c] This synthesis is shown in Scheme 1. It involves, as its key step, the acid-catalyzed condensation between 1 equiv of 3,4-diethylpyrrole (**19**)[23] and 2 equiv of the (acetoxymethyl)-pyrrole[24] **20**. This produces tripyrrane **21**, which, following debenzylation (to yield **22**) and Clezy-type formylation,[25] provides the diformyltripyrrane, **23**, required for subsequent texaphyrin syntheses. Related chemistry, starting with pyrrole **24**, provides the bis-(hydroxypropyl)-substituted diformyltripyrrane **28**.[12i] At first, yields on the order of 50–75% were obtained for each of these steps. Now, however, as a result of optimization and scale up, *overall yields* as high as 80% are routinely obtained.

The next step in the synthesis of texaphyrins is shown in Scheme 2. It involves the acid-catalyzed condensation between a diformyltripyrrane, such as **23** or **28**, and an *o*-phenylenediamine derivative, such as **29–33**.[12c] This results in the production of tripyrrane-containing Schiff base macrocycles such as those given by formulas **34–40**, in yields that often exceed 90%. This same basic strategy has also been used to prepare a wide range of related products, including those defined by structures **8**, **9**, and **13**[12,20] as well as the immediate precursors to compounds H·10–H·12 and the large "expanded texaphyrin" system **14**.[22]

A critical feature of compounds **34–40** (as well as **8**, **9**, and **13**) is that they are nonaromatic. As such, they act more as "expanded porphyrinogens" than as true expanded porphyrins.[12c] For instance, they are essentially colorless when pure and moderately unstable toward oxidation. Nonetheless, it proved possible to obtain an X-ray quality single crystal of the HSCN salt of **34**[12c] as well as of the mono HCl adduct of **13**.[21] In

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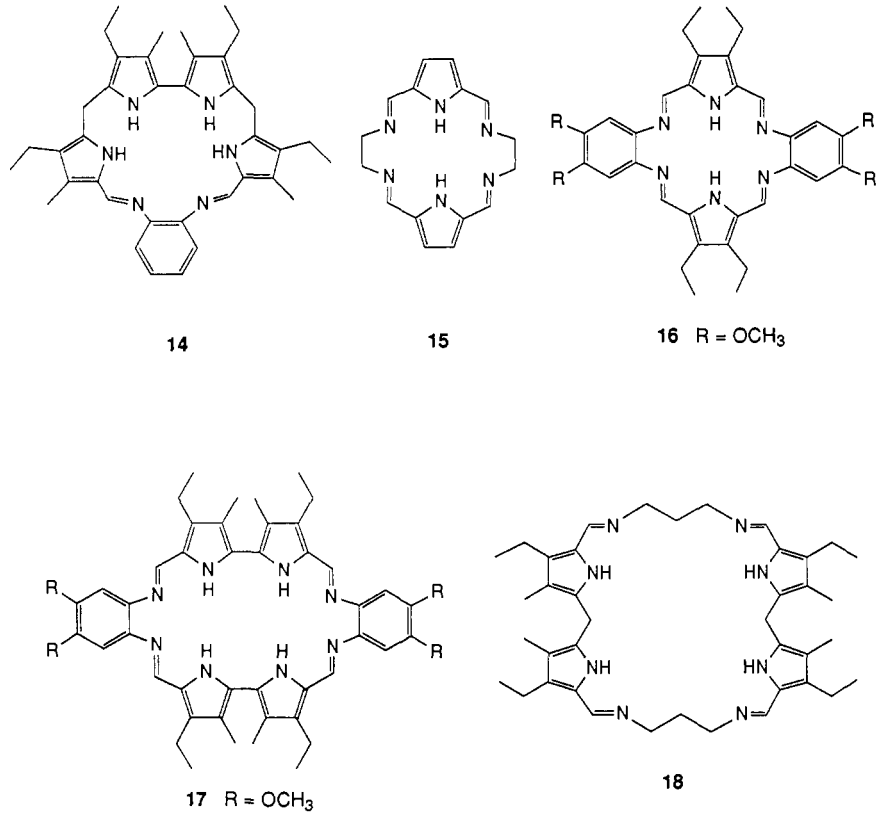
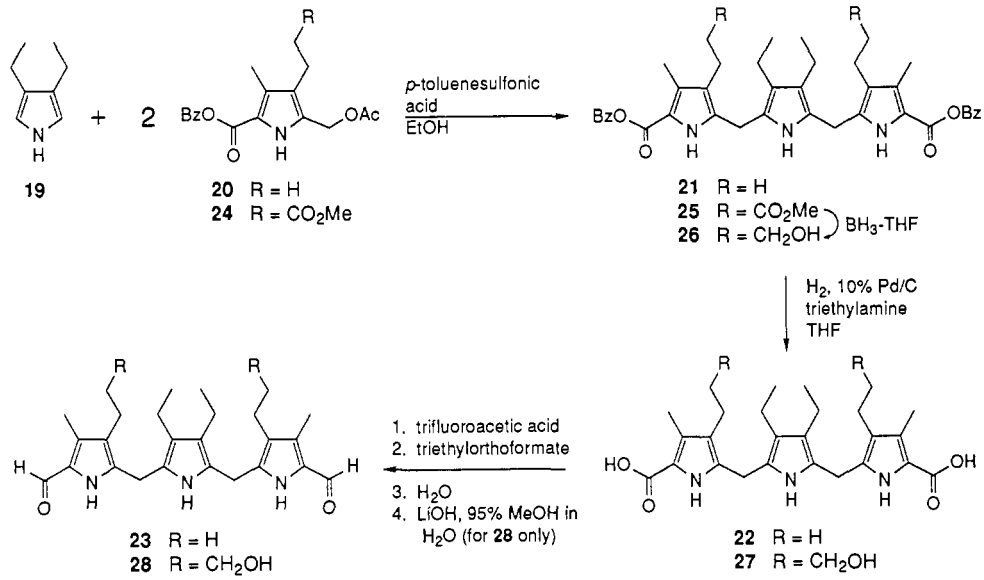



**Figure 2.** Structures of other Schiff base expanded porphyrins.

**Scheme 1**

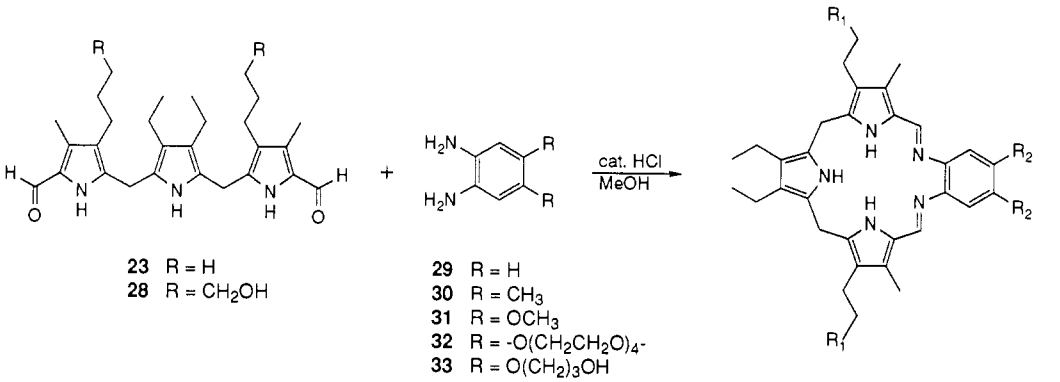



both cases, "coordination" of the anions was observed.[2b] These findings, along with supporting solution-phase experiments, have led us to suggest that these and other expanded porphyrins could possibly act as anion-specific chelating agents. This is discussed in greater detail in a separate review.[2b]

Unfortunately, efforts to obtain stable, nonlabile metal complexes with the above nonaromatic macrocycles proved unsuccessful. It was thought, however, that, were the corresponding four-electron-oxidized, aromatic forms (e.g., H·1–H·7) available, they would prove more effective in this regard.[12c] In the case of H·1, this oxidation was effected by stirring the reduced macrocycle in air-saturated chloroform–methanol containing a Brønsted base (Scheme 3).[12e] Although the yield is low (≤12%), unlike its precursor, the aromatic product (H·1), isolated as a green solid, appears stable once formed.

Texaphyrin H·1 may be considered as being an aromatic 22-$\pi$ benzannulene containing both 18- and 22-$\pi$-electron delocalization pathways. Such an aromatic formulation would account for the improved stability of H·1 as compared to **34** and is also consistent with the available spectroscopic data. For instance, in the $^1$H NMR spectrum of H·1, the single NH proton signal (at $\delta$ 0.9 ppm) was found to be shifted upfield by over 10 ppm as compared to the relevant signals of its reduced precursor **34**, leading us to suggest that the strength of the diamagnetic ring current present in H·1 is similar to that of the porphyrins.[12e]

**Scheme 2**

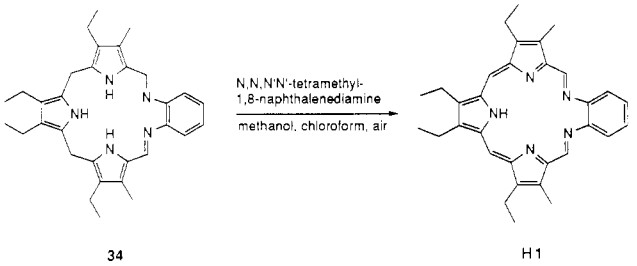



23 R = H
28 R = $CH_2OH$

29 R = H
30 R = $CH_3$
31 R = $OCH_3$
32 R = -$O(CH_2CH_2O)_4$-
33 R = $O(CH_2)_3OH$

34 $R_1 = R_2 = H$
35 $R_1$ =H; $R_2$ = Me
36 $R_1$ = H; $R_2$ = OMe
37 $R_1$ = H; $R_2$ = -$O(CH_2CH_2O)_4$-
38 $R_1$ = H; $R_2$ = $O(CH_2)_3OH$
39 $R_1$ = $CH_2OH$; $R_2$ = $O(CH_2)_3OH$
40 $R_1$ = $CH_2OH$; $R_2$ = H

**Scheme 3**




34 H1

## Cadmium(II) Complexes

Unfortunately, efforts to reproduce and/or generalize the above oxidative chemistry proved difficult. Thus, ways were sought that would allow the direct oxidative insertion of metal cations into the precursor, nonaromatic forms (e.g., **34–40**). Here, the idea was that during the course of oxidation the flexible, reduced ligand would wrap around the metal, thus stabilizing the resulting metallotexaphyrin complex. This strategy, which is illustrated in Scheme 4, was first enacted successfully using cadmium(II) as the templating cation and air as the oxidant.[12a] Subsequently, it was discovered that this same approach could be used effectively with a number of different reduced texaphyrin precursors (such as **H·2–H·7** and **H·10–H·12**)[12g,h] and with a wide range of other large cations, including those of the lanthanide series, provided an excess of a nonnucleophilic base is also added to the reaction mixture.[12f,i] This newer chemistry is discussed later on in this Account.

In the case of $CdCl_2$ the product obtained is [Cd·1]·Cl. The optical spectrum of this metallotexaphyrin bears some resemblance to those of other aromatic pyrrole-containing macrocycles such as the sapphyrins and pentaphyrins.[3–8] The dominant electronic transition, in chloroform, is a Soret-like band at 427 nm ($\epsilon$ = 72 700 $mmol^{-1}$), which is considerably less intense than that seen for CdOEP·py (OEP = octaethylporphyrin; py = pyridine).[12a] This is flanked by exceptionally strong N- and Q-like bands at higher and lower energies. As would be expected for a larger $\pi$-system,[2a] both the lowest energy Q-like absorption ($\lambda_{max}$ = 767.5 nm, $\epsilon$ = 41 200 $mmol^{-1}$) and emission ($\lambda_{max}$ = 792 nm) bands of [Cd·1]·Cl are substantially red-shifted (by >150 nm!) as compared to those of typical cadmium porphyrins.[26]

In the course of optimizing the synthesis of the cadmium complex $[Cd·1]^+$, $Cd(NO_3)_2$ was also tried as the cadmium source.[12a,e] Now, the product obtained proved to be a mixture of crystalline and noncrystalline solids. A single-crystal X-ray diffraction study of the crystalline portion of the sample gave an unexpected result. It revealed a six-coordinate pentagonal pyramidal cadmium(II) complex, $[Cd·1·BzIm]^+$ (cf. Figure 3), where one of the two possible axial ligation sites was occupied by a benzimidazole (BzIm). The benzimidazole was thought to result from electrophilic aromatic deacylation of a tripyrrane $\alpha$-carbon and subsequent condensation with *o*-phenylenediamine.[12e] Treatment of the remaining inhomogeneous material with pyridine gave only a single crystalline aromatic product, $[Cd·1·(py)_2]^+$. X-ray structural analysis (Figure 4) confirmed the coordination of pyridine and established the texaphyrin core as being roughly 20% larger (center-to-nitrogen radius ($r$) $\approx$ 2.4 Å)[12a,e] than that of typical porphyrins ($r \approx$ 2.0 Å).[27] Interestingly, in the case of the six-coordinate complex, the metal is pulled out of the pentaaza plane by 0.338(4) Å, whereas in the seven-coordinate species, the cadmium is held rigorously within this plane. In both cases, however, the complexes are extremely stable with exposure to excess sulfide anion, for instance, failing to effect demetalation.[12e]

As support for the above solid-state work, $^1H$ NMR spectral titrations were also carried out. They revealed that, in the case of bulky benzimidazole, the monoligated, six-coordinate species $[Cd·1·BzIm]^+$ is favored under most solution-phase conditions ($K_1 = 1.8 \times 10^4$ $M^{-1}$ and $K_2 \approx 13$ $M^{-1}$ in $CDCl_3$). By contrast, pyridine favors the formation of a bisligated, seven-coordinate species (i.e., $[Cd·1·(py)_2]^+$) under a range of conditions ($K_1 \approx 2$ $M^{-1}$ and $K_2 = 315$ $M^{-1}$ in $CDCl_3$). These conclusions were later independently confirmed by Ellis and Kennedy using a $^{113}Cd$ NMR spectroscopic analysis.[28]

As further characterization of these cadmium complexes, detailed investigations of the photoexcited triplet state of the free-base (H·1) and cadmium complex

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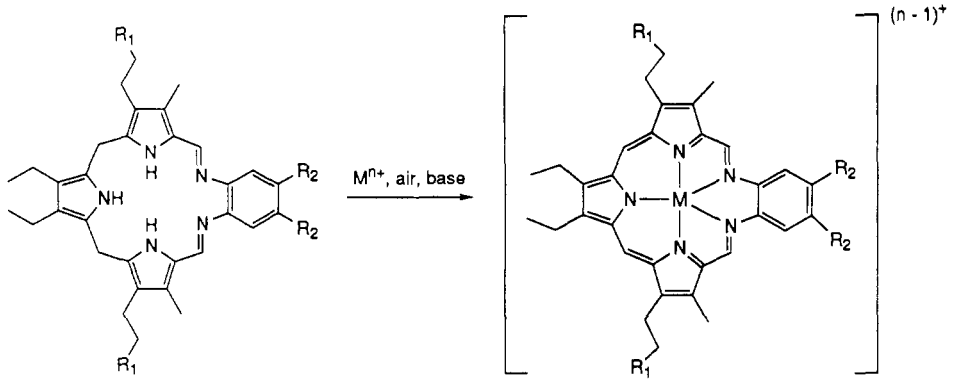
**Scheme 4**




**34** $R_1 = R_2 = H$
**35** $R_1$ =H; $R_2$ = Me
**36** $R_1$ = H; $R_2$ = OMe
**37** $R_1$ = H; $R_2$ = -$O(CH_2CH_2O)_4$-
**38** $R_1$ = H; $R_2$ = $O(CH_2)_3OH$
**39** $R_1$ = $CH_2OH$; $R_2$ = $O(CH_2)_3OH$
**40** $R_1$ = $CH_2OH$; $R_2$ = H

$[M\cdot\mathbf{1}]^{[n-1)+}$ $R_1 = R_2 = H$
$[M\cdot\mathbf{2}]^{[n-1)+}$ $R_1$ =H; $R_2$ = Me
$[M\cdot\mathbf{3}]^{[n-1)+}$ $R_1$ = H; $R_2$ = OMe
$[M\cdot\mathbf{4}]^{[n-1)+}$ $R_1$ = H; $R_2$ = -$O(CH_2CH_2O)_4$-
$[M\cdot\mathbf{5}]^{[n-1)+}$ $R_1$ = H; $R_2$ = $O(CH_2)_3OH$
$[M\cdot\mathbf{6}]^{[n-1)+}$ $R_1$ = $CH_2OH$; $R_2$ = $O(CH_2)_3OH$
$[M\cdot\mathbf{7}]^{[n-1)+}$ $R_1$ = $CH_2OH$; $R_2$ = H

M = Cd(II), Zn(II), Hg(II), Mn(II), etc.; n = 2
M = Gd(III), La(III), Lu(III), Ce(III), Eu(III), Dy(III), Nd(III), Y(III), In(III), etc.; n = 3

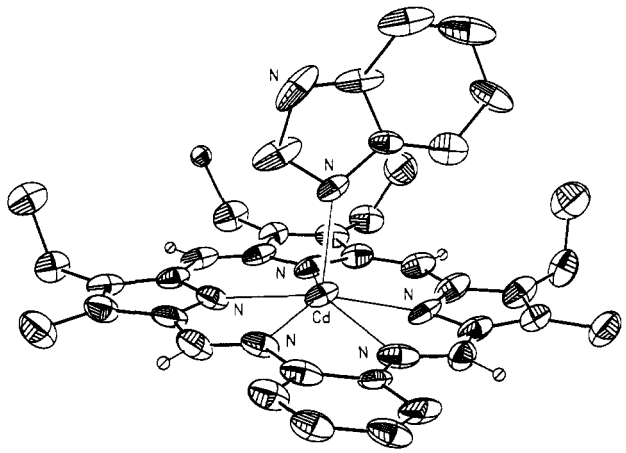



**Figure 3.** View of $[Cd\cdot\mathbf{1}\cdot BzIm]^+$ showing the six-coordinate Cd center. The benzimidazole apical ligand is bound at an N-to-Cd distance of 2.310(9) Å. The metal center itself is 0.338(4) Å above the mean-square pentaaza plane. In this figure and Figures 4–7, the thermal ellipsoids are scaled to the 30% probability level.

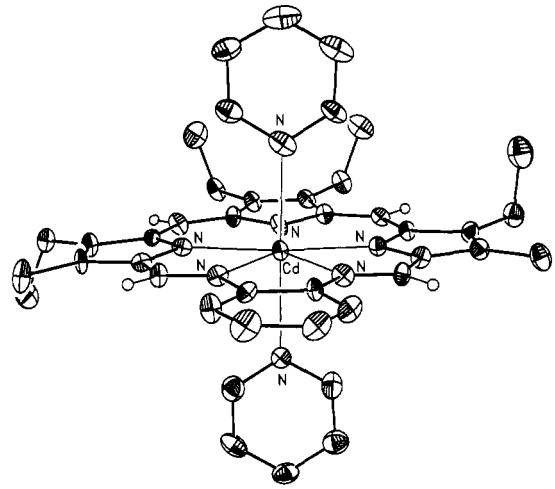



**Figure 4.** View of $[Cd\cdot\mathbf{1}\cdot(py)_2]^+$ showing the overall seven-coordinate Cd center. The Cd atom lies within the plane of the nearly planar macrocycle with the two coordinated pyridine N-to-Cd distances being 2.438(14) and 2.437(12), respectively. The average texaphyrin N-to-Cd distance is 2.392 ± 0.129 Å.

$[Cd\cdot\mathbf{1}]^+$ were carried out as a function of matrix environment by Levanon and co-workers using laser-excitation time-resolved EPR spectroscopy.[29,30] Also, in other physical chemical analyses, the perimeter model was employed by Michl and Waluk to analyze the spectral intensities and MCD signals for a series of porphyrinoid macrocycles derived from the $C_{20}H_{20}^{2+}$ perimeter, including a number of substituted cadmium texaphyrins such as $[Cd\cdot\mathbf{1}]^+$, $[Cd\cdot\mathbf{2}]^+$, $[Cd\cdot\mathbf{11}]^+$, and $[Cd\cdot\mathbf{12}]^+$.[31,32] The results obtained confirmed that the perimeter model accounts in a simple way for the signs of the MCD *B* terms associated with these metallotexaphyrins.

## Cadmium(II) and Other Diamagnetic Texaphyrins as PDT Photosensitizers

To date, considerable effort has been devoted to exploring the ground- and excited-state optical properties of metallotexaphyrins. Much of the impetus here comes from an appreciation that the texaphyrins absorb strongly in the 720–780-nm spectral region. This spectral region is of particular interest in photodynamic therapy (PDT).[33] In general terms, PDT uses a localizing, light-absorbing dye to bring about the oxygen-dependent, photosensitized destruction of unwanted tissue, such as carcinomas. At present, diamagnetic porphyrins and their derivatives are the dyes

(29) Regev, A.; Berman, A.; Levanon, H., Sessler, J. L.; Murai, T. *Chem. Phys. Lett.* **1989**, *160*, 401–409.
(30) Regev, A.; Levanon, H.; Murai, T.; Sessler, J. L. *J. Chem. Phys.* **1990**, *92*, 4718–4723.
(31) Waluk, J.; Michl, J. *J. Org. Chem.* **1991**, *56*, 2729–2735.
(32) Waluk, J.; Hemmi, G.; Sessler, J. L.; Michl, J. *J. Org. Chem.* **1991**, *56*, 2735–2742.
(33) For reviews of PDT, see: (a) Sindelar, W. F.; DeLaney, T. F.; Tochner, Z; Thomas, G. F.; Dachoswki, L. J.; Smith, P. D.; Friauf, W. S.; Cole, J. W.; Glatstein, E. *Arch. Surg.* **1991**, *126*, 318–324. (b) Grossweiner, L. I. *Lasers Surg. Med.* **1991**, *11*, 165–173. (c) Henderson, B. W.; Dougherty, T. J. *Photochem. Photobiol.* **1992**, *55*, 145–157. (d) Moan, J.; Berg, K. *Photochem. Photobiol.* **1992**, *55*, 931–948.

of choice for PDT,[33] in part because they localize and/or are retained selectively in rapidly growing tissues such as sarcomas and carcinomas. Unfortunately, however, porphyrin PDT dyes generally absorb at approximately the same wavelengths as endogenous porphyrins. Thus, the photodynamic effect is drastically reduced. The texaphyrins, on the other hand, absorb in the spectral region where living tissues are relatively transparent (i.e., 700–1000 nm).[12] Thus, they might represent a new type of alternative PDT photosensitizer.[34,35]

The photophysical properties of a number of metallotexaphyrins, namely, $[Cd\cdot\mathbf{1}]^+$, $[Cd\cdot\mathbf{10}]^+$, $[Cd\cdot\mathbf{11}]^+$, $[Cd\cdot\mathbf{12}]^+$, $[Sm\cdot\mathbf{2}]^{2+}$, $[La\cdot\mathbf{6}]^{2+}$, and $[Lu\cdot\mathbf{6}]^{2+}$, have been studied and have revealed three important and near-unique optical properties: (1) strong absorbance in the physiologically important far-red spectral region, (2) high yields for the production of long-lived triplet states, and (3) remarkable efficiency as singlet oxygen producing photosensitizers.[35] In the context of these studies, it was also found that modifying the texaphyrin skeleton (e.g., from $[Cd\cdot\mathbf{10}]^+$ to $[Cd\cdot\mathbf{1}]^+$ to $[Cd\cdot\mathbf{11}]^+$) would allow for a variation of the lowest energy Q-type band absorption maximum anywhere from 629 to 864 nm without reducing substantially the singlet oxygen quantum yield.[35b,c]

To date, several preliminary investigations of the photodynamic activity of the diamagnetic texaphyrins have been carried out.[35c–e] For instance, in one representative *in vitro* study, carried out by Ehrenberg and co-workers,[35b] the cadmium texaphyrin complex $[Cd\cdot\mathbf{1}]^+$ was investigated and found to be very effective in the photoeradication of K562 leukemic cells, being considerably more potent than hematoporphyrin. Importantly, in this and other studies, evidence was also obtained indicating that the macrocycle remained unaffected by the irradiation process.[35] In more recent work, Dr. Alan Oseroff of Roswell Park has found that the diamagnetic lanthanum complex $[La\cdot\mathbf{6}]^{2+}$ is photoactive *in vivo* at the 10 μmol/kg level, sufficing to effect a 65% reduction in a murine adenocarcinoma following a single irradiation with 500 J of 746-nm light.[36a] Similar results have also been obtained by Dr. Michael Burns using $[Lu\cdot\mathbf{6}]^{2+}$.[36b] Taken together, these results have led us to suggest that complexes such as $[La\cdot\mathbf{6}]^{2+}$, $[Lu\cdot\mathbf{6}]^{2+}$, or their analogues could prove useful as PDT sensitizers in a clinical setting.[37]

## Other Metal Complexes. Lanthanide Cation Chelation

Once the basic chemistry of the cadmium complexes had been defined, it became of interest to see if the texaphyrins could be used to support the coordination of other metal cations. Here, it was quickly discovered[12f] that the best non-cadmium(II) salts were those of the trivalent lanthanides, and indeed, texaphyrin complexes of this entire series (except radioactive Pm(III)) have now been prepared.[12i]

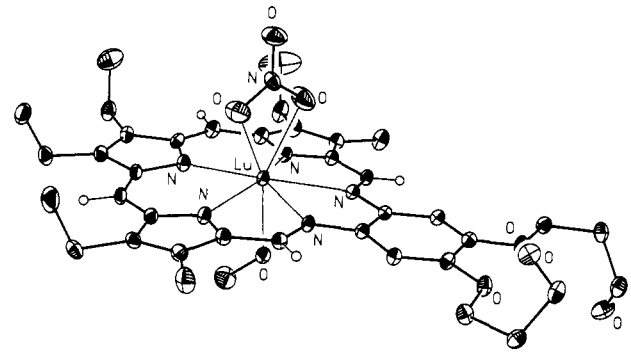



**Figure 5.** View of $[Lu\cdot\mathbf{5}\cdot MeOH\cdot NO_3]^+$ showing the eight-coordinate nature of the complex. The metal center is 0.269 Å above the mean-square pentaaza plane.

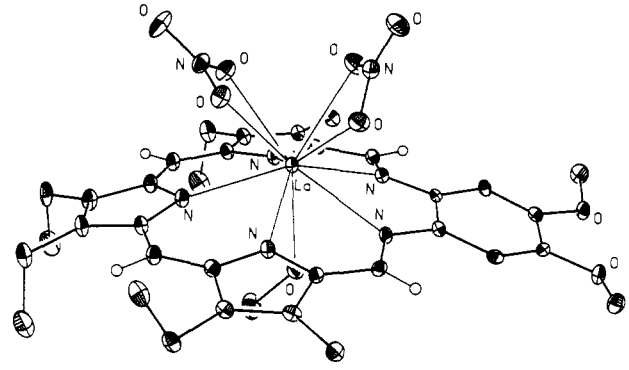



**Figure 6.** View of $[La\cdot\mathbf{3}\cdot MeOH\cdot(NO_3)_2]$ showing the 10-coordinate nature of the complex. The metal center is 0.914 Å above the mean-square pentaaza plane.

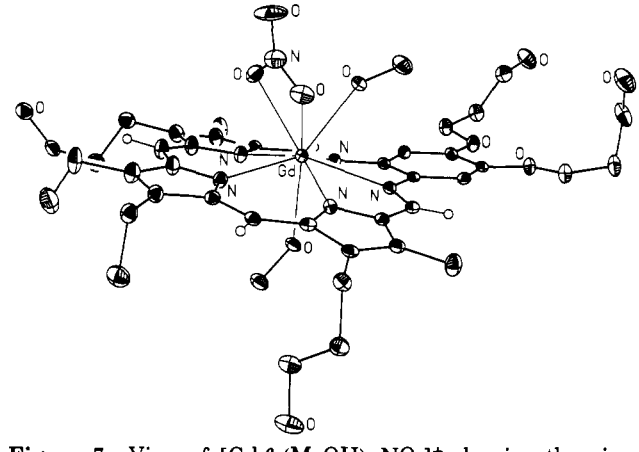



**Figure 7.** View of $[Gd\cdot\mathbf{6}\cdot(MeOH)_2\cdot NO_3]^+$ showing the nine-coordinate nature of the complex. The metal center is 0.595 Å above the mean-square pentaaza plane.

To date, six independent X-ray diffraction crystal structures have been obtained for lanthanide(III) texaphyrin complexes.[12i,38] Four of these, considered representative, are reproduced here as Figures 5–8. The first, shown in Figure 5, is that of the 1:1 lutetium(III) texaphyrin complex, $[Lu\cdot\mathbf{5}\cdot MeOH\cdot NO_3]^+$.[12i] Here, this smallest of the lanthanide(III) cations (eight-coordinate ionic radius, $r_{8c}$ = 0.98 Å[39]) is found to be roughly 0.27 Å above the mean $N_5$ texaphyrin plane. It is also found to be eight-coordinate, being ligated by the five near-planar texaphyrin nitrogens, an apical methanol, and

(34) For a review of new photosensitizers, see: Kreimer-Birnbaum, M. *Sem. in Hematol.* **1989**, *26*, 157–173.

(35) (a) Harriman, A.; Maiya, B. G.; Murai, T.; Hemmi, G.; Sessler, J. L.; Mallouk, T. E. *J. Chem. Soc., Chem. Commun.* **1989**, 314–316. (b) Maiya, B. G; Harriman, A.; Sessler, J. L.; Hemmi, G.; Murai, T.; Mallouk, T. E. *J. Phys. Chem.* **1989**, *93*, 8111–8115. (c) Sessler, J. L.; Hemmi, G.; Maiya, B. G.; Harriman, A.; Judy, M. L.; Boriak, R.; Matthews, J. L.; Ehrenberg, B.; Malik, Z.; Nitzan, Y. Rück, A. *Proc. SPIE Int. Opt. Eng.* **1991**, *1426*, 318–329. (d) Ehrenberg, B.; Malik, Z.; Nitzan, Y.; Ladan, H.; Johnson, F. M.; Hemmi, G.; Sessler, J. L. *Lasers Med. Sci.* **1993**, *8*, 197–203. (e) Harriman, A. Unpublished results.

(36) (a) Oseroff, A. Unpublished results. (b) Berns, M. Unpublished results.

(37) Sessler, J. L. *Discover* **1993**, *13*, 44–49.

(38) Lynch, V. Unpublished results.

(39) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751–767.

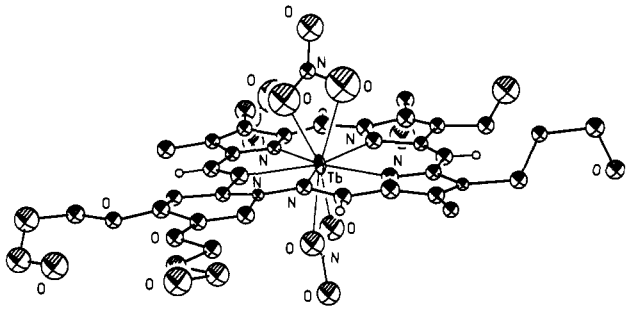


**Figure 8.** View of [Tb·6·$(NO_3)_2$] showing the in-plane nature of the nine-coordinate metal center. Except for the Tb(III) atom, the structure was refined isotropically. Thermal ellipsoids are scaled to the 20% probability level.

an $\eta^2$ nitrate anion. On the other hand, the near-congeneric lanthanum complex [La·3·MeOH·$(NO_3)_2$],[12i] shown in Figure 6, is 10-coordinate and has this largest of the lanthanide(III) cations ($r_{10c}$ = 1.27 Å[39]) raised up out of the mean $N_5$ plane by roughly 0.91 Å. Finally, X-ray structural analysis of the two intermediate-sized lanthanide cations, gadolinium(III) and terbium(III) ($r_{9c}$ = 1.11 and 1.10 Å, respectively[39]), reveals that both are nine-coordinate when complexed to the tetrahydroxylated texaphyrin, H·6 (Figures 7 and 8). In the case of the gadolinium complex,[12i] [Gd·6·$(MeOH)_2$·$NO_3$]$^+$ (Figure 7), the metal center is found to lie 0.595 Å above the mean $N_5$ plane while being bound not only by the pentadentate texaphyrin ligand but also by a bidentate nitrate anion and a pair of transverse-ligating methanol molecules. By contrast, the metal center in the terbium complex, [Tb·6·$(NO_3)_2$] (Figure 8),[38] is revealed to be rigorously within the ca. 2.4 Å radius pentaaza core. In this latter instance, however, the non-texaphyrin ligation sphere is found to be completely symmetric. Thus, these comparative results, which are reminiscent of those obtained earlier in the case of cations [Cd·1·BzIm]$^+$ and [Cd·1·$(py)_2$]$^+$ (Figures 3 and 4),[12e] serve to highlight the way in which the intimate details of the various lanthanide(III) texaphyrin structures are a sensitive function of the number and type of axial ligand.

The near-to-complete in-plane metal coordination observed for the lanthanide *texaphyrins* stands in marked contrast to what is observed in the case of lanthanide *porphyrins*. Here, dimeric 2:1 or trimeric 3:2 sandwich-type structures or very-far-out-of-plane 1:1 "sitting atop" complexes are always observed.[40] Such structures, which are reflective of the poor match between the large trivalent lanthanide ions and the small (relatively speaking) central porphyrin core, are characterized by a degree of solution phase complex instability that is not observed in the corresponding texaphyrin complexes. For instance, whereas gadolinium(III) porphyrins are known to undergo rapid demetalation in the presence of EDTA,[41] the water soluble gadolinium(III) texaphyrin complex, [Gd·6]$^{2+}$, was found to be stable for over 2 months when stored in solution at room temperature in the presence of a $10^4$ molar excess of EDTA.[12i] This enhanced stability has led us, in turn, to suggest that the lanthanide texaphyrins could find use in a range of applications, including magnetic resonance imaging enhancement, where the more labile porphyrins might prove unsuitable.[12b,i,37]

(40) See, for instance: (a) Schaverien, C. J.; Orpen, A. G. *Inorg. Chem.* **1991**, *30*, 4968–4978. (b) Buchler, J. W.; De Cian, A.; Fischer, J.; Kihn-Botulinski, M.; Paulus, H.; Weiss, R. *J. Am. Chem. Soc.* **1986**, *108*, 3652–3659. (c) Buchler, J. W.; Löffler, J.; Wicholas, M. *Inorg. Chem.* **1992**, *31*, 524–526 and references cited therein.

(41) Hambright, P.; Adams, C.; Vernon, K. *Inorg. Chem.* **1988**, *27*, 1660–1662.

## Gadolinium(III) Texaphyrin Complexes as Potential MRI Contrast Agents

Magnetic resonance imaging, or MRI, is now firmly entrenched as a clinical tool of prime import. It is used, for instance, in the diagnosis and staging of a variety of diseases.[42] Unfortunately, however, the difference in MRI signal for diseased *vs* normal tissues is often small, and this militates against the use of this approach in certain clinical situations. To overcome this problem, considerable effort is currently being devoted to the preparation of MRI contrast reagents. Here, highly paramagnetic metal complexes, such as those derived from gadolinium(III) (which has seven unpaired electrons), have been the focus of greatest attention.[42b,c]

At present, three gadolinium(III)-derived MRI contrast agents have been approved for human clinical use in the United States, namely, the bis-*N*-methylglucamine salt of Gd(III) diethylenetriaminepentaacetic acid (DTPA) (Magnevist), the bis-*N*-methylamide of Gd(III) DTPA (Omniscan), and the Gd(III) chelate of the 10-(2-hydroxypropyl) derivative of 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-1,4,7-triacetic acid (Prohance). All three of these agents are carboxylate-containing, water soluble complexes that act as so-called extracellular markers. As such, they allow for an increase in image intensity and resolution in cases that are associated with changes in blood flow. They do not, however, work well for the contrast enhancement of many internal organs or for the imaging of most solid tumors. Thus, there is considerable interest associated with the development of target-specific MRI contrast agents that might allow for the improved imaging of these loci.

As mentioned above in the context of PDT, one of the more promising approaches to achieving selective tumor targeting involves the use of porphyrins. They, thus, represent a logical choice for the development of tumor-targeting MRI contrast agents, and indeed, considerable work along these lines is currently being carried out in the context of Mn(III) systems.[43] Unfortunately, however, gadolinium(III), which is the single most paramagnetic atomic cation, is not held well by the porphyrins (see discussion above), making this particular metal–ligand combination unsuitable for use *in vivo*.[44] The fact that the texaphyrins chelate gadolinium(III) while retaining many of the basic

(42) For reviews of MRI , see: (a) Edelman, R.; Warach, S. *N. Engl. J. Med.* **1993**, *328*, 708–716. (b) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901–927. (c) Tweedle, M. F.; Brittain, H. G.; Eckelman,W. C.; Gaughan, G. T.; Hagan, J. J.; Wedeking, P. W.; Runge, V. M. In *Magnetic Resonance Imaging*, 2nd ed.; Partain, C. L., Ed.; W. B. Saunders: Philadelphia, 1988; Vol. 1, pp 793–809. (d) Moonen, C. T.; van-Zijil, P. C.; Frank, J. A.; Le-Bihan, D.; Becker, E. D. *Science* **1990**, *250*, 53–61. (e) Young, S. W. *Magnetic Resonance Imaging: Basic Principles*; Raven Press: New York, 1988; pp 1–282.

(43) See, for instance: (a) Chen, C.-W.; Cohen, J. S.; Myers, C. E.; Sohn, M. *FEBS Lett.* **1984**, *168*, 70–74. (b) Patronas, N. J.; Cohen, J. S.; Knop, R. H.; Dwyer, A. J.; Colcher, D.; Lundy, J.; Mornex, F.; Hambright, P.; Sohn, M.; Myers, C. E. *Cancer Treat. Rep.* **1986**, *70*, 391–395. (c) Bohdiewicz, P. J.; Lavallee, D. K.; Fawwaz, R. A.; Newhouse, J. H.; Oluwole, S. F.; Alderson, P. O. *Invest. Radiol.* **1990**, *25*, 765–770 and references therein. See also refs 42b and 44.

(44) Lyon, R. C.; Faustino, P. J.; Cohen, J. S.; Katz, A.; Mornex, F.; Colcher, D.; Baglin, C.; Koenig, S. H.; Hambright, P. *Magn. Reson. Med.* **1987**, *4*, 24–33.

features of the porphyrins could make them advantageous in MRI.[12i,37,45]

As a first step toward testing the above possibility, measurements of the *in vitro* relaxivity of $[Gd\cdot\mathbf{6}]^{2+}$ were made. Here, Sherry and Geraldes found the longitudinal relaxivity, $R_1$, of this complex to be 16.9 ± 1.5 $mM^{-1}$ $s^{-1}$ at 50 MHz in aqueous solution at room temperature,[46] a value that was later confirmed by Stuart Young and co-workers.[45,47] Then, as the next step, this same complex was tested *in vivo* at Stanford using a variety of animal models. Here, for instance, it was found that good image enhancement of implanted V2 carcinomas could be achieved in rabbits at doses as low as 5 μmol/kg (Figure 9) and that viable liver image augmentation was obtained in these same animals when doses as low as 2 μmol/kg were used.[45b] Further, no signs of acute toxicity were observed in the context of any of these studies, and indeed, no serious toxicity has been observed in healthy rats given daily 20 μmol/kg doses of $[Gd\cdot\mathbf{6}]\cdot(acetate)_2$.[45] Thus, the quantities needed for tumor and target organ enhancement appear to be safe in both an acute and a subchronic sense. This is considered to augur well for the eventual use of this or related Gd(III) texaphyrin-type agents in clinical MRI applications.

## Conclusions

The texaphyrins and their metal complexes represent a new type of expanded porphyrin with tremendous promise. For instance, in terms of biomedicine, it is conceivable that they will have a role to play in both MRI and PDT. Indeed, it is not too difficult to imagine that it might be possible to detect a benign or malignant tumor *via* MRI using a paramagnetic gadolinium(III)-containing texaphyrin and then, by switching to an analogous diamagnetic complex, destroy this same tumor mass photodynamically.[37] On the chemical front, the texaphyrins could help to open up the coordination chemistry of less explored areas of the periodic table. For instance, the finding that congeneric lanthanide complexes may be stabilized within the context of a near-planar pentadentate coordination geometry[12i,38] and that crystalline uranyl complexes may be stabilized in related pyrrole-containing Schiff base systems (e.g., **16**)[18] affords the opportunity for future studies of chemical reactivity. Likewise, the discovery that anionic entities are complexed by nonaromatic texaphyrins, such as **13** and **34**,[2b,12c,21] and that neutral substrates may be bound by big systems, such as the crystallographically characterized, bipyrrole-derived octaaza system **17**,[19] leads us to suggest that the generalized class of pyrrole-containing Schiff base macrocycles may have an important role to play in the ever-emerging area of molecular recognition. Thus, we feel that the texaphyrins and related systems could be of interest for years to come.

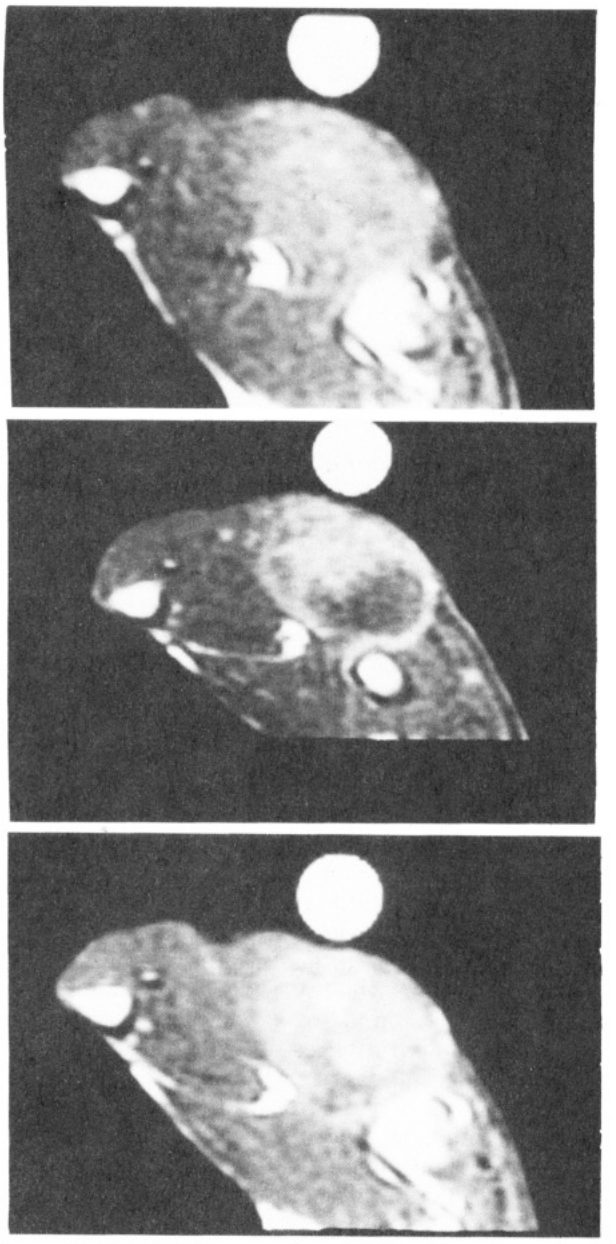


**Figure 9.** Axial MRI scans of a rabbit bearing a transplanted V2 carcinoma in thigh muscle (a, top) before, (b, middle) 30 min after, and (c, bottom) 3 h after the administration of 5 μmol of Gd(III) texaphyrin $[Gd\cdot\mathbf{6}]\cdot(acetate)_2$/kg of body weight. See ref 45b for further details.

*We are grateful to the numerous cited collaborators whose dedicated efforts have helped advance the state of texaphyrin-related chemistry. We are particularly grateful to Dr. Vincent Lynch for his help with crystallography and to Drs. A. Dean Sherry, Carlos F. G. C. Geraldes, Alan Oseroff, and Michael Burns for making results available prior to publication. Support to J.L.S. from the National Institutes of Health (AI 28845), National Science Foundation (PYI 1986 and CHE 9122161), Camille and Henry Dreyfus Foundation, Alfred P. Sloan Foundation, and Pharmacyclics, Inc., is also acknowledged with deep appreciation.*

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(46) Sherry, A. D.; Geraldes, C. F. G. C. Unpublished results.

(47) This exceptionally high relaxivity is rationalized both in terms of the X-ray structure of $[Gd\cdot\mathbf{6}\cdot(MeOH)_2\cdot NO_3]^+$, which suggests that between four and five water molecules could have access to the metal center in aqueous solution, and in terms of spin–orbit interactions between the texaphyrin π-system and the chelated metal center. These latter interactions have been postulated previously in the case of water soluble Mn(III) porphyrins. See ref 43a.