Synthesis and characterization of a novel series of bis-linked diaza-18-crown-6 porphyrins

Caroline Comte,[a] Claude P. Gros,[a] Sylvain Koeller,[a] Roger Guilard,*[,a] Daniel J. Nurco[b] and Kevin M. Smith[b]

[a] *Laboratoire d'Ingénierie Moléculaire pour la Séparation et les Applications des Gaz (LIMSAG, CNRS UMR 5633), Faculté des Sciences "Gabriel", 6, boulevard Gabriel, 21000 Dijon, France*
[b] *Department of Chemistry, University of California, Davis, CA 95616, USA*

The synthesis and physicochemical characterization of a novel family of 'crowned-porphyrins' is presented. The compounds uniquely possess a 5,15-di(2-alkylamidophenyl)etioporphyrin bis-linked to the nitrogens on opposite sides of a 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane moiety. The size of the cavity in between the porphyrin and the diaza-18-crown-6 ring has been regulated by varying the length of the alkylamido linking units. The structures of **5** and **7** bear diacetamido linkers whereas **6** is linked *via* dipropionamido groups. The synthetic pathway presented is generalized such that a wide variety of useful porphyrin-based bis-macrocycles can be prepared. Products have been fully characterized by elemental analysis, mass spectrometry, spectrophotometry, ^{1}H NMR, ^{13}C NMR and ^{1}H–^{13}C heteronuclear correlation NMR spectroscopies. X-Ray structural data are presented for the free-base porphyrin **6** and the Zn^{II} porphyrin **7**. The structural data confirm that the porphyrins and their diaza-18-crown-6 substituents adopt cofacial orientations. The size of the cavity between the macrocycles, while demonstrated to accommodate small molecules as shown by the binding of H_2O as an axial ligand to the central Zn^{II} ion in the crystal structure of **7**, will probably not accommodate large ligands or substrates. Moreover, these compounds should allow sequential metallations to yield heterobimetallic species. Therefore, they are ideally suited for study as model systems for biologically important heme-dependent phenomena such as xenon-129 binding to myoglobin or the mimicking of processes related to the structure and function of cytochrome c oxidase.

Porphyrin-type chromophores and reduced porphyrin derivatives are of importance as mimics for a variety of biological processes[1–10] such as those catalyzed by cytochrome c oxidase and monooxygenase enzymes.[11–14] A large number of natural porphyrin-based systems have two active sites held in close proximity to each other, and this has prompted substantial interest in the chemistry of ditopic receptors. Included among this area of research are projects involving synthetic materials in which porphyrins and other heteromacrocycles are covalently linked.[15–21] Approaches towards this goal have yielded a multitude of structurally diverse porphyrins located in well-defined chemical environments. Most of these compounds are embellished derivatives of the basic di- and tetra-arylporphyrin frameworks due to their ease of preparation and high symmetry;[22–24] in some cases, the molecular architecture of 5,15-diarylporphyrins can be more readily manipulated than that of the corresponding tetraarylporphyrins.[25,26] Numerous researchers have also focused on the selective recognition of organic molecules and gases by metallohosts[27] and on the growing field of ditopic receptor synthesis.

One of our major interests is to study possible interactions between xenon and tailor-made 'bridged' porphyrins. Most reported bridged porphyrins have been prepared in order to probe the steric contribution to the differentiation between CO and O_2 binding that occurs in the hemoproteins.[15,16] However, little attention, if any, has been given to whether or not a physical interaction occurs between xenon and synthetic mimics of natural systems containing two closely positioned active sites (*e.g.*, a crown ether and a porphyrin). It is now well-established that xenon, which is sometimes considered to be 'inert', interacts with many biological and synthetic systems including myoglobin and hemoglobin. For example, Claessens *et al.*[28] have shown that an uncharged and spherical species like xenon can be complexed by cyclic molecules like crown ethers. The reasons for these interactions appear to be rooted in both the presence of oxygen atoms in the crown ether and in the shapes of the substrate and host molecules.[28] Xenon-129 NMR spectroscopy is a potential probe for the structural and dynamic aspects of the molecular environment of the xenon atom in physical and biological media, and chemical shifts are especially reflective of an atom's environment due to its large polarizable electron cloud. It has been found that during xenon anesthesia about 45% of the xenon in blood is carried by hemoglobin.[29,30] X-Ray diffraction analysis has shown that xenon binds to a specific site on sperm whale myoglobin. This site, which is buried in the interior of the protein, is nearly equidistant from the heme prosthetic group and the ring of the heme-linked histidine.[31–34]

With this background, we wish to report the synthesis of two novel ditopic ligands. These ligands feature a 5,15-di(2-alkylamidophenyl)etioporphyrin doubly bridged to a diaza-18-crown-6 moiety, and they possess well-defined binding sites on the crown ring, which is held in close proximity to the porphyrin core. Moreover, such 'crowned-porphyrins' also have the ability to accommodate a transition metal ion and a Group 1A or 2A cation simultaneously.

Experimental

Physical measurements

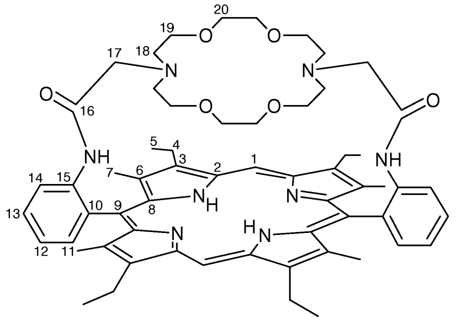
UV/VIS spectra were recorded on a Varian Cary 1 spectrophotometer. Mass spectra were obtained with a Kratos Concept 32 S spectrometer in LSIMS mode (matrix: *m*-nitrobenzyl alcohol) or in EIMS mode. Data were collected and processed using a Sun 3/80 workstation. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 Fourier transform spectrometer at the Centre de Spectrométrie Moléculaire de l'Université de Bourgogne. All chemical shifts are given downfield from internal tetramethylsilane. NMR data are presented in the following order: chemical shift, integration, peak multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, *etc.*) and assignment. The compounds 5,15-bis(*o*-nitrophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin **1** and 5,15-bis(*o*-aminophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin **2** were synthesized by previously reported methods.[23,25,26]

Syntheses

5,15-Bis(*o*-chloroacetamidophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 3. A 250 mL Erlenmeyer flask was charged with porphyrin **2** (150 mg, 0.23 mmol), chloroform (100 mL) and a solution of chloroacetyl chloride (72 μL, 0.91 mmol) in chloroform (10 mL). Stirring at room temperature was continued for 2 h before a 10^{-2} M aqueous potassium hydroxide solution (10 mL) was added. The organic phase was separated, washed with water (to pH 7), then brine (30 mL), dried over $MgSO_4$ and evaporated to dryness. The *cis* dichloroporphyrin **3** was isolated as a purple powder (168 mg, 90%). UV/VIS [dichloromethane, λ_{max}/nm ($\varepsilon \times 10^{-3}$/mol^{-1} 1 cm^{-1})]: 407 (179), 506 (15.1), 540 (6.5), 574 (6.6), 625 (3.0). MS (EI): 814 ($[M]^+$, 100), 778 ($[M - Cl]^+$, 9), 764 ($[M - CH_2Cl]^+$, 26), 736 ($[M - COCH_2Cl]^+$, 15), 721 ($[M - NHCOCH_2Cl]^+$, 18). ^1H NMR ($CDCl_3$) δ: −2.40 (2H, s, NH), 1.83 (12H, t, CH_2CH_3), 2.60 (12H, s, CH_3), 3.48 (4H, s, CH_2Cl), 4.10 (8H, q, CH_2CH_3), 7.60 (2H, t, H_{12}), 7.90 (4H, m, H_{11} and H_{13}), 8.30 (2H, s, NH amide), 8.83 (2H, d, H_{14}), 10.30 (2H, s, *meso*). ^{13}C NMR ($CDCl_3$) δ: 14.0 (CH_3), 18.0 (CH_2CH_3), 20.4 (CH_2CH_3), 42.9 (CH_2Cl), 97.6 (*meso*), 111.2, 120.8, 125.2, 130.6, 132.0, 134.3, 136.0, 138.4, 142.3, 145.6, 146.0, 164.7 (CO). Anal. calcd for $C_{48}H_{50}Cl_2N_6O_2$: C, 70.84; H, 6.19; N, 10.33. Found: C, 70.56; H, 6.09; N, 10.09.

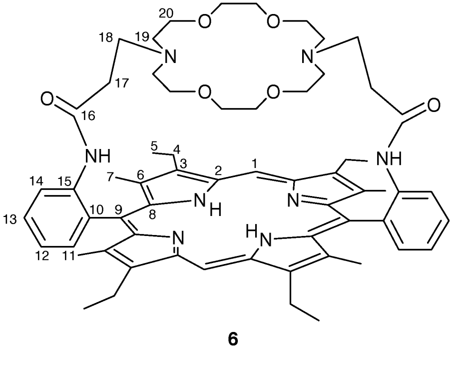
5,15-Bis(*o*-chloropropionamidophenyl)-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 4. This compound was prepared by the method used for **3** using the *cis* diaminoporphyrin **2** (110 mg, 0.17 mmol), chloroform (80 mL) and a solution of chloropropionyl chloride (63 μL, 0.67 mmol) in chloroform (10 mL). The *cis* dichloro-porphyrin **4** was isolated as a purple powder (140 mg, 89%). UV/VIS [dichloromethane, λ_{max}/nm ($\varepsilon \times 10^{-3}$/mol^{-1} 1 cm^{-1})]: 407 (173.2), 507 (14.7), 541 (6.6), 574 (6.7), 626 (3.0). MS (EI): 842 ($[M]^+$, 100), 807 ($[M - Cl]^+$, 8). ^1H NMR ($CDCl_3$) δ: −2.4 (2H, s, NH), 1.76 (4H, t, CH_2CH_2Cl), 1.81 (12H, t, CH_2CH_3), 2.58 (12H, s, CH_3), 3.26 (4H, t, CH_2CH_2Cl), 4.06 (8H, q, CH_2CH_3), 7.02 (2H, s, NH amide), 7.58 (2H, t, H_{12}), 7.90 (4H, m, H_{11} and H_{13}), 8.85 (2H, d, H_{14}), 10.33 (2H, s, *meso*). ^{13}C NMR ($CDCl_3$) δ: 14.0 (CH_3), 18.0 (CH_2CH_3), 20.6 (CH_2CH_3), 39.8, 40.5, 97.6 (*meso*), 111.6, 121.2, 124.8, 130.5, 131.3, 134.0, 136.4, 139.0, 142.2, 145.6, 146.1, 168.2 (CO). Anal. calcd for $C_{50}H_{54}Cl_2N_6O_2$: C, 71.33; H, 6.46; N, 9.98. Found: C, 71.06; H, 6.55; N, 9.70.

5,15-[2,2′-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)diacetamidophenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 5. A 250 mL round-bottom flask, equipped with a reflux condenser, was charged with porphyrin **3** (150 mg, 0.185 mmol), ethanol (150 mL) and 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (243 mg, 0.923 mmol) and refluxed for 2 days. After evaporating the solvent under vacuum, the residue was taken up in dichloromethane (150 mL) and the organic solution was washed with water, dried over $MgSO_4$ and evaporated to dryness to give a brown residue. The residue was chromatographed on a silica gel column eluted with dichloromethane–methanol (95 : 5). The product **5** was isolated as a lustrous purple powder (141 mg, 76%) after precipitation from dichloromethane–heptane. UV/VIS [dichloromethane, λ_{max}/nm ($\varepsilon \times 10^{-3}$/mol^{-1} 1 cm^{-1})]: 407 (186), 505 (15.7), 539 (5.2), 573 (6.7), 625 (2.8). MS (LSIMS): 1004 ($[M + H]^+$, 100), 1027 ($[M + Na]^+$, 21). ^1H NMR ($CDCl_3$) δ: −2.30 (2H, s, NH), −0.10 [8H, b, $(CH_2)_{crown\ ether}$], 0.58 [8H, b, $(CH_2)_{crown\ ether}$], 1.50 [8H, b, $(CH_2)_{crown\ ether}$], 1.90 (12H, t, CH_2CH_3), 2.60 (12H, s, CH_3), 2.70 [4H, s, $(CH_2)_{bridge}$], 4.10 (8H, q, CH_2CH_3), 7.50 (2H, t, H_{12}), 7.72 (2H, d, H_{11}), 7.86 (2H, t, H_{13}), 9.00 (2H, d, H_{14}), 9.47 (2H, s, NH amide), 10.30 (2H, s, H *meso*). ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_3), 18.3 (CH_2CH_3), 20.3 (CH_2CH_3), 53.8 $(CH_2)_{crown\ ether}$, 61.8 $(CH_2)_{bridge}$, 68.1 $(CH_2)_{crown\ ether}$, 68.5 $(CH_2)_{crown\ ether}$, 97.4 (*meso*), 113.0, 120.0 (C_{14}), 124.0 (C_{12}), 130.6 (C_{13}), 130.9, 134.5 (C_{11}), 137.0, 139.0, 141.7, 145.4, 145.9, 170.1 (CO). Anal. calcd for $C_{60}H_{74}N_8O_6$: C, 71.83; H, 7.43; N, 11.17. Found: C, 71.61; H, 7.24; N, 10.83.



5

5,15-{2,2′-[3,3′-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)dipropionamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 6. This compound was prepared in the same fashion as **5** using the porphyrin **4** (100 mg, 0.12 mmol), 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (156 mg, 0.59 mmol) and ethanol (150 mL). After silica gel column chromatography, eluted with dichloromethane, the porphyrin **6** was isolated as a purple powder (30 mg, 25%). UV/VIS [dichloromethane, λ_{max}/nm ($\varepsilon \times 10^{-3}$/mol^{-1} 1 cm^{-1})]: 410 (229), 506 (18.3), 541 (6.6), 574 (7.7), 625 (2.7). MS (LSIMS): 1055 ($[M + Na]^+$, 100), 1033 ($[M + H]^+$, 29). ^1H NMR ($CDCl_3$) δ: −2.30 (2H, s, NH), −0.10 [8H, b, $(CH_2)_{19}$], 1.00 [8H, b, $(CH_2)_{20}$], 1.90 (12H, t, CH_2CH_3), 2.00 [4H, t, $(CH_2)_{17/18}$], 2.15 [18H, m, $(CH_2)_{17/18}$ and $(CH_2)_{21}$], 2.60 (12H, s, CH_3), 4.10 (8H, m, CH_2CH_3), 7.40 (2H, t, H_{12}), 7.50 (2H, d, H_{11}), 7.80 (2H, t, H_{13}), 9.00 (2H, d, H_{14}), 10.30 (2H, s, H *meso*), 11.00 (2H, s, NH amide). ^{13}C NMR ($CDCl_3$) δ: 13.9 (CH_3), 18.3 (CH_2CH_3), 20.3 (CH_2CH_3), 34.0 [$(CH_2)_{17/18}$], 46.8 [$(CH_2)_{17/18}$], 50.6 [$(CH_2)_{19}$], 65.8 [$(CH_2)_{20}$], 68.6 [$(CH_2)_{21}$], 97.4 (*meso*), 114.5, 121.5 (C_{14}), 124.0 (C_{12}), 130.2 (C_{13}), 131.1, 134.8 (C_{11}), 137.0, 140.2, 141.9, 145.4, 146.1, 172.4 (CO). Anal. calcd for $C_{62}H_{78}N_8O_6 \cdot H_2O$: C, 70.96; H, 7.68; N, 10.67. Found: C, 70.90; H, 7.45; N, 10.62.



6

Zinc(II) 5,15-[2,2′-(1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)diacetamidophenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 7. A 250 mL round-bottom flask, equipped with a reflux condenser, was charged with the porphyrin **5** (32 mg, 0.032 mmol) and dichloromethane (30 mL). Zinc acetate dihydrate (9 mg, 0.048 mmol) in methanol (20 mL) was added. The mixture was heated under reflux for 1 h followed by removal of the solvent. The residue was taken up in dichloromethane (150 mL), washed with water, dried over $MgSO_4$ and evaporated to dryness. The porphyrin **7** was isolated as a lustrous purple powder (30 mg, 90%) after precipitation from dichloromethane–heptane. UV/VIS [dichloromethane, λ_{max}/nm ($\varepsilon \times 10^{-3}$/mol^{-1} 1 cm^{-1})]: 418 (312), 546 (17.8), 582 (9.1). MS (LSIMS): 1090 ($[M + Na]^+$, 12), 1068 ($[M + H]^+$, 100). ^1H NMR ($CDCl_3$) δ: 0.63 [4H, b, $(CH_2)_{crown\ ether}$], 0.90 [4H, b, $(CH_2)_{crown\ ether}$], 1.50 [4H, b, $(CH_2)_{crown\ ether}$], 1.57 [4H, b, $(CH_2)_{crown\ ether}$], 1.84 (12H, t, CH_2CH_3), 2.18 [8H, b, $(CH_2)_{crown\ ether}$], 2.49 (12H, s, CH_3), 2.57 [4H, s, $(CH_2)_{bridge}$], 3.98 (8H, q, CH_2CH_3), 7.50 (2H, t, H_{12}), 7.80 (2H, d, H_{11}), 7.82 (2H, t, H_{13}), 9.14 (2H, d, H_{14}), 9.23 (2H, s, NH amide), 10.30 (2H, s, H *meso*). ^{13}C NMR ($CDCl_3$) δ: 14.4 (CH_3), 18.6 (CH_2CH_3), 20.3 (CH_2CH_3), 54.7 59.8 $(CH_2)_{bridge}$, 68.4, 69.0, 97.6 (*meso*), 111.0, 119.3, 124.3, 130.0, 133.0, 135.3, 138.0, 139.3, 145.1, 146.7, 148.2, 169.9 (CO). Anal. calcd for $C_{60}H_{72}N_8O_6Zn \cdot H_2O$: C, 66.44; H, 6.88; N, 10.33. Found: C, 66.58; H, 6.85; N, 10.37.

X-Ray crystallography

5,15-{2,2′-[3,3′-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)dipropionamido]phenyl}-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 6. Single crystals were grown from $CDCl_3$–*n*-hexane. The selected specimen was a purple block with dimensions of 0.44 × 0.38 × 0.30 mm. Experimental parameters were as follows: $C_{62}H_{78}N_8O_6$, $M = 1031.36$, triclinic, space group $P\bar{1}$ (no. 2), $a = 10.793(2)$ Å, $b = 14.955(2)$ Å, $c = 17.147(3)$ Å, $\alpha = 82.010(12)°$, $\beta = 79.725(13)°$, $\gamma = 86.694(12)°$, $U = 2695.5(7)$ Å^3 (determined from 41 centered reflections, $6.5° < 2\theta < 74.3°$), $Z = 2$, $\rho_{calc} = 1.274$ g cm^{-3}, $F(000) = 1111$, $\mu = 0.66$, $t_{min} = 0.81$, $t_{max} = 0.85$. Of 7717 reflections collected (with 2.2% decay of two standards measured every 200 reflections) 7043 were unique ($R_{int} = 0.03$). The structure was solved using direct methods. The diaza-18-crown-6 ring exhibited disorder in the positions of several of its carbon and all of its oxygen atoms, with most of these atoms occupying two or three sites. The disordered atoms were refined with fixed isotropic thermal parameters. The occupancies for all of the sites for each disordered atom were summed to unity. A few hydrogens, found on a difference map, were assigned to the well-behaved portion of the diaza-18-crown-6 ring and allowed to refine freely; otherwise the rest of the diaza-18-crown-6 ring was not assigned hydrogens. Hydrogens in the porphyrin core and on the amides were located on difference maps and allowed to refine freely. All other hydrogens were generated by their idealized geometry and refined with a riding model. The final cycle of refinement converged with $R1 = 0.085$ [observed data $> 2\sigma(I)$], $wR2 = 0.275$ (all data),[35] and g.o.f. = 0.946. The final difference map had a largest peak of 0.57 e Å^{-3} and a largest hole of -0.63 e Å^{-3}; 745 parameters and 13 restraints were used in the refinement.

Zinc(II) 5,15-[2,2′-(1,4,10,13-tetraoxa-7,16-diazacyclooctadecan-7,16-diyl)diacetamidophenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin 7. Single crystals were grown from MeOH–THF–H_2O. The selected specimen was a red parallelepiped with dimensions of 0.34 × 0.14 × 0.08 mm. Experimental parameters were as follows: $C_{60}H_{74}N_8O_7Zn$, $M = 1084.64$, monoclinic, space group $P2_1/c$ (no. 14), $a = 18.098(3)$ Å, $b = 16.917(2)$ Å, $c = 17.421(6)$ Å, $\beta = 96.90(2)°$, $U = 5295(2)$ Å^3 (determined from 28 centered reflections, $7.2° < 2\theta < 86.7°$), $Z = 4$, $\rho_{calc} = 1.361$ g cm^{-3}, $F(000) = 2304$, $\mu = 1.15$, $t_{min} = 0.85$, $t_{max} = 0.92$. Of 7554 reflections collected (with no decay of 2 standards measured every 200 reflections) 7283 were unique ($R_{int} = 0.020$). The structure was solved by location of the Zn on the Patterson map and a subsequent structure expansion. The central Zn^{II} ion was pentacoordinate and featured an axial H_2O in between the porphyrin macrocycle and the attached diaza-18-crown-6 ring. Hydrogens on the amines and the H_2O were located on a difference map; the amide hydrogens were allowed to refine freely and the H_2O hydrogens had bond lengths restricted to 1.00(5) Å. All other hydrogens were generated by their idealized geometry and refined with a riding model. The final cycle of refinement converged with $R1 = 0.042$ [observed data $> 2\sigma(I)$], $wR2 = 0.105$ (all data),[35] and g.o.f. = 1.024. The final difference map had a largest peak of 0.64 e Å^{-3} and a largest hole of -0.33 e Å^{-3}; 709 parameters were used in the refinement.

For the structures of both **6** and **7** crystals were transferred directly from their mother liquors of crystallization to a light hydrocarbon oil (Paraton N) in which they were examined and cut as necessary. The selected specimens were affixed to glass fibers with a small amount of silicon grease and mounted on a Siemens P4 diffractometer equipped with a locally modified LT-2 cooling device [operating at 130(2) K] and a rotating anode [λ(Cu Kα) = 1.54178 Å (nickel filtered)] operating at 15.0 kW. Calculations were performed with Siemens SHELXTL V. 5.03 software. Scattering factors were used as provided with the software package. The structures were refined (based on $|F^2|$ using all independent reflections) with full-matrix least-squares methods. Empirical absorption corrections were applied.[36] Unless otherwise noted all non-hydrogen atoms were refined with anisotropic thermal parameters.

CCDC reference number 440/030.

Results and Discussion

Syntheses

In light of the foregoing introduction, it is not surprising that considerable research has been devoted to the development of the practical syntheses of bridged, capped and fenced porphyrins.[15,16] The syntheses of strapped porphyrins are generally accomplished either by using a benzaldehyde that is already combined with a strapping unit for construction of the porphyrin macrocycle in a Rothemund-type reaction[25,37–41] or by pre-synthesizing a porphyrin bearing an appropriately reactive functional group to which a strap can subsequently be affixed.[15,25,42–47] The latter approach was used in the present study in which we chose to strap the α,α-atropisomer of the symmetrical diarylaminoporphyrin **2** to a diaza-18-crown-6 ring. Indeed, many synthetic functionalized porphyrin systems are based on 5,15-diaryl-2,3,7,8,12,13,17,18-octaalkylporphyrins, due to their ease of preparation, high symmetry and the thermal stability of the atropisomers obtained.[15,22–25] The synthesis of 5,15-diarylporphyrins from a 5,5′-unsubstituted dipyrromethane and aromatic aldehydes was first reported by Ogoshi *et al.*[48] and later improved by Gunter and Mander,[25] Young and Chang[23] and Manka and Lawrence.[26] Our parent porphyrin (**2**) was synthesized according to these reported procedures. Preparation of the starting material (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane) was easily achieved in a one-step decarboxylation (ethanolamine reflux) from its diester precursor.[49] Direct condensation of equimolar amounts of our dipyrromethane and *o*-nitrobenzaldehyde in dilute methylene chloride solution (5×10^{-3} M) containing trifluoroacetic acid, and a subsequent oxidation, yielded the di-(*o*-nitrophenyl) porphyrin **1** as a mixture of α, α and α,β atropisomers in 56% yield (Scheme 1). Diphenyletioporphyrins are substantially more soluble in organic solvents than are their octamethylporphyrin analogues and as such, the atropisomers of **1** were easily separated on a large scale using column chromatography.

The goal of our synthetic efforts has been to prepare a system in which the cavity between the diaza-18-crown-6 moiety and the metalloporphyrin is large enough so that small molecules (*e.g.*, oxygen, carbon monoxide, xenon, *etc.*) are able to coordinate with the porphyrin metal, yet small enough to prevent the binding of bulky ligands. In this light, and with the aim previously described above, we decided to fabricate our strapping units such that their lengths corresponded with those shown for compounds **5** and **6** as illustrated in Scheme 1. We accomplished this by using chloroacetyl chloride and chloropropionyl chloride as our activating agents in the reactions to produce **3** and **4**, respectively, in yields greater than 89%. Only the acyl halide groups react with the free amino groups of the porphyrin and the resulting activated halomethylporphyrin can further react with amino groups of any suitable diazacrown ether under well-known reaction conditions. The isolated α,α atropisomers (**3** and **4**) were very stable; only under prolonged heating at greater than 60 °C could the α,β isomers be observed, and then only in small proportion. Bromoacetyl bromide has also been used as an activating agent but its higher reactivity leads to a mixture of $\mathrm{RNH{-}CO{-}CH_2{-}Br}$ and $\mathrm{RNH{-}CH_2{-}CO{-}Br}$ functionalized groups. High dilution conditions were then used in the coupling reaction of the diaza-18-crown-6 moiety (*i.e.*, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane) with **3** and **4** to give **5** and **6**, respectively, in 76 and 25% yield. All of the final products were purified using extensive silica gel flash column chromatography. The relatively high yield obtained for **5** in this condensation is a reflection of the restricted conformational freedom of the porphyrin co-reactant and may also be a result of the complementary geometries of the diacid chloride porphyrin and the diaza-18-crown-6 ring. We attribute the lower yield of 25% obtained for **6** to the diminished reactivity of the $\mathrm{RNH{-}CO{-}CH_2{-}CH_2{-}Cl}$ functional groups on the starting material **4** in comparison to the $\mathrm{RNH{-}CO{-}CH_2{-}Cl}$ functional groups on **3**, which led to a 76% yield of **5**. Although we present the synthesis of only two specific crowned-porphyrins, this method should be of wide utility in the preparation of a variety of porphyrin–azamacrocycle compounds.

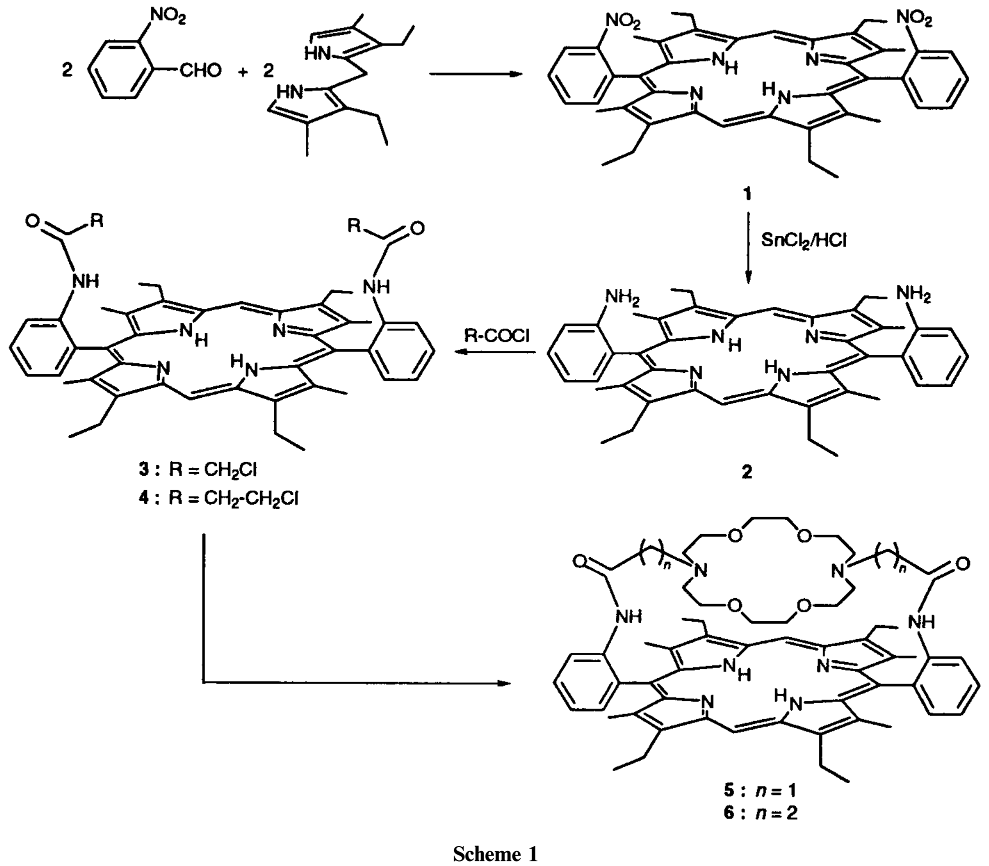
Characterizations

Visible spectroscopy

The electronic spectra of the free-base bimacrocycles **5** and **6** display etio-type features that are typical of monomeric porphyrins with six or more β-alkyl groups.[50] Specifically, a very intense Soret band was observed at 407 nm for compound **5** (and 410 nm for **6**) as were four Q bands of decreasing intensity in the region between 500 and 700 nm. The electronic spectra of **3** and **4** were very similar to those observed for **5** and **6**. However, the Soret and Q bands from porphyrins **5** and **6** were very weakly red-shifted (from 1 to 3 nm) with respect to those of the intermediate functionalized porphyrins **3** and **4**. These results suggest that introduction of the strapped diaza-18-crown-6 ring leads to very small distortions of the porphyrin mean plane (as discussed later in connection with the X-ray structures of **6** and **7**).

Mass spectrometry. Mass spectral data are reported in the Experimental section. For diaza-18-crown-6-containing compounds (**5** to **7**), an extra peak corresponding to the sodium complex appeared in LSIMS mode at $m/z = \mathrm{M} + 23$. This can be explained by the presence of sodium ion in the source as an impurity of the used reference (CsI). In addition to the systematically observed molecular peak, one can identify fragments corresponding to the loss of the nonaromatic macrocycle unit. In all cases, such peaks are of very weak intensity due to the stability of the parent compounds.

NMR spectroscopy. All of the synthesized compounds (and their intermediates) have been characterized by NMR spec-



Scheme 1

troscopy; these data are available in the Experimental section. Peak assignments were made on the basis of chemical shift, multiplicity, integration, spectral intercomparisons, homodecoupling studies and crosspeak identification in ^1H–^{13}C heteronuclear correlation spectra. The ^1H NMR spectra of **5** and **6** showed that the diaza-18-crown-6 resonance had moved considerably upfield when compared with the spectra of **3** and **4**. This is consistent with exposure of these protons to the porphyrin ring current anisotropy, which would be observed with a structure in which the diaza-18-crown-6 was strapped across the face of the porphyrin. The resonance for the *meso*-phenyl proton *ortho* to the amide was moved considerably downfield due to the deshielding effects of the amide carbonyl, and such a shift is consistent with those observed for other amidophenyl porphyrin derivatives.[47,50–52] The ^1H–^{13}C heteronuclear correlation spectra of **5** and **6** were measured and used to facilitate peak assignments in the ^1H and ^{13}C spectra; a selected region from the heteronuclear correlation spectrum of **6** (with peak identifications) is presented in Fig. 1. Of particular interest are the eight peaks observed in the aliphatic region (10–70 ppm) of the ^{13}C NMR spectrum. This is due to the existence of two planes of symmetry in this molecule. These signals have been assigned as follows: two signals at 34.0 and 46.8 ppm due to the bridging carbons 17 and 18, three signals at 50.6, 65.8 and 68.6 ppm due respectively to the diaza-18-crown-6 carbons 19, 20 and 21, and three signals observed at 13.9, 18.3 and 20.3 ppm due to the porphyrin β-pyrrolic carbons (respectively 7, 5 and 4).

X-Ray crystallography. The crystal structures of free-base porphyrin **6** and Zn^{II} porphyrin **7** both revealed conformations in which the porphyrin macrocycles and the diaza-18-crown-6 moieties were generally cofacial, as shown in Fig. 2 and 3. In the structure of **6** the distance between the porphyrin 4-N center and the diaza-18-crown-6 center[53] was 3.89 Å. The porphyrin macrocycle displayed a slight saddle shape[54] with a mean deviation of 0.140 Å for the macrocyclic atoms from the porphyrin mean plane.[55] The conformation of the porphyrin macrocycle in **7**, while being nearly planar (with a mean deviation of 0.076 Å for the macrocyclic atoms from the porphyrin mean plane), did however display a lightly ruffled conformation.[54] The central Zn^{II} ion, which was bound to an axial H_2O [2.092(2) Zn^{II}—O bond length], was typical of pentacoordinate Zn^{II} ions in porphyrins in that it was positioned above (by 0.353 Å) rather than in the porphyrin mean plane.[56] An average Zn^{II}—N bond length of 2.079(8) Å was observed. The axial H_2O was hydrogen-bonded to two oxygen atoms of the diaza-18-crown-6 ring with H bond distances of 1.95 Å and 1.83 Å. The center of the diaza-18-crown-6[53] ring was 4.30 Å from the porphyrin 4-N center and 4.00 Å from the Zn^{II} ion. As mentioned previously, our goal in the preparation of these compounds was to regulate the size of the cavity in between the porphyrin macrocycle and the diaza-18-crown-6 ring in order that small molecules, such as oxygen and carbon monoxide, might enter the cavity but such that large ligands/substrates would be sterically excluded. The size of the cavities observed in **6** and **7**, along with the presence of the axial H_2O in the cavity of **7**, confirm that our present models fit these criteria.

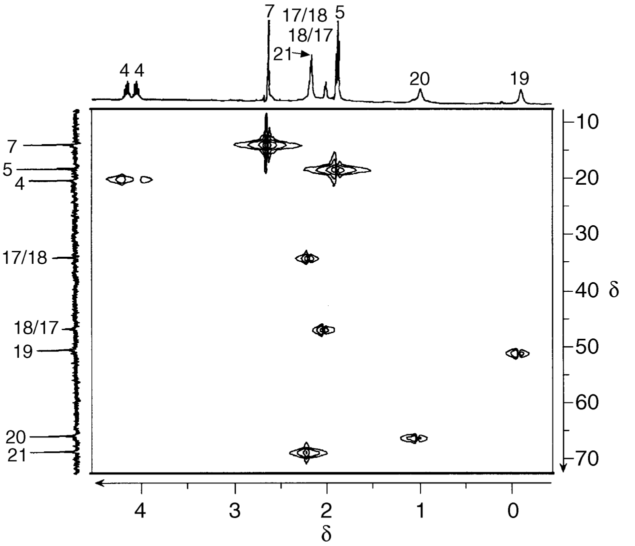


Fig. 1 A selected region of the ^1H–^{13}C heteronuclear correlation spectrum of **6**

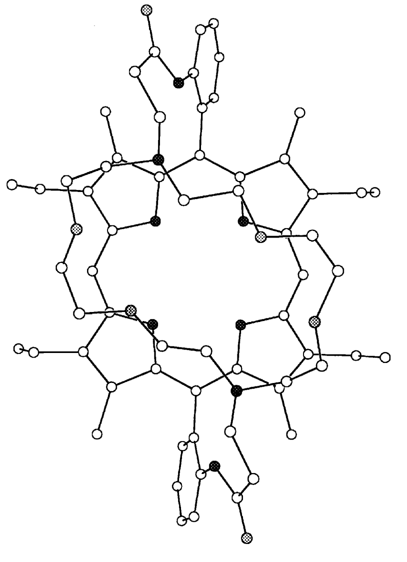


Fig. 2 The molecular structure of **6**; hydrogens have been omitted for clarity

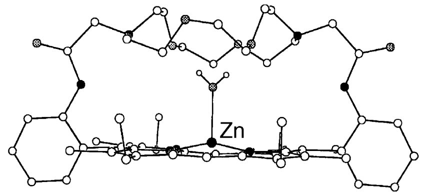


Fig. 3 The molecular structure of **7**; hydrogens (except for H_2O hydrogens) have been omitted for clarity

Conclusion

We have developed a facile synthetic pathway leading to a novel family of 'crowned-porphyrins' composed of a 5,15-diaryletioporphyrin and a diaza-18-crown-6 macrocycle. The cofacial conformation of the two macrocycles was ensured by the presence of two bridging spacers, the lengths of which have been varied in order to obtain optimal bridge size. The high yields obtained, together with the small number of steps involved, permit large-scale syntheses of these compounds. The synthetic pathway we present is a method by which a wide variety of porphyrin-based bimacrocycles can be prepared, and should be of utility to many researchers working in the field of porphyrin chemistry. Crystallographic data for two of the members in this family, free-base porphyrin **6** and Zn^{II} metalloporphyrin **7** confirmed that the porphyrin and the diaza-18-crown-6 moiety adopted cofacial orientations. The size of the cavity between the macrocycles, while demonstrated to accommodate small molecules as shown by the binding of H_2O as an axial ligand to the central Zn^{II} ion in the crystal structure of **7**, will probably not accommodate large ligands or substrates. Recent ^{129}Xe NMR studies realized in our laboratory have shown no specific interactions between xenon and compounds **5** and **6**. Chemical shifts of ^{129}Xe dissolved in $CDCl_3$ and in solutions of $CDCl_3$ containing 18-K-6 or diaza-18-crown-6 porphyrins **5** or **6** have been shown to be correlated with the temperature. However, compounds **5** and **6** should allow sequential metallations to yield heterobimetallic species, making them ideally suited for study as model systems for biologically important heme-dependent phenomena such as the mimicking of processes related to the structure and function of cytochromes such as cytochrome c oxidase.

References

1 P. Leighton and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1985, 856.
2 J. A. Cowan, J. K. M. Sanders, G. S. Beddard and R. J. Harrison, *J. Chem. Soc., Chem. Commun.*, 1987, 55.
3 H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. I*, 1995, 2223.
4 R. P. Bonar-Law and J. K. M. Sanders, *J. Am. Chem. Soc.*, 1995, **117**, 259.
5 R. P. Bonar-Law and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. I*, 1995, 3085.
6 D. R. Jones, D. A. Summerville and F. Basolo, *Chem. Rev.*, 1979, **79**, 139.
7 G. Malmström, *Chem. Rev.*, 1990, **90**, 1247.
8 J. A. Ibers and R. H. Holm, *Science*, 1980, **209**, 223.
9 J. W. Buchler, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 407.
10 J. Peisach, W. E. Blumberg and A. Adler, *Ann. N. Y. Acad. Sci.*, 1973, **206**, 310.
11 V. Bulach, D. Mandon and R. Weiss, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 572.
12 C. A. Koch, C. A. Reed, G. A. Brewer, N. P. Rath, W. R. Scheidt, G. Gupta and G. Lang, *J. Am. Chem. Soc.*, 1989, **111**, 7645.
13 H. Sakurai and T. Yoshimura, *J. Inorg. Biochem.*, 1985, **24**, 75.
14 A. R. Battersby and A. D. Hamilton, *J. Chem. Soc., Chem. Commun.*, 1980, 117.
15 J. E. Baldwin and P. Perlmutter, *Top. Curr. Chem.*, 1984, **121**, 181.
16 M. Momenteau and C. A. Reed, *Chem. Rev.*, 1994, **94**, 659.
17 S. Koeller, P. Cocolios and R. Guilard, *New J. Chem.*, 1994, **18**, 849.
18 L. Jaquinod, N. Kyritsakas, J. Fischer and R. Weiss, *New J. Chem.*, 1995, **19**, 453.
19 A. D. Hamilton, J-M. Lehn and J. L. Sessler, *J. Chem. Soc., Chem. Commun.*, 1984, 311.
20 A. Hamilton, J. M. Lehn and J. L. Sessler, *J. Am. Chem. Soc.*, 1986, **108**, 5158.
21 M. Gubelmann, A. Harriman, J-M. Lehn and J. L. Sessler, *J. Chem. Soc., Chem. Commun.*, 1988, 77.
22 V. Kràl, M. Pànkovà, J. Günterova, M. Belohradsky and P. J. Anzenbacher, *Collect. Czech. Chem. Commun.*, 1994, **59**, 639.
23 R. Young and C. K. Chang, *J. Am. Chem. Soc.*, 1985, **107**, 898.
24 H. K. Hombrecher, G. Horter and C. Arp, *Tetrahedron*, 1992, **48**, 9451.
25 M. J. Gunter and L. N. Mander, *J. Org. Chem.*, 1981, **46**, 4792.
26 J. S. Manka and D. S. Lawrence, *Tetrahedron Lett.*, 1989, **30**, 6989.
27 J. W. Canary and B. C. Gibb, in *Progress in Inorganic Chemistry*, ed. K. D. Karlin, John Wiley & Sons, New York, 1st edn., 1997, vol. 45, p. 1.
28 M. Claessens, O. Fabre, D. Zimmermann and J. Reisse, *Bull. Soc. Chim. Belg.*, 1984, **93**, 983.
29 S. C. Cullen and E. G. Gross, *Science*, 1951, **113**, 580.
30 C. Muehlbacher, F. L. De Bon and R. M. Featherstone, *Intern. Anesthesi. Clinics*, 1963, **1**, 937.
31 B. P. Schoenborn, H. C. Watson and J. C. Kendrew, *Nature (London)*, 1965, **207**, 28.
32 B. P. Schoenborn and C. L. Nobbs, *Mol. Pharmacol.*, 1966, **2**, 495.
33 R. F. Tilton Jr. and I. D. Kuntz Jr., *Biochemistry*, 1982, **21**, 6850.
34 R. F. Tilton Jr., I. D. Kuntz Jr. and G. A. Petsko, *Biochemistry*, 1984, **23**, 2849.
35 $R1 = \Sigma \| F_o - F_c \| / \Sigma | F_o |$ and $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{\frac{1}{2}}$; $w = 1/[\sigma^2(F_o^2) + ((X)P)^2 + (Y)P]$ where $P = (F_o^2 + 2F_c^2)/3$; for **6** $X = 0.172$ and $Y = 4.639$, for **7** $X = 0.040$ and $Y = 6.692$.
36 S. R. Parkin, B. Moezzi and H. J. Hope, *J. Appl. Crystallogr.*, 1995, **28**, 53.
37 J. E. Baldwin, T. Klose and M. Peters, *J. Chem. Soc., Chem. Commun.*, 1976, 881.
38 A. Osuka, F. Kobayashi, T. Nagata and K. Maruyama, *Chem. Lett.*, 1990, 287.
39 J. A. Wytko, E. Graf and J. Weiss, *J. Org. Chem.*, 1992, **57**, 1015.
40 A. Diebold, J. Fischer and R. Weiss, *New J. Chem.*, 1996, **20**, 959.
41 M. J. Gunter and M. R. Johnston, *J. Chem. Soc., Chem. Commun.*, 1992, 1163.
42 B. Andrioletti, B. Boitrel and R. Guilard, *C. R. Sceances Acad. Sci. (Paris)*, 1996, **323**, 859.
43 B. Boitrel and R. Guilard, *Tetrahedron Lett.*, 1994, **35**, 3719.
44 C. K. Chang, *J. Am. Chem. Soc.*, 1977, **99**, 2819.
45 N. M. Richardson, I. O. Sutherland, P. Camilleri and J. A. Page, *Tetrahedron Lett.*, 1985, **26**, 3739.
46 M. J. Gunter and M. R. Johnston, *Tetrahedron Lett.*, 1990, **31**, 4801.
47 M. J. Gunter and M. R. Johnston, *J. Chem. Soc., Perkin Trans. I*, 1994, 995.
48 H. Ogoshi, H. Sugimoto, T. Nishiguchi, T. Watanabe, Y. Matsuda and Z-i. Yoshida, *Chem. Lett.*, 1978, 29.
49 M. A. Lopez, Thèse de Doctorat, Université de Bourgogne, 1990.
50 K. M. Smith, in *Porphyrins and Metalloporphyrins*, ed. K. M. Smith, Elsevier, Amsterdam, 1st edn., 1975, vol. I, p. 3.
51 S. Licoccia, M. Paci, P. Tagliatesta, R. Paolesse, S. Antonaroli and T. Boschi, *Magn. Reson. Chem.*, 1991, **29**, 1084.
52 B. Boitrel, E. Camilleri, Y. Fleche, A. Lecas and E. Rose, *Tetrahedron Lett.*, 1989, **30**, 2923.
53 The diaza-18-crown-6 center was defined as the center of all of the atoms (or disordered atom positions) in the diaza-18-crown-6 ring.
54 D. J. Nurco, C. J. Medforth, T. P. Forsyth, M. M. Olmstead and K. M. Smith, *J. Am. Chem. Soc.*, 1996, **118**, 10918.
55 Herein, 'porphyrin mean plane' refers to the least-squares plane calculated for the 24 core carbon and nitrogen atoms.
56 M. O. Senge, T. P. Forsyth and K. M. Smith, *Z. Kristallogr.*, 1996, **211**, 176.

Received in Montpellier, France, 3rd October 1997;
Paper 7/09181H