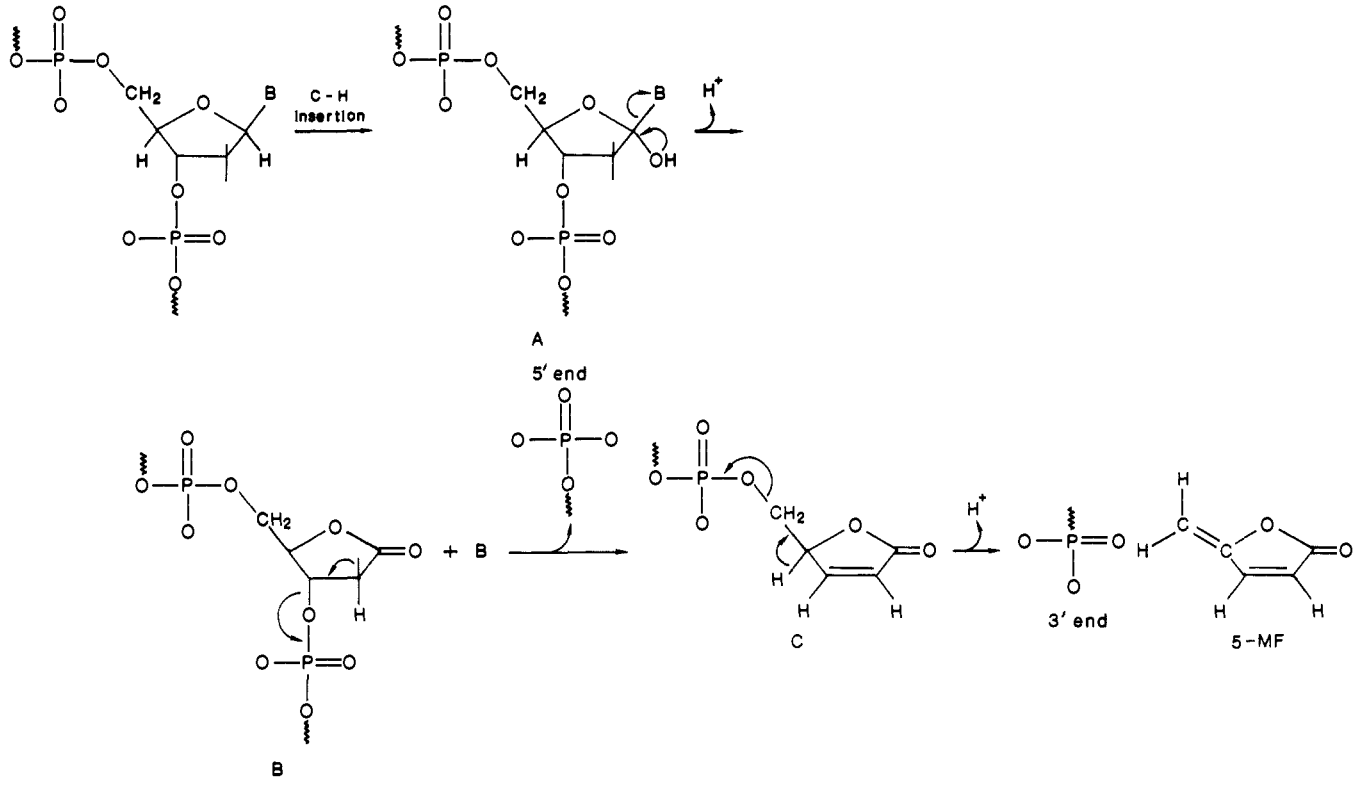
Scheme I



The product distribution from the 3′ labeled RNA strand is compared to that from the 3′ labeled noncoding DNA strand of the Eco R1 restriction fragment by using I as the nucleolytic agent (Figure 2). In both cases, the major cutting sites are clustered between positions 19–24. This interval of predominant cutting sites 2–3 nucleotides in both directions from the tethered 1,10-phenanthroline can be due to the diffusibility of the oxidative species or the flexibility of the 1,10-phenanthroline linked terminal deoxyadenosine that can be inferred from the RNase H hybridization studies. The kinetics of the cutting reaction are similar with both RNA and DNA. After incubation for 2 h at 37 °C, approximately 20% of the parent band is converted to one of the oligonucleotide products.

Primer extension assays were also used to monitor the reaction of I with RNA.[13] These assays reflect phosphodiester bond scission as well as any oxidative damage that may block polymerization. Since the pattern of products obtained were similar to those using 3′ labeled RNA, there is no evidence for reaction that does not lead to strand scission. In previous studies of the DNase activity of 1,10-phenanthroline–copper ion, no reaction without strand scission has ever been observed.[14,15]

The similarity in the digestion patterns suggests that the phosphodiester backbones of RNA and DNA are comparably reactive to the chemical nuclease activity of 1,10-phenanthroline–copper. The extension of these findings to other oxidative nucleolytic activities, e.g., ferrous-EDTA and iron porphyrins,[16-20] will require direct experimental tests in view of bleomycin's inability to nick RNA.

Acknowledgment. We thank M. D. Kuwabara, J.-F. Constant, D. Nierlich, and G. Murakawa for useful conversations. D. Nierlich and G. Murakawa kindly provided us with the plasmid to prepare the truncated lac mRNA transcript. This research was supported by USPHS GM-21199.

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Regio- and Stereoselective Reduction of N(21),N(22)-Bridged Porphyrin Hydroperchlorates to Stable 5*H*-Phlorins

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Hydroporphyrins with saturated meso carbon(s) are important in the redox chemistry and the biosynthesis of porphyrin.[1] Phlorins, 5*H*,22*H*-dihydroporphyrins, are usually so air-sensitive that only a few have been fully characterized so far[2] including those with the steric crowding of peripheral substituents which is relieved upon hybridization change from sp^2 to sp^3 of the meso carbon as shown in the Woodward's approach to chlorophyll *a*.[3]

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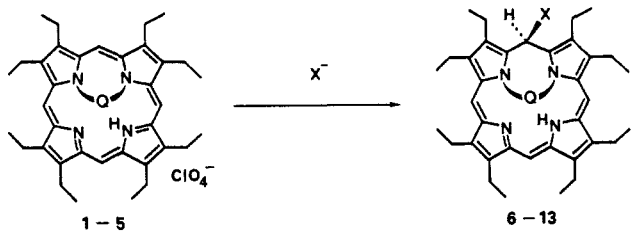
Scheme I[a]



[a] Q: HC=CH (**1**, **6**), PhC=CPh (**2**, **7**, **11–13**), (*o*-Tol)C=C(*o*-Tol) (**3**, **8**), CH_2CH_2 (**4**, **9**), C=C(C_6H_4-*p*-Cl)$_2$ (**5**, **10**); X: H(D) (**6–10**), CN (**11**), CH_2COMe (**12**), CH_2COPh (**13**).

Table I. ^1H Chemical Shift (δ) and Spin–Lattice Relaxation Time (T_1) of 5*H*-Phlorins **6–8**[a]

		endo-H		exo-H	
compd	R[b]	δ	T_1	δ	T_1
6	H	5.05	0.20	3.33	0.27
7	C_6H_5	5.36	0.19	3.53	0.25
8	*o*-$CH_3C_6H_4$	5.42	0.14	4.15	0.15

[a] δ and T_1 were measured in $CDCl_3$. [b] Substituent on the etheno bridge as shown in Figure 1.

This paper describes a new means to stabilize phlorin structure through the introduction of an N(21),N(22)-bridging group which exerts a strain on a porphyrin plane so that 5-meso carbon favors a tetrahedral configuration.

Treatment of THF solution of *N*(21),*N*(22)-ethenooctaethylporphyrin hydroperchlorate[4] (**1**) with $NaBH_4$ (2.5-fold molar excess) under argon gave a blue compound which can be extracted into hexanes. Removal of hexanes afforded satisfactorily pure powders of *N*(21),*N*(22)-ethenooctaethyl-5*H*-phlorin[5] (**6**) in 73% yield. **6** was cleanly air-oxidized to **1** under acidic conditions. The visible spectrum of **6** is characteristic of a phlorin chromophore.[6] ^1H NMR spectrum of **6** is indicative of the disappearance of a ring current effect and the presence of a symmetry plane which contains a C(5)–C(15) axis and bisects the N(21),N(22)-bridge. *N*(21),*N*(22)-(1,2-Diphenyletheno)- and *N*(21),*N*(22)-(1,2-di(*o*-tolyl)etheno)octaethylporphyrin hydroperchlorate,[4,7] (**2**) and (**3**), were analogously reduced to the corresponding 5*H*-phlorins,[8] **7** and **8**, in 84% and 45% yields, respectively. One of the two AB doublets due to the saturated meso methylene protons appeared at 3.3–4.2 ppm and the other at 5.0–5.5 ppm in the ^1H NMR spectra of **6–8** (see Table I). Irradiation of the methyl signal (1.52 ppm) of the bridge *o*-tolyl groups of **8** resulted in 11% NOE enhancement of only the higher field AB doublet (4.15 ppm). A positive NOE effect was also observed between the doublet (5.77 ppm) due to the bridge ortho-phenyl protons of **7** and the higher field AB doublet (3.53 ppm). Therefore, the higher field AB doublet is associated with the 5-meso (not 15-meso) methylene proton at the same side as the bridge (exo side), meaning that reduction takes place regioselectively at the 5-meso position which is surrounded by the N(21),N(22)-bridge. This assignment of the AB doublets is consistent with the fact that spin–lattice relaxation time (T_1) of the higher field doublet decreases in a larger quantity than that of the lower field doublet due to an increase in the number of the etheno bridge protons which can interact with the 5-exo proton, as shown in Table I. Furthermore, the fact that T_1 of the endo proton is always shorter than that of the exo proton implies that the endo proton is in close proximity to the 3- and 7-ethyl group. This requires the seven-membered ring consisting of N(21), C(4), C(5), C(6), N(22), and two etheno bridge carbons of the 5*H*-phlorins to take a boat form rather than a chair form (see Figure 1).

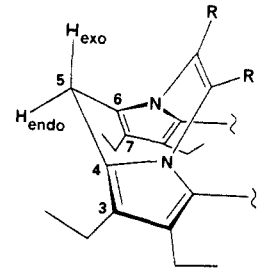


Figure 1. A preferred boat form conformation of **6–8**.

N(21),*N*(22)-Ethano- and *N*(21),*N*(22)-(bis(*p*-chlorophenyl)vinylideno)octaethylporphyrin hydroperchlorate,[9,10] (**4**) and (**5**), were analogously reduced to the corresponding 5*H*-phlorins,[11] **9** and **10**, in 51% and 65% yields, respectively. Their spectral properties are quite similar to those of **6–8**. The higher field signal due to the 5-exo proton disappeared completely, and the 5-endo proton appeared as a singlet in the ^1H NMR spectra of the deuteriated 5*H*-phlorins, **7d**, **9d**, and **10d**, which were obtained by the reaction of **2**, **4**, and **5** with $NaBD_4$. Therefore, a deuteride was incorporated exclusively at the 5-exo position stereoselectively. Nucleophilic addition of natrium cyanide, kalium acetone enolate, and lithium acetophenone enolate to **2** occurred in preference to deprotonation, affording very stable 5-substituted 5*H*-phlorins,[12] **11**, **12**, and **13**, in 74%, 84%, and 81% yields, respectively. Since the chemical shifts of the saturated 5-meso protons of **11–13** are very low (7.2–6.8 ppm), they are assignable to the endo side where a greater deshielding effect is exerted by the substituted pyrrole rings in a boat form. Thus, cyanide and enolates add to **2** regio- and stereoselectively in exactly the same manner as hydride.

The single-crystal X-ray analysis of *N*(21),*N*(22)-(1,2-diphenyletheno)tetraphenylporphin hydroperchlorate indicates that the etheno bridge forces the substituted pyrrole rings to be highly canted toward the endo side by 22.9° and 20.6° from the mean

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(5) **6**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 6.85 (s) (×2), 6.10 (s), 5.05 (d, J = 15.6 Hz), 3.33 (d); CH_2 2.9–2.6 (m); CH_3 1.30 (t), 1.29 (t), 1.24 (t), 1.15 (t); NH 8.9 (br); H_{vinyl} 5.30 (s) ppm; MS, 561 (M + 1); UV–vis (CH_2Cl_2) λ_{max} 392, 644 nm; Anal. satisfactory C, H, N for $C_{38}H_{48}N_4$.

(6) Phlorins have the broadened UV and visible bands with considerably reduced extinction coefficients.[2c,h-j]

(7) Callot, H. J.; Cromer, R.; Louati, A.; Metz, B.; Chevrier, B. *J. Am. Chem. Soc.* **1987**, *109*, 2946.

(8) **7**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 6.56 (s) (× 2), 6.36 (s), 5.36 (d, J = 15.6 Hz), 3.53 (d); CH_2 2.8–2.5 (m); CH_3 1.31 (t), 1.24 (t), 0.99 (t), 0.85 (t); NH 8.9 (br); H_p 6.55 (t); H_m 6.52 (t); H_o 5.77 (d) ppm; MS, 712 (M); UV–vis (CH_2Cl_2) λ_{max} 401, 649 nm; Anal. satisfactory C, H, N for $C_{50}H_{56}N_4$. **8**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 6.45 (s) (×2), 6.28 (s), 5.42 (d, J = 16.1 Hz), 4.15 (d); CH_2 2.8–2.5 (m); CH_3 1.36 (t), 1.25 (t), 1.03 (t), 0.94 (t); NH 9.3 (br); $H_{m,p}$ 6.58 (m); H_m 6.28 (d); H_o 5.99 (d); $PhCH_3$ 1.52 (s) ppm; UV–vis (CH_2Cl_2) λ_{max} 405, 624 nm; Anal. satisfactory C, H, N for $C_{52}H_{60}N_4$.

(9) Preparation of **4** is to be reported elsewhere.

(10) **5** was prepared according to the method for the TPP analogue: (a) Lange, M.; Mansuy, D. *Tetrahedron Lett.* **1981**, *22*, 2561. (b) Wisnieff, T. J.; Gold, A.; Evans, S. A., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 5616.

(11) **9**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 7.02 (s) (×2), 6.30 (s), 5.22 (d, J = 16.2 Hz), 3.50 (d); CH_2 2.9–2.7 (m); CH_3 1.33 (t) (×2), 1.24 (t), 1.12 (t); NH 8.6 (br); bridge CH_2 3.65 (d), 2.50 (d) ppm; UV–vis (CH_2Cl_2) λ_{max} 397, 634 nm; Anal. satisfactory C, H, N for $C_{38}H_{50}N_4$. **10**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 5.77 (s) (×2), 5.76 (s), 5.16 (d, J = 18.6 Hz), 4.51 (d); CH_2 2.6–2.3 (m); CH_3 1.28 (t), 1.20 (t), 1.05 (t), 1.03 (t); NH 14.5 (br); H_m 6.81 (d); H_o 6.44 (d) ppm; MS, 783 (M + 3); UV–vis (CH_2Cl_2) λ_{max} 389, 681 nm; Anal. satisfactory C, H, N for $C_{50}H_{54}N_4Cl_2$.

(12) **11**: ^1H NMR ($CDCl_3$, 270 MHz) H_{meso} 6.58 (s) (×2), 6.48 (s), 7.06 (s); CH_2 2.9–2.5 (m); CH_3 1.39 (t), 1.36 (t), 1.05 (t), 0.92 (t); NH 8.9 (br); H_p 6.76 (t); H_m 6.63 (t); H_o 6.04 (d) ppm; MS, 737 (M); UV–vis (CH_2Cl_2) λ_{max} 382, 620 nm; Anal. satisfactory C, H, N for $C_{51}H_{55}N_5$. **12**: ^1H NMR (C_6D_6, 270 MHz) H_{meso} 6.90 (s) (×2), 6.84 (s), 6.87 (t); CH_2 3.4–2.5 (m); CH_3 1.41 (t), 1.39 (t), 0.99 (t) (×2); NH 9.5 (br); $H_{m,p}$ 6.57 (m); H_o 6.16 (m); $COCH_2$ 2.78 (d); $COCH_3$ 1.59 (s) ppm; MS, 769 (M + 1); UV–vis (CH_2Cl_2) λ_{max} 393, 638 nm; Anal. satisfactory C, H, N for $C_{53}H_{60}N_4O$. **13**: ^1H NMR (C_6D_6, 270 MHz) H_{meso} 6.91 (s) (×2), 6.86 (s), 7.21 (t); CH_2 3.4–2.5 (m); CH_3 1.45 (t), 1.40 (t), 0.98 (t) (×2); NH 9.5 (br); bridge H_p 6.54 (t); bridge H_m 6.47 (t); bridge H_o 6.19 (d); $COCH_2$ 3.49 (d); meso H_o 7.74 (d); meso H_p 6.90 (t); meso H_m 6.71 (t) ppm; UV–vis (CH_2Cl_2) λ_{max} 394, 637 nm; Anal. satisfactory C, H, N for $C_{58}H_{62}N_4O$.

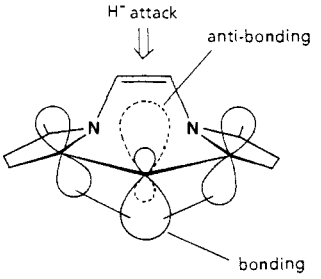

Figure 2. Exo-side attack of nucleophiles on **1-3** under the stereoelectronic control.

plane that contains four pyrrole nitrogens.[7] As the tilt of the pyrrole rings causes a greater overlap of the p-orbital of C(5) with that of C(4) or C(6) in the endo region than in the exo region, the anti-bonding π-orbital which interacts with nucleophiles should extend more to the exo side at C(5) (see Figure 2). This rationalizes the observed stereoselectivity, and a similar stereoelectronic effect should be expected for the NAD^+ model compounds[13] which are closely related to **1-5** in the sense that they are monocationic nitrogen heterocycles.

Finally, it should be emphasized that there are only a few examples of nucleophilic attack on the porphyrin system[2a,14] and that an N(21),N(22)-bridging group is removable in principle as has been demonstrated for the TPP analogue of **5**.[15] Thus, the present reaction is of importance not only as a new porphyrin redox system but also as a facile synthetic method for the meso-substitution of porphyrin by the use of ordinary carbanions.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

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Cupped- and Cappedophanes, Two New General Classes of Compounds with Molecular Cavities

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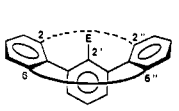
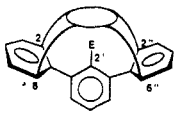
We describe here the first examples of two broad classes of molecules which should have potential as molecular hosts[1] and other novel structural features. Their structures are based on an *m*-terphenyl framework in which the outer rings are orthogonal to the central ring. Compounds of type **1** may have any set of



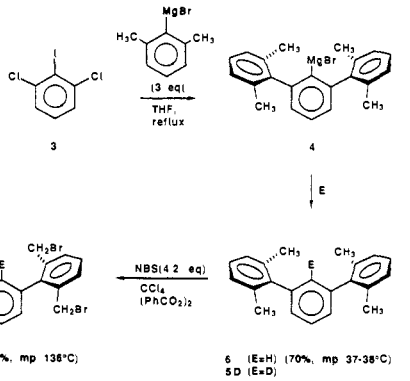
1



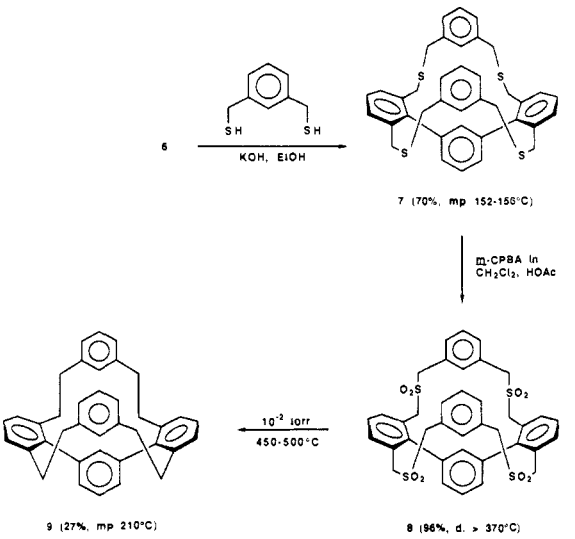
2

(1) For inspiring recent reviews of this now vast area of science, see: Lehn, J.-M. *Angew. Chem., Int. Ed. Engl.* **1985**, *27*, 90-112; "Molecular Inclusion and Molecular Recognition. Clathrates I", Weber, E., Ed. *Top. Curr. Chem.* **1987**, *140*. Rebek, J., Jr. *Science (Washington, D.C.)* **1987**, *235*, 1478-1484. Cram, D. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1039-1057. Lehn, J.-M. *Science (Washington, D.C.)* **1985**, *227*, 849-856. *Inclusion Compounds*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2. Vögtle, F.; Müller, W. M. *J. Inclusion Phenom.* **1984**, *1*, 369-386. Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161-170. For imaginative proposals for spheres, saucers, pots, collars, bowls, and other molecular cavities, see: Cram, D. J. *Science* (Washington, D.C.) *219*, 1177-1183.

Scheme I



Scheme II



atoms linking the 2,2″ and 6,6″ positions, thus forming a molecular bowl; as a consequence of the synthetic methodology, groups E other than hydrogen can also readily be incorporated, covalently bound to carbon 2′ in the middle of the bowl. Compounds of type **2**, which resemble a canopied gondola in shape, have a capping unit linked to the "outer" terphenyl rings.[2] If the connecting arms are long enough, these structures may include a passenger group E at position 2′.

Because of their shapes and cyclophane[3] character, we refer to **1** and **2** as cupped- and cappedophanes, respectively. Several examples of each type, that can be synthesized in just a few steps, are described here.

The key intermediate **6** for the cuppedophanes and cappedophanes reported here was prepared as shown in Scheme I. The conversion of **3** to **4** involves tandem aryne reactions recently developed in our group;[4] quenching allows the introduction of electrophiles (for example, deuterium) on the central ring at this stage.

Addition of a benzene solution of **6** and *m*-xylylenedithiol[5] (2 equiv) under high dilution techniques[6] to ethanolic KOH afforded tetrathia cuppedophane **7** in good yield. Oxidation gave the

(2) The examples described here have the "cap" linked to carbons 2,2″,6 and 6″ of the *m*-terphenyl unit, but other loci for attaching the "cap" should also be possible; the links between the "cap" and the *m*-terphenyl unit need not have identical lengths.

(3) For reviews, see: "*Cyclophanes*", Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vols I and II. "*Cyclophanes I and II*", Vögtle, F., Ed. *Top. Curr. Chem.* **1983**, *113* and *115*.

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