reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-102645 (**1**) and CCDC-102646 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[1] P. B. Hitchcock, M. F. Lappert, M. Layh, *Chem. Commun.* **1998**, 201.
[2] P. B. Hitchcock, M. F. Lappert, D.-S. Liu, *J. Chem. Soc. Chem. Commun.* **1994**, 1699.
[3] P. B. Hitchcock, M. F. Lappert, S. Tian, unpublished results.
[4] P. B. Hitchcock, M. F. Lappert, M. Layh, *Chem. Commun.* **1998**, 2179.
[5] a) A. Heine, R. Herbst-Irmer, G. M. Sheldrick, D. Stalke, *Inorg. Chem.* **1993**, *32*, 2694; b) H. V. R. Dias, M. M. Olmstead, K. Ruhlandt-Senge, P. P. Power, *J. Organomet. Chem.* **1993**, *462*, 1.
[6] P. B. Hitchcock, M. F. Lappert, M. Layh, *Tetrahedron Lett.* **1998**, *39*, 4745.
[7] J. Niesmann, U. Klingebiel, S. Rudolph, R. Herbst-Irmer, M. Noltemeyer, *J. Organomet. Chem.* **1996**, *515*, 43.
[8] K. Tamao, Y. Nagakawa, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 218.
[9] P. Lassacher, A. G. Brook, A. J. Lough, *Organometallics* **1995**, *14*, 4359.
[10] M. Ishikawa, T. Horio, Y. Yuzuriha, A. Kunai, T. Tsukihara, H. Naitou, *Organometallics* **1992**, *11*, 597; M. Ishikawa, S. Matsuzawa, K. Hirotsu, S. Kamitori, T. Higuchi, *Organometallics* **1984**, *3*, 1930; A. G. Brook, A. Baumegger, A. J. Lough, *Organometallics* **1992**, *11*, 3088; M. Ishikawa, H. Sugisawa, H. Akitomo, K. Matsusaki, S. Kamitori, K. Hirotsu, T. Higuchi, *Organometallics* **1986**, *5*, 2447; M. J. Fink, D. B. Puranik, M. P. Johnson, *J. Am. Chem. Soc.* **1988**, *110*, 1315.
[11] B. Teclé, W. H. Ilsley, J. P. Oliver, *Organometallics* **1982**, *1*, 875; S. Harder, J. Boersma, L. Brandsma, J. A. Kanters, *J. Organomet. Chem.* **1988**, *339*, 7; M. P. Bernstein, F. E. Romesberg, D. J. Fuller, A. T. Harrison, D. B. Collum, Q.-Y. Liu, P. G. Williard, *J. Am. Chem. Soc.* **1992**, *114*, 5100; M. A. Nichols, P. G. Williard, *J. Am. Chem. Soc.* **1993**, *115*, 1568; D. Hoffmann, A. Dorigo, P. von R. Schleyer, H. Reif, D. Stalke, G. M. Sheldrick, E. Weiss, M. Geissler, *Inorg. Chem.* **1995**, *34*, 262; H. Braunschweig, B. Gehrhus, P. B. Hitchcock, M. F. Lappert, *Z. Anorg. Allg. Chem.* **1995**, *621*, 1922.
[12] See, for example, H. Sakurai, Y. Nakadaira, A. Hosomi, Y. Eriyama, C. Kabuto, *J. Am. Chem. Soc.* **1983**, *105*, 3359; R. Appel, C. Casser, F. Knoch, *Chem. Ber.* **1984**, *117*, 2693.
[13] J. J. Mayerle, M. A. Flandera, *Acta Crystallogr. Sect. B* **1978**, *34*, 1374.
[14] Y. Ito, T. Matsuura, S. Nishimura, M. Ishikawa, *Tetrahedron Lett.* **1986**, *27*, 3261.

Selective Vesicle Formation from Calixarenes by Self-Assembly**

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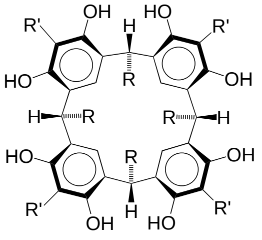
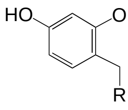
All living systems are compartmentalized by vesicles, in which various membrane proteins including channel proteins are incorporated, and thus specific biological functions can be carried out. The characterization of the shape, size, and properties of vesicles formed from various amphiphiles, including some synthetic ones, is crucial not only for the study of the structure and function of model membranes,[1] but also for the potential application of these membrane system as sensors and in technologies such as drug entrapment and release, and photochemical solar energy conversion.[2] Previously we reported that a simple polyhydroxy macrocyclic amphiphile, calix[4]resorcarene (**1**), behaves as an artificial potassium ion channel when embedded in planar bilayers of soybean lecithin.[3] The cylindrical macrocycle formed by four benzene rings and four extended alkyl chains provides the channel pore for ion passage through the lipid bilayer.[3] One would expect that amphiphiles such as **1** and calix[4]pyrogallolarene (**2**) would be aggregated in water and yield a specific self-assembled structure. Here we describe the selective formation of vesicles from the polyhydroxy macrocyclic amphiphiles **1** and **2**.[4]



1 R = $CH_3(CH_2)_{16}$, R' = H
2 R = $CH_3(CH_2)_{16}$, R' = OH



3 R = $CH_3(CH_2)_{16}$

Injection of a solution of **1** or **2** (6.7 mM) in tetrahydrofuran (0.4–2.0 mL) into a buffer (HEPES–Tris 5 mM, 4 mL, pH 7.0; HEPES = 2-[4-(hydroxyethyl)piperazine-1-yl]ethanesulfonic acid, Tris = tris(hydroxymethyl)aminomethane) at 60 °C immediately gave a dispersion of amphiphiles.[5] The dispersion was a slightly white suspension and remained in this form for more than a few months. Several characteristics of typical self-assembled structures have been observed for the dispersion obtained.

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1) Negatively stained (1.5 % phosphotungstic acid, pH 7) and freeze-fracture replica micrographs revealed the formation of spherical and ellipsoidal particles. The diameters of the particles ranged from 50 to 200 nm for both **1** and **2** (Figure 1).[6]

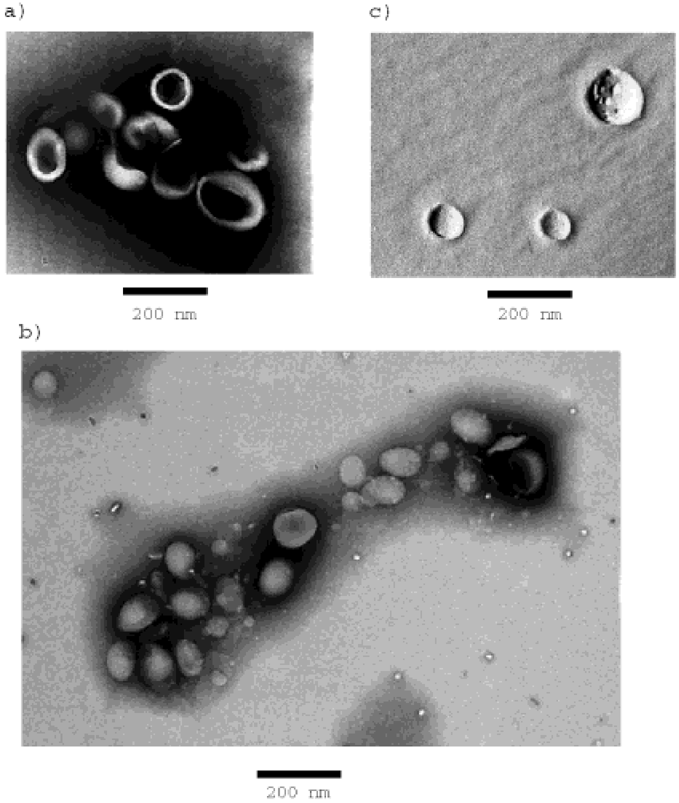

Figure 1. Transmission electron micrographs of vesicles formed from a) **1** and b) **2** (negative staining, magnification 40000 times, 80 kV), and c) **2** (freeze-fracture replica, magnification 40000 times, 100 kV).

2) Atomic force microscopy (AFM) images of the dispersion spread on a mica plate also indicated the presence of particles with diameters in the range of 40 to 250 nm (Figure 2).[7, 8]

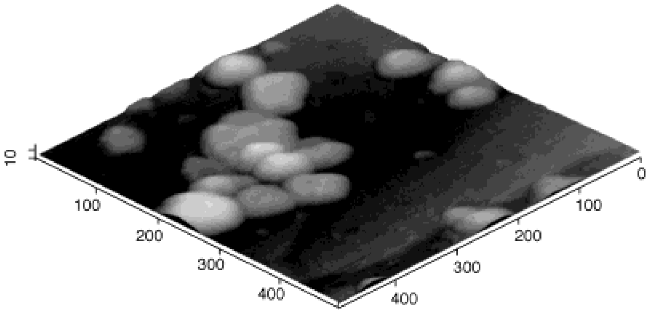

Figure 2. Atomic force micrograph of vesicles of **1** adsorbed on a mica plate. Scale in nm.

3) These particle sizes were also confirmed by dynamic light scattering experiments conducted with an Otsuka SELS-800Y instrument.

The size distribution is between 30 and 240 nm (4.0×10^{-4} M), and the maximum population of particles is at about 53 nm. These results indicate that the dispersion consists of spherical and ellipsoidal vesicles with uniform diameters. Each of the vesicles consist of noncovalent self-assemblies of the macrocyclic amphiphiles. The vesicles obtained were deduced to be closed systems—a typical vesicular property—from dye encapsulation experiments.[1, 9] Particles with the same size and shape as described above were observed after two weeks by transmission electron microscopy (TEM) and AFM, indicating the stability of vesicles formed in water over this time. In addition, no obvious change of morphology was observed after isolation of these vesicles, dehydration by drying under a high vacuum, and subsequent rehydration of the dried vesicles by addition of water.

Compounds **1** and **2** adopt the configuration in which the four alkyl chains are all-axial and all-*cis*.[10] The fully extended alkyl chains on the macrocyclic moiety are about 2.6 nm in length, as estimated from space-filling models and by molecular simulation. When the vesicle solution was spread on a mica plate and dried in vacuo, AFM measurements indicated that the vesicle particles had a flattened shape with rounded edges and a slightly convex top surface. The average vertical cross-sectional thickness of more than ten particles formed from either **1** or **2** was about 10 nm. This was consistent with the thickness of two bilayers of **1** or **2** (Figure 3). Similar AFM measurements have been carried out on unilamellar liposomes from phosphatidylcholine.[11] The average observed thickness of approximately 9.5 nm for the liposome is in good agreement with that of two phosphatidylcholine bilayers, which has previously been reported.[12] The bilayer structure was also confirmed by differential scanning calorimetry (DSC) measurements of the vesicle solution prepared from **1**.[13] The endothermic peak (recorded when the sample temperature was rising) was observed at 65.1 °C, probably due to the gel-to-liquid-crystal phase transition, which is one of the fundamental characteristics of bilayer membranes.[14] This suggests that the vesicles from **1** and **2** are composed of unilamellar membranes, in which the macrocyclic amphiphiles are aligned with their hydrophilic hydroxyl groups facing the aqueous phase.

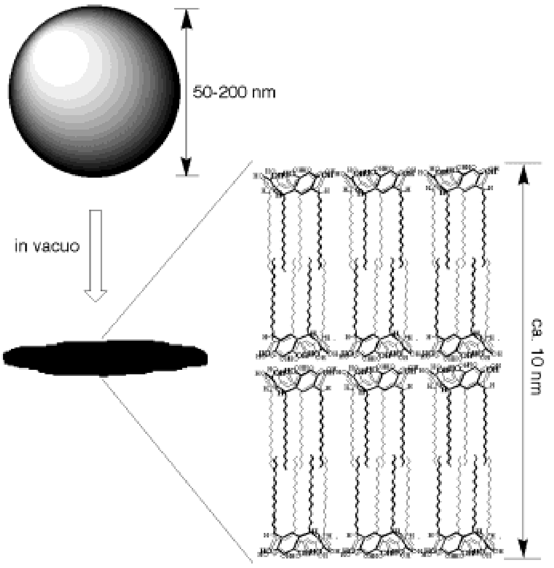

Figure 3. A hypothetical representation of the vesicle formed from **2** and its flattened image.

Amphiphiles with different chemical structures and arrangement of hydrophilic and hydrophobic groups have been reported, and their structural features determine the morphological and functional properties of those self-assemblies formed in water.[15] The formation of vesicles from monoalkylphenol derivatives is in theory unexpected because of the conelike shape of the molecules and the high pK_a value of the OH groups. In fact, alkylresorcinol **3**, which has an alkyl chain as long as that in **1** and **2** but lacks a macrocyclic structure, forms micellelike aggregates under conditions identical to those described here. Aggregates of **3** with diameters less than 16 nm were confirmed by AFM.[16] In contrast, owing to the macrocyclic structures of **1** and **2** composed of four alkylresorcinol and alkylpyrogallol moieties, respectively, the amphiphiles have a cylindrical shape, and thus vesicles are the preferred morphology of aggregates formed in water.

The FT-IR spectrum of the dehydrated vesicles of **1** shows the stretching band of the hydrogen-bonded OH groups ($3500\ \text{cm}^{-1}$).[17] A pair of hydroxyl groups on adjacent benzene rings form a hydrogen bond due to their proximity, which stabilizes the all-axial and all-*cis* configuration, and probably promotes the dissociation of one OH group in the pair at the experimental pH. This also suggests the existence of intermolecular $OH \cdots O$ hydrogen bonds. This phenomenon along with the shape of the amphiphile and hydrogen bonds in **1** and **2** should help stabilize the vesicle structure. To the best of our knowledge this is the first example in which a phenolic surfactant self-assembles to furnish a vesicle.

We have shown that a macrocycle consisting of four phenolic amphiphiles and having a cylindrical molecular shape self-assembles selectively to form a vesicle. The intra- and intermolecular hydrogen bonds between OH groups on **1** and **2** play an essential role in stabilizing the assembled structure. This work, therefore, may open the way for the study of calixarenes in assembled form, in contrast to previous studies dealing mainly with their unimolecular function.

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[1] a) J. H. Fendler, *Membrane Mimetic Chemistry*, Wiley, New York, **1982**; b) T. Kunitake, *Angew. Chem.* **1992**, *104*, 692; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 709.

[2] a) *Liposomes as Drug Carriers: Recent Trends and Progress*, (Ed.: G. Gregoriadis), Wiley, Chichester, **1988**; b) A. Kay, M. Grätzel, *J. Phys. Chem.* **1993**, *97*, 6272.

[3] Y. Tanaka, Y. Kobuke, M. Sokabe, *Angew. Chem.* **1995**, *107*, 717; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 693.

[4] For the formation of vesicles from macrocyclic amphiphiles see: a) S. Arimoto, T. Nagasaki, S. Shinkai, *J. Chem. Soc. Perkin Trans. 2* **1995**, 679; b) P. Ghosh, T. Khan, P. K. Bharadwaj, *Chem. Commun.* **1996**, 189, and references therein. For the self-assembly of calix[4]resorcarene in an organic solvent see: c) L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469.

[5] To remove the organic solvent the aqueous buffer was heated at 60 °C. The spherical particles were also obtained by sonication of the buffer containing macrocyclic amphiphiles. Compound **2** was obtained as colorless crystals and the spectroscopic data (^{1}H and ^{13}C NMR, IR, and mass spectra) were consistent with the given structure. The dodecaacetylated derivative of **2** was used to obtain a correct C,H,O analysis because of the extremely high hygroscopicity of unsubstituted **2**.

[6] Electron micrographs were recorded on JEOL TEM-2000F and TEM-1010 instruments. The freeze-fracture replicas were fabricated with a JEOL JFD-9010 instrument.

[7] For AFM measurements of vesicles and the determination of their shape, diameter, and thickness, and estimation of the number of membrane layers, see: S. Singh, D. J. Keller, *Biophys. J.* **1991**, *60*, 1401.

[8] AFM images were recorded on an SPI-3700 instrument from Seiko Instruments Inc. operating in cyclic contact and noncontact modes using a silicon cantilever with force constants of $20\ \text{N}\,\text{m}^{-1}$ and $3\ \text{N}\,\text{m}^{-1}$, respectively, under atmospheric conditions. These two operating modes provided almost the same images for an identical sample.

[9] The vesicle solution (2.5×10^{-3} M, 4 mL) containing a fluorescent dye (sodium 8-amino-1,3,6-naphthalenetrisulfonate, 34.2 mg) was separated with Sephadex G-50 (1 cm × 20 cm) using the buffer as the eluent. The vesicles were obtained in the 0.36–0.63 mL fraction, whereas the free dye was obtained after elution of 0.9 mL. The vesicle fraction fluoresced at 515 nm when irradiated at 370 nm.

[10] a) Y. Aoyama, Y. Tanaka, S. Sugahara, *J. Am. Chem. Soc.* **1989**, *111*, 5397; b) Y. Tanaka, Y. Aoyama, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3343.

[11] J. Sunamoto, K. Iwamoto, H. Kondo, *Biochem. Biophys. Res. Commun.* **1980**, *94*, 1367.

[12] J. N. Israelachvili, *Intermolecular and Surface Forces*, 2nd ed., Academic Press, London, **1992**.

[13] DSC was recorded on a Perkin Elmer Pyris 1 instrument. Measurements were repeated four times for the same sample with a heating cycle of 15 to 90 °C. The reproducibility of the peak top temperature (T_c) was ±0.5 °C. After the sample had been cooled to −50 °C it showed a higher T_c of 82.6 °C.

[14] Y. Okahata, R. Ando, T. Kunitake, *Ber. Bunsen-Ges. Phys. Chem.* **1981**, *85*, 789.

[15] J. N. Israelachvili, D. J. Mitchell, B. W. Ninham, *J. Chem. Soc. Faraday Trans. 1* **1976**, *72*, 1525.

[16] C. Huang, J. T. Mason, *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 308.

[17] For IR spectra of the dried vesicles and the contribution of hydrogen bonds towards the stabilization of the vesicle, see: T. Shimizu, M. Kogiso, M. Masuda, *Nature* **1996**, *383*, 487.

Adsorption of Acetone onto MgO: Experimental and Theoretical Evidence for the Presence of a Surface Enolate**

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Basic catalysts are widely used in heterogeneous catalytic processes either as supports or active components. Among these processes, aldol condensation of ketones is of out-

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