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Electrostatic Assembly of Dendrimer Electrolytes: Negatively and Positively Charged Dendrimer Porphyrins[**]

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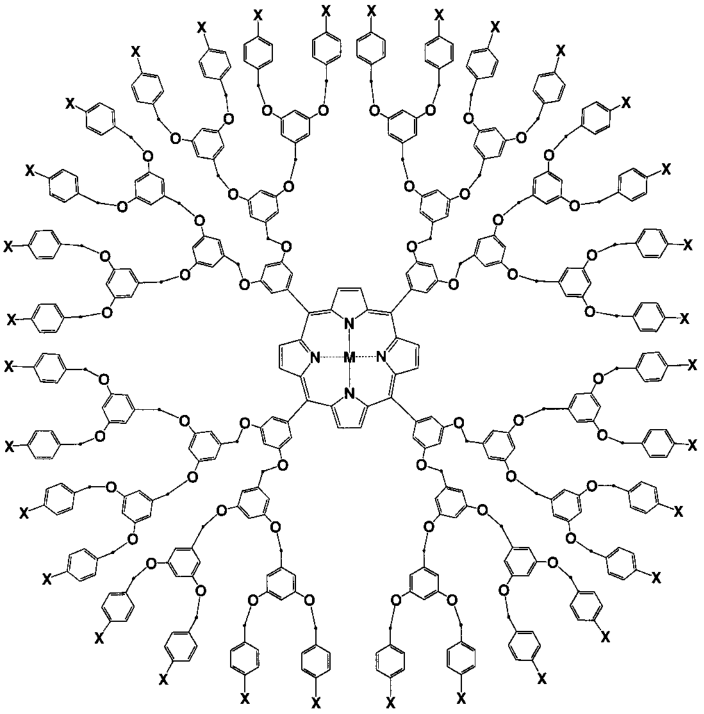
Dendrimers are nanosized hyperbranched macromolecules with well-defined three-dimensional shapes[1] and are potential building blocks for the construction of organized functional materials with nanometric precision. Therefore, it is important to develop a synthetic method that enables controlled spatial arrangement of functional dendrimers. Recently some conelike dendrimers (dendrons) were reported to self-assemble with the aid of van der Waals, hydrogen-bonding, and metal-ligating interactions into superstructures with spherical, disklike, and other configurations.[2, 3] Here we present results of the first study on electrostatic assembly of dendrimer electrolytes.[4] For this purpose we utilized negatively and positively charged dendrimers that contain within their frameworks a fluorescence probe in the form of a porphyrin (either as a free base or as a zinc complex).

We previously reported the convergent synthesis[5] of a negatively charged, water-soluble dendrimer zinc porphyrin (32[−]DPZn) with 32 carboxylate ion functionalities on its exterior surface.[6] This photofunctional macromolecule consists of a four-layered aryl ether dendrimer framework, and is expected to adopt a spherical conformation with an estimated diameter of 4–5 nm.[7] We have now synthesized from 32[HO$_2$C]DPZn[6] a positively charged dendrimeric zinc porphyrin, 32[+]DPZn, with 32 ammonium ion functionalities on its periphery.



32[MeO$_2$C]DPH$_2$: X = CO$_2$Me, M = H$_2$
32[MeO$_2$C]DPZn: X = CO$_2$Me, M = Zn
32[HO$_2$C]DPH$_2$: X = CO$_2$H, M = H$_2$
32[HO$_2$C]DPZn: X = CO$_2$H, M = Zn
32[−]DPH$_2$: X = CO$_2^-$K$^+$, M = H$_2$
32[−]DPZn: X = CO$_2^-$K$^+$, M = Zn
32[Me$_2$N]DPZn: X = CONH(CH$_2$)$_2$NMe$_2$, M = Zn
32[+]DPZn: X = CONH(CH$_2$)$_2$N$^+$Me$_3$Cl$^-$, M = Zn

To investigate the possibility of electrostatic assembly between the negatively and positively charged dendrimer electrolytes 32[−]DPH$_2$ (free-base porphyrin) and 32[+]DPZn, the transmittance at 500 nm[8] was monitored when solutions of the two in phosphate buffer (pH 6.9, 1.5 μM) were mixed at 20 °C. As shown in Figure 1, the transmittance of the solution was highly dependent upon the molar ratio of the two dendrimer electrolytes, and it dropped sharply when the two concentrations were nearly equal. Fluorescence microscopy of a 100 μM phosphate buffer solution of either 32[−]DPZn (Figure 2a) or 32[+]DPZn excited at 400–440 nm (Soret bands) revealed strong, homogeneous emission from the entire solution. On the other hand, when the two solutions were mixed in an equimolar ratio ([32[−]DPZn]:[32[+]DPZn] = 1:1) the microscope image became dark, and large fluorescent aggregates (10–20 μm) were observed (Figure 2b). If this mixture was allowed to stand for a day at room temperature, the aggregates continued to grow and then precipitated out of the solution. If either 32[−]DPZn or 32[+]DPZn was present in excess, no aggregate formation was detected. Thus, 32[−]DPZn and

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[**] Supporting information for this article is available on the WWW under http://www/wiley-vch.de/home/angewandte/ or from the author.

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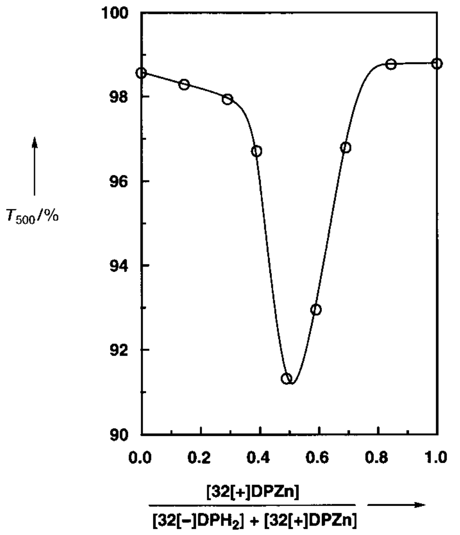


Figure 1. Change in transmittance at 500 nm when phosphate buffer solutions (pH 6.9, 1.5 μM) of 32[−]DPH$_2$ and 32[+]DPZn are mixed at 20 °C.[8]

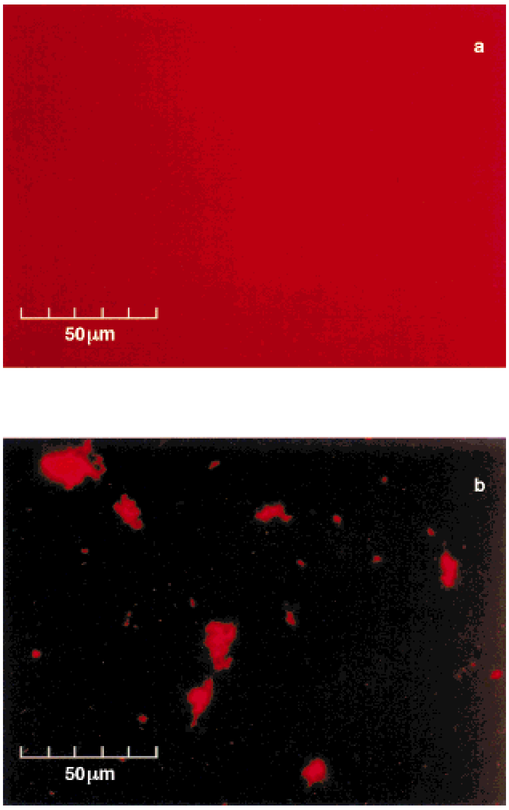


Figure 2. Fluorescence microscopic images of aqueous solutions (100 μM) of a) 32[−]DPZn and b) an equimolar mixture of 32[−]DPZn and 32[+]DPZn upon excitation at 400–440 nm (Soret band) at room temperature.

32[+]DPZn are able to assemble electrostatically in aqueous media to form a polyelectrolyte complex whose size is highly dependent upon the molar ratio of the negatively and positively charged dendrimers. This contrasts sharply with the general trend for electrostatic assembly of linear polyelectrolytes in aqueous media, where precipitates form over a wide range of molar ratios for the polyanion and polycation.

Mixtures of the two dendrimer electrolytes in alcoholic media do not form precipitates, irrespective of the composition. We therefore conducted spectroscopic investigations on interactions of these materials. First, a fluorescence-polarization profile was investigated for 32[−]DPH$_2$ upon addition of 32[+]DPZn.[9] In general, excitation by polarized light of a chromophore with limited rotatability produces polarized fluorescence. The degree of polarization P is expressed as $(I_{\parallel}-I_{\perp})/(I_{\parallel}+I_{\perp})$, where $I_{\parallel}$ and $I_{\perp}$ are fluorescence intensities of the parallel and perpendicular components. Thus, P should increase with the size of the fluorescent molecule or aggregate. Excitation with polarized light at 520 ± 1 nm (Q band) of a solution of 32[−]DPH$_2$ (1.25 μM) in methanolic KOH (0.1 M) at 20 °C caused the free-base porphyrin to emit polarized florescence at 654 and 718 nm, with P(718 nm) = 0.04. Addition of 32[+]DPZn[10] to this solution resulted in an increase in P, with a clear inflection point in the titration curve at a molar ratio [32[+]DPZn]:[32[−]DPH$_2$] = 4:1 (Figure 3a, ●).[11] On the other hand, when negatively charged 32[−]DPZn[10] was mixed with 32[−]DPH$_2$ under otherwise identical conditions, P increased only slightly (○),[12] where no saturation tendency was evident.

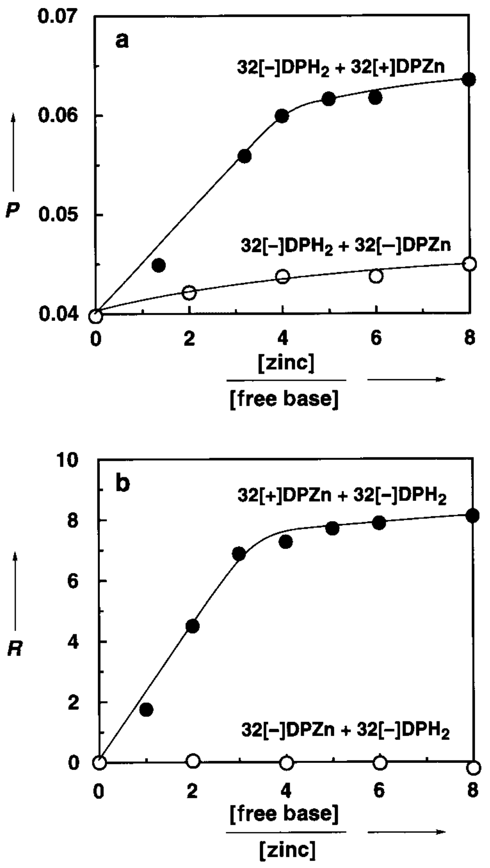
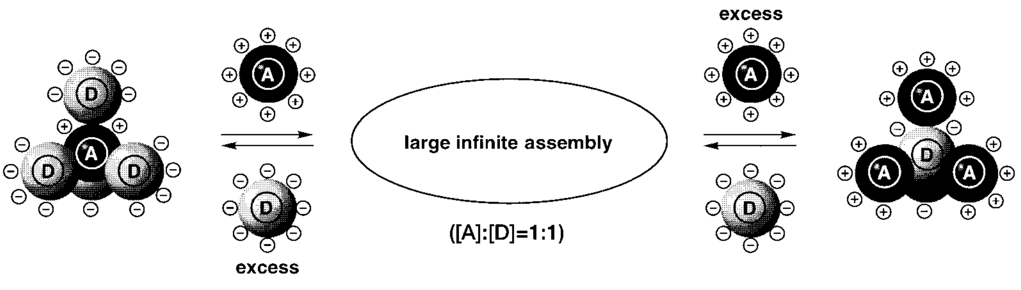


Figure 3. Fluorescence profiles of the systems 32[−]DPH$_2$/32[+]DPZn and 32[−]DPH$_2$/32[−]DPZn in deoxygenated methanolic KOH at 20 °C: a) fluorescence polarization $P=(I_{\parallel}-I_{\perp})/(I_{\parallel}+I_{\perp})$ of 32[−]DPH$_2$ in the presence of 32[+]DPZn (●) or 32[−]DPZn (○) upon excitation at 520 ± 1 nm ($I_{\parallel}$ and $I_{\perp}$ represent fluorescence intensities of the parallel and perpendicular components, respectively) and b) degree of energy transfer $R=I_{\text{free base}}/I_{\text{zinc}}$ from 32[+]DPZn (●) observed at 718 and 613 nm) or 32[−]DPZn (○, observed at 718 and 608 nm) to 32[−]DPH$_2$ upon excitation at 439 ± 1 nm.[14]

In the course of this study we also investigated the assembly of the dendrimer electrolytes with energy-transfer measurements as the probe. Zinc and free-base porphyrins, when they are in sufficiently close proximity, interact photochemically by energy transfer from the zinc compound to the free-base compound.[13] We therefore studied the energy transfer communication between 32[+]DPZn as a donor (1.25 μM) and 32[−]DPH$_2$ as an acceptor in 0.1 M methanolic KOH. When 32[+]DPZn alone was excited at 439 ± 1 nm (Soret band), the zinc porphyrin within the molecule fluoresced at 613 and 664 nm. In the presence of an equimolar amount of 32[−]DPH$_2$ the fluorescence bands from 32[+]DPZn decreased in intensity and new fluorescence bands appeared at 654 and 718 nm[14] associated with 32[−]DPH$_2$ and suggestive of a singlet energy transfer from 32[+]DPZn to 32[−]DPH$_2$. A plot of the degree of energy transfer R (relative fluorescence intensity $I_{\text{free base}}/I_{\text{zinc}}$)[14] again displays a clear saturation point at a molar ratio [32[−]DPH$_2$]:[32[+]DPZn] of approximately 4:1 (Figure 3b, ●). This indicates that there is a critical concentration of 32[−]DPH$_2$ for the efficient transfer of energy from 32[+]DPZn to 32[−]DPH$_2$. In sharp contrast, no energy transfer from 32[−]DPZn to 32[−]DPH$_2$ took place under the same conditions with the electrostatically repulsive combination 32[−]DPZn/32[−]DPH$_2$ (○). When one takes into account the saturation phenomenon in the fluorescence polarization (Figure 3a), the energy-transfer profile in Figure 3b (●) indicates that 32[+]DPZn can bind at most four molecules of 32[−]DPH$_2$ within a range that permits energy transfer (Scheme 1). For reference purposes, the energy-transfer profile of 32[+]DPZn was investigated with 5,10,15,20-tetrakis(4-carboxyphenyl)porphine (TCPPH$_2$), an anionic acceptor that bears only four negative charges. The fluorescence of 32[+]DPZn was in this case much less efficiently quenched by the addition of TCPPH$_2$ ($I_{\text{free base}}/I_{\text{Zinc}} = 1.6$ at [TCPPH$_2$]:[32[+]DPZn] = 4:1).

Energy transfer rate constants are known to reflect the distance between donor and acceptor.[13] We measured the fluorescence lifetime τ_0 of 32[+]DPZn in methanolic KOH (2.5 μM) at 20 °C to be 1.7 ns, which is close to that observed for 32[−]DPZn (1.4 ns)[6] under the same conditions. In the presence of 32[−]DPH$_2$ (1.25 μM) as acceptor, a new, short-lived component ($\tau = 0.3$ ns, 70 %) appeared in the fluorescence-decay profile of 32[+]DPZn. The energy transfer rate constant k_{ENT} ($k_{\text{ENT}} = \tau^{-1} - \tau_0^{-1}$) was $3.0 \times 10^9\ \text{s}^{-1}$. Based on reported k_{ENT} values for fixed-distance energy-transfer sets,[13] the observed k_{ENT} value is reasonable for a model in which the donor 32[+]DPZn and the acceptor 32[−]DPH$_2$ interact with each other directly.



Scheme 1. Schematic representation of the electrostatic interaction between negatively and positively charged dendrimer electrolytes. D represents a donor and A an acceptor in energy transfer.

We have thus demonstrated that oppositely charged dendrimer electrolytes in protic media interact electrostatically to form an organized assembly (Scheme 1) in which the topology of functionalities within the molecule is established in advance. The present study therefore provides a new strategy for the controlled spatial arrangement, with nanometric precision, of two functionalities that communicate; this is a strategy that could contribute significantly toward progress in nanoscopic chemistry and nanomaterials science. Although dendrimer electrolytes bear a morphologic resemblance to ionic micelles, they are not subject to loss of their own structural identities when assembled electrostatically because they consist of single molecules characterized by covalent linkages.

Experimental Section

32[−]DPH$_2$: Methyl ester 32[MeO$_2$C]DPH$_2$[15] was hydrolyzed with KOH in THF/water for 30 h. The reaction mixture was poured into acetic acid, and the resulting precipitate was collected by centrifugation, washed with dilute aqueous HCl, and freeze-dried to give 32[HO$_2$C]DPH$_2$. ^{1}H NMR (270 MHz, [D$_6$]DMSO, 80 °C): $\delta = 8.84$ (s, 8H, pyrrole-β), 7.80, 7.32 (both d, $^3J = 8.10$ Hz, 128H, Ar-o-H, Ar-m-H), 7.48 (s, 8H, Ar-o-H), 7.14 (s, 4H, Ar-p-H), 6.76 (d, $^4J = 2.7$ Hz, 16H, Ar-o-H), 6.61 (d, $^4J = 2.7$ Hz, 32H, Ar-o-H), 6.58 (s, 8H, Ar-p-H), 6.51 (d, $^4J = 2.7$ Hz, 16H, Ar-p-H), 5.18 (s, 16H, OCH$_2$), 4.95 (s, 64H, OCH$_2$), 4.93 (s, 32H, OCH$_2$). 32[HO$_2$C]DPH$_2$ was dissolved in phosphate buffer (pH 6.8) or 0.1 M KOH in methanol to generate 32[−]DPH$_2$. UV/Vis (KOH/MeOH): $\lambda_{\max}$ (lgε) = 427 (5.29), 517.8, 553, 592, 648.4 nm; fluorescence (KOH/MeOH): $\lambda = 654$, 718 nm.

32[−]DPZn: 32[HO$_2$C]DPZn was prepared from 32[MeO$_2$C]DPZn by alkaline hydrolysis of the exterior methyl ester groups and isolated as described for 32[−]DPH$_2$. MALDI-TOF-MS (3-indolacrylic acid matrix): $m/z = 8030$ (calcd 8028); ^{1}H NMR (270 MHz, [D$_6$]DMSO, 80 °C): $\delta = 8.81$ (s, 8H, pyrrole-β), 7.81, 7.33 (both d, $^3J = 8.34$ Hz, 128H, Ar-o-H, Ar-m-H), 7.43 (s, 8H, Ar-o-H), 7.09 (s, 4H, Ar-p-H), 6.74 (s, 16H, Ar-o-H), 6.60 (s, 32H, Ar-o-H), 6.55 (s, 8H, Ar-p-H), 6.50 (s, 16H, Ar-p-H), 5.17 (s, 16H, OCH$_2$), 4.96 (s, 64H, OCH$_2$), 4.91 (s, 32H, OCH$_2$); ^{13}C NMR (68 MHz, [D$_6$]DMSO, 20 °C): $\delta = 166.85$ (CO$_2$H), 159.32, 159.10, 141.59, 139.24, 129.91, 129.22, 127.06, 106.30, 101.04 (aromatic C), 69.07, 68.58 (CH$_2$O). 32[HO$_2$C]DPZn was dissolved in 0.1 M KOH/methanol to produce 32[−]DPZn.[6] UV/Vis (KOH/MeOH): $\lambda_{\max}$ (lgε) = 429.5 (5.44), 559.8, 600.4 nm; fluorescence (KOH/MeOH): $\lambda = 608$, 660 nm.

32[+]DPZn: A solution of 32[HO$_2$C]DPZn (20.4 mg, 2.54×10^{-3} mmol), 1-methyl-2-chloropyridinium iodide (427 mg, 1.67 mmol),[16] and N,N-dimethylethylenediamine (0.7 mL, 6.3 mmol) in N,N-dimethylacetamide (10 mL, distilled) was heated at 50 °C for 6 d. The reaction mixture was then subjected to dialysis against water for 4 d and freeze-dried to give 32[Me$_2$N]DPZn (23.2 mg, 88.9 %). MALDI-TOF-MS (3-indolacrylic acid matrix): $m/z = 10261$ (calcd 10268); ^{1}H NMR (270 MHz, [D$_6$]DMSO, 80 °C): $\delta = 8.87$ (s, 8H, pyrrole-β), 8.14 (s, 32H, amide-NH), 7.74, 7.32 (both d, $^3J = 8.23$ Hz, 128H, Ar-o-H, Ar-m-H), 7.45 (s, 8H, Ar-o-H), 7.13 (s, 4H, Ar-p-H), 6.76 (s, 16H, Ar-o-H), 6.61 (s, 32H, Ar-o-H), 6.58 (s, 8H, Ar-p-H), 6.52 (s, 16H, Ar-p-H), 5.17 (s, 16H, OCH$_2$), 4.97 (s, 64H, OCH$_2$), 4.93 (s, 32H, OCH$_2$), 3.28 (br, 128H, NCH$_2$ and NHCH_2, overlapped with H$_2$O), 2.22 (s, 192H, NCH$_3$); ^{13}C NMR (68 MHz, [D$_6$]DMSO, 20 °C): $\delta = 165.65$ (CONH), 159.28, 159.06, 139.72, 139.11, 133.48, 127.15, 126.89, 106.37, 100.98 (aromatic C), 69.14, 68.60 (CH$_2$O), 57.46 (CH$_2$N), 44.35 (CH$_3$N), 36.52 (NHCH$_2$). Quantitative conversion of the acid into the amide function was confirmed by the absence of a signal at $\delta = 166.85$. A mixture of 32[Me$_2$N]DPZn (15.2 mg, 1.48×10^{-3} mmol) and methyl iodide (0.60 mL, 9.6 mmol) in DMSO

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(10 mL, distilled) was refluxed for 3 d. After removal of volatile fractions from the reaction mixture the residue was subjected to dialysis against pure water for 3 d and freeze-dried to give the iodide salt of 32[+]DPZn (17.3 mg, 79.0 %). This salt was then dialyzed for 2 d against saturated NaCl solution and an additional 2 d against pure water, after which it was freeze-dried. ^{1}H NMR (270 MHz, [D$_6$]DMSO, 80 °C): $\delta = 8.97$ (s, 8H, pyrrole-β), 8.73 (s, 32H, amide-NH), 7.84, 7.43 (d, $^3J = 7.42$ Hz, 128H, Ar-*o*-H, Ar-*m*-H), 7.51 (s, 8H, Ar-*o*-H), 7.23 (br s, 4H, Ar-*p*-H), 6.87 (s, 16H, Ar-*o*-H), 6.72 (s, 32H, Ar-*o*-H), 6.66 (s, 8H, Ar-*p*-H), 6.57 (s, 16H, Ar-*p*-H), 5.27 (s, 16H, OCH_2), 5.07 (s, 64H, OCH_2), 5.01 (s, 32H, OCH_2), 3.68, (br q, 64H, CH_2), 3.54 (br t, 64H, CH_2), 3.14 (s, 288H, NCH_3); ^{13}C NMR (68 MHz, [D$_6$]DMSO, 20 °C): $\delta = 166.02$ (CONH), 159.30, 159.10, 140.25, 139.18, 132.82, 127.20, 106.68, 100.95 (aromatic C), 68.68 (CH_2O), 63.68 (CH_2N), 52.57 (CH_3N), 33.75 ($NHCH_2$); UV/Vis (KOH/MeOH): λ_{max} (lgε) = 436.5 (5.49), 563, 608 nm; fluorescence (KOH/MeOH): $\lambda = 613$, 664 nm.

Electronic absorption spectra were recorded with a Jasco Model V-560 UV/Vis spectrometer. Fluorescence-polarization and energy-transfer experiments were performed at 20 °C with a Jasco Model FP-777 fluorescence spectrometer. In the energy-transfer experiments with 32[−]DPH$_2$ as acceptor, undesirable contamination of the fluorescence bands as a result of direct excitation of the acceptor was evaluated by a control experiment without donor under otherwise identical conditions. The spectrum that resulted was subtracted from the overall fluorescence spectrum for the donor/acceptor systems. The spectral profile of 32[−]DPH$_2$ in the control experiment was shown to obey the Lambert–Beer law.

Fluorescence lifetimes were measured in deoxygenated 0.1 M methanolic KOH at 20 °C with a Hamamatsu Model C4780 picosecond fluorescence lifetime measuring system equipped with a Model C4334 streak scope and a N_2 laser pumped coumarin 440 dye laser as excitation source. The N_2 laser was an LN120C2 device (15 Hz, peak width (FWHM) 350 ps, 10 mJ per pulse), and the excitation wavelength was 430 nm. Fluorescence bands were isolated from scattered laser light by a 600 nm glass cutoff filter. Emission was collected in the wavelength range 600–680 nm and analyzed with the program Photolumi version 2.4.4 after deconvolution of the instrument-response function (time resolution 50 ps).

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A Synthetic Cation-Transporting Calix[4]arene Derivative Active in Phospholipid Bilayers[**]

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The transport of cations through bilayer barrier membranes is a ubiquitous biological process, and one of the most critical for sustaining life. Cation transport in vivo is usually mediated by proteins having one or more transmembrane helices that organize into pores. Increasing evidence suggests that channel function may also be achieved by compounds such as the remarkable C peptide.[1] Although a vast amount is known about the biophysics of membrane transport, much of this information is descriptive and does not reveal mechanistic details;[2, 3] how transport occurs is simply not understood at the molecular level. Thus, several model ion transporters have been devised, including short-chain or "minimalist" peptides[4] and a variety of synthetic organic compounds such as tubelike structures, "half-channel" elements, single-strand compounds,[5, 6] and the tris(macrocyclic) channel model **4** that we devised.[7] Compound **4** has proved to be an effective conductor of Na$^+$ ions.[7] The two distal diaza[18]crown-6 macrocycles serve as headgroups in the amphiphilic sense, and as entry and exit points for cations traversing the bilayer.[8] Passage of the transient cation through the medial macrocycle, however, is not necessary.[7]

We describe herein two new channel compounds **1** and **2** having a calix[4]arene central unit in a 1,3-*alternate* conformation. Passage of cations through the center of such a rigid

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