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Amphiphilic bipolar duplex α-cyclodextrin forming vesicles

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Abstract—We synthesized a duplex cyclodextrin with two aliphatic links and functionalized with eight pentyl ethers orientated towards the centre of the duplex. We found that this molecule self-assembled in water to form stable vesicles with a diameter within the range 1–10 μm.

1. Introduction

The generation of supramolecular structures of interest usually relies on molecular self-assembly and auto-organization processes. Amongst self-assembled structures, vesicles,[1] i.e., closed membranes separating two water media, have been widely studied particularly as cell models[2] or drug delivery systems.[3] Vesicle-forming molecules are typically amphiphilic compounds such as phospholipids,[4] diblock copolymers,[5] gemini surfactants,[6] etc. Recent studies showed that hydrophobically modified cyclodextrin (CD) can also self-assemble to form nanoparticles or bilayered vesicles.[7] The actual challenge of incorporating CD moieties in a vesicle membrane is motivated by the perspective to use CD as channels in the vesicle membrane for specific molecular recognition, ion exchange, or translocation of biopolymers (proteins, nucleic acids). All the CD-based amphiphilic molecules, which have been demonstrated to form vesicles up to now, were composed of one polar head (the cyclodextrin moiety) and lipophilic chains, thio-alkyls, for example. The formed vesicles were from nanometres to a few micrometres in diameter and the membrane was composed of modified CD organized in a bilayered fashion with the hydrophilic CD moieties orientated towards the inner and outer aqueous medium while apolar tails are facing inside the bilayer. On the other hand, we recently synthesized doubly-bridged CD dimers composed of two polar CD heads separated by aliphatic chains such as **1**,[8] we therefore wondered if a modification of those bipolar compounds could induce them to form vesicles (Fig. 1).

2. Results and discussion

In the following, we will refer to duplexes for the doubly-bridged CD dimers and to dimers for the singly-bridged derivatives as this distinctive feature compared with singly linked dimers led the authors to coin the name duplex cyclodextrins for that family of derivatives.[9] Our strategy towards these rather complex molecules was based on the easy access to $6^A,6^D$ diol **2** by the very efficient benzylation, debenzylation sequence.[10] As illustrated in Scheme 1, a truncated cone is commonly used to represent the CD torus, so that the $6^A,6^D$ diol is conveniently depicted as shown.

The metathesis reaction was the other key tool for the synthesis: a self metathesis of CD **3** led to dimer **4** after

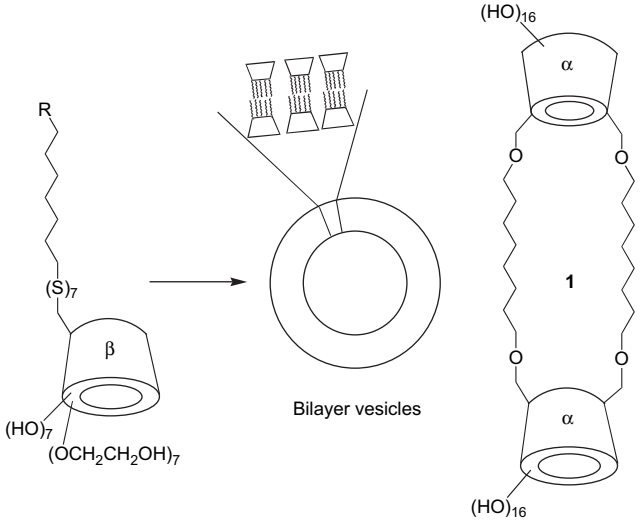

Figure 1. Cyclodextrin bilayer vesicle and structure of duplex **1**.

Keywords: Cyclodextrins; Vesicles; Amphiphile.
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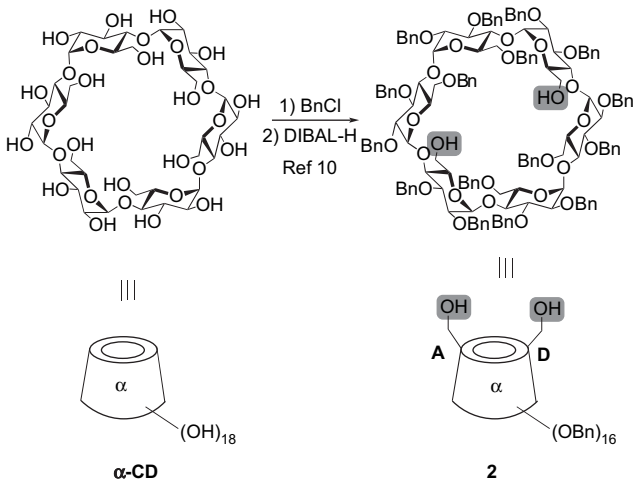
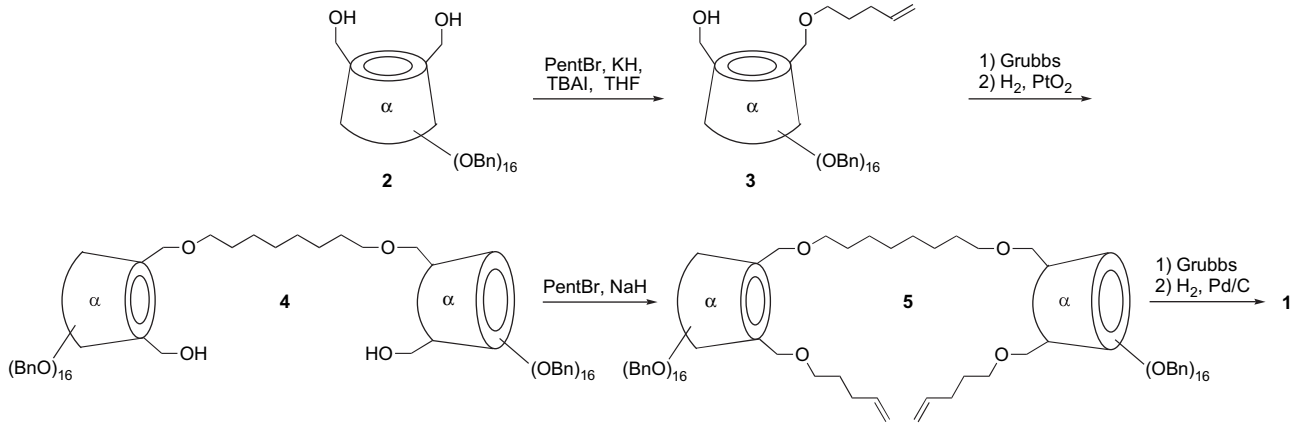


Scheme 1. Synthesis of diol **2** and schematic representation of CDs.

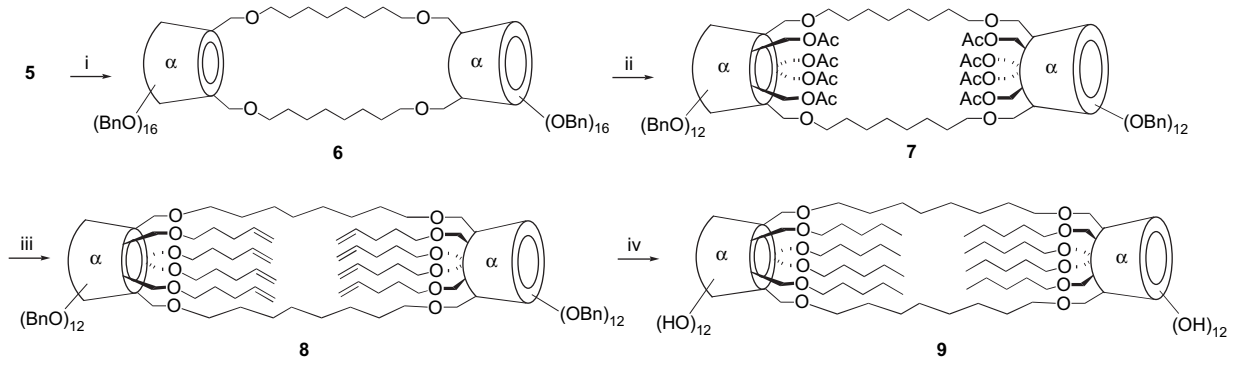
saturation of the double bond, and a ring closing metathesis of CD **5** afforded **1** after hydrogenation[8] (Scheme 2).

The obvious modification of duplex CD **1** to form vesicles is the introduction of aliphatic chains. For this purpose, we started from dimer **5** and formed the perbenzylated duplex CD **6** thanks to a ring closing metathesis and saturation of the double bond. This benzylated compound was then submitted to a selective acetolysis affording the octaacetate **7**. After deacetylation and pentenylation of the transient octaol, the polyalkene **8** was obtained. The reason why we used pentenyl chains was that we first envisaged a poly ring closing metathesis to obtain a dimer of CD linked with six arms, but the result of this reaction remains unclear. We therefore saturated the double bonds as well as removed the benzyl groups through the action of H_2 and Pd–C to give the final bipolar amphiphilic duplex **9** with two octamethylenic links and functionalized with eight pentyl groups (Scheme 3).

The amphiphilic structure of CD **9**, which is composed of two polar heads (cyclodextrins) separated by apolar aliphatic chains, is somehow analogous to that of a dimer of phospholipid molecules within a lipid bilayer of a liposome where the polar heads are orientated towards the inner and outside aqueous medium while apolar tails are facing inside the bilayer.[4] Therefore, to investigate the ability of CD **9** to self-assemble into micrometre-sized vesicles, CD **9** films were electroswollen in a sucrose solution by the so-called electroformation technique,[11] which is classically used to prepare Giant Unilamellar Vesicles (GUV) from phospholipid films, i.e., liposomes. After 14 h of electroswelling in a 0.1 M sucrose solution, we observed that some vesicles with a size ranging from 1 μm to 30 μm have been formed. Figure 2 shows typical microscopy images of such formed vesicles.



Scheme 2. Synthesis of duplex **1**.



Scheme 3. Synthesis of the amphiphilic bipolar duplex **9**. Reagents and conditions: (i) (1) $Cl_2(PCy_3)_2Ru{=}CHPh$ (5 mol %), CH_2Cl_2 (10^{-1} M), reflux, 3 h, then $Pb(OAc)_4$, rt, overnight; (2) H_2, PtO_2, EtOAc, 12 h, 84% over two steps; (ii) Ac_2O, TMSOTf, −30 °C, 30 min, 52%; (iii) (1) MeONa, MeOH, CH_2Cl_2, rt, 12 h; (2) 5-bromo-pent-1-ene, NaH, DMF, rt, 93%; (iv) H_2, Pd–C, MeOH, AcOH, rt, 12 h, 95%.

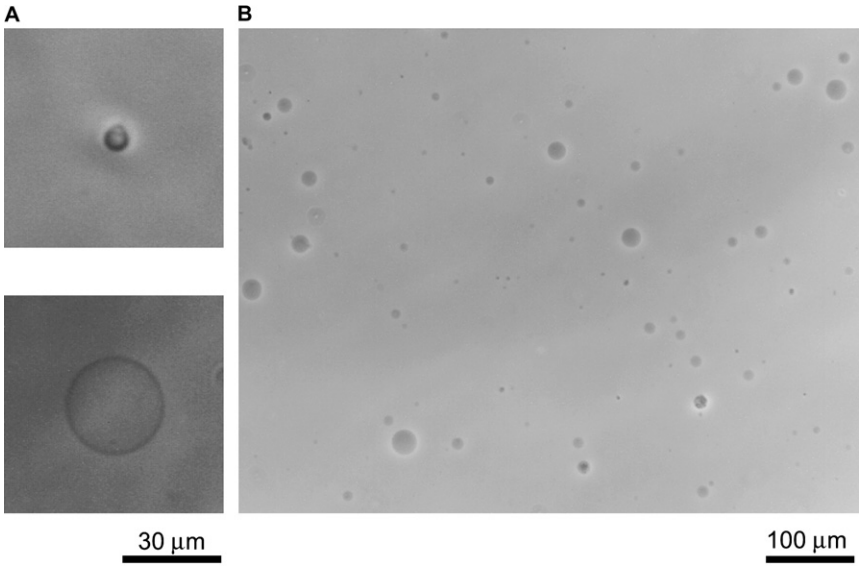


Figure 2. Typical phase contrast microscopy images of CD **9** vesicles obtained by electroswelling CD **9** films in a sucrose solution (~0.1 M, 104 mOsmol/l). (A) Vesicles in a sucrose solution (~0.1 M, 104 mOsmol/l). Most vesicles are 1–10 μm in diameter (top). The largest vesicles are about 30 μm in diameter (bottom). (B) Vesicles in a glucose solution (~0.1 M, 104 mOsmol/l) after 2 h of decantation.

When vesicles were directly observed in the sucrose solution, i.e., inner and outer medium of vesicles is sucrose, the membrane appeared to be very thin, which suggests that the membrane is composed of one or a small number of layers of CD **9** molecules. Most vesicles were typically 1–10 μm in diameter (Fig. 2A top) but some larger vesicles with a diameter up to 30 μm were also observed (Fig. 2A bottom). Then, vesicle suspension in sucrose was mixed with a glucose solution of the same osmolarity but a lower density and put in a microscopy observation chamber. After 2 h of decantation, most vesicles were collected on the glass slide at the bottom of the observation chamber and observed by microscopy. Figure 2B shows a typical phase contrast microscopy image of the collected vesicles. The contrast difference between the inner and outer parts of vesicles is due to difference in refractive index between the sucrose solution inside the vesicle and the glucose+sucrose solution outside and indicates that the encapsulated pure sucrose solution remains inside the vesicles. It shows also that a relatively small but significant amount of vesicles was obtained and that most vesicles are typically 1–10 μm in diameter while a small proportion of vesicles have a diameter between 10 and 30 μm. To quantify the ability of CD **9** molecules to form vesicles, it is interesting to make the comparison with a common phospholipid such as Egg PC. For this purpose, CD **9** and Egg PC films were prepared and electroswollen under exactly the same conditions. We observed that, compared to EPC, the vesicles formed with CD **9** were approximately 10 times less in number and in size (EPC vesicles were typically from 10 to 300 μm in diameter).

3. Conclusion

Therefore, we demonstrated for the first time that CD dimers have the ability to form closed vesicles with typical diameters between 1 and 10 μm. The yield of vesicles' production is still very low compared to common phospholipids classically used to prepare liposomes. By optimizing the molecular parameters of CD dimers, such as the length of alkyl spacer or CD substitution, higher yield of preparation and vesicles of larger size (10–100 μm) might be obtained. Further combined with supramolecular chemistry and biochemistry, CD-based cell-sized vesicles might be used as cell models or smart materials with the advantage to use CD dimers as molecular channels for ion exchange, specific molecular recognition or biopolymer translocation.

4. Experimental part

4.1. General

MALDI mass spectra were recorded with a PerSeptive Biosystems Voyager Elite (Framingham, MA, USA) time-of-flight mass spectrometer. This instrument was equipped with a nitrogen laser (337 nm), a delayed extraction and a reflector. PEG standards were used to calibrate the mass scale using the two points calibration software 3.07.1 from PerSeptive Biosystems. The matrix, 2,5-dihydroxybenzoic acid (2,5-DHB), was from Sigma (France) and used without further purification. ESI mass spectra were recorded with a Q-TOF1 (Micromass) time-of-flight mass spectrometer with a sample cone of 40 V. ^{1}H NMR spectra were recorded with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ or pyridine-d_5 at ambient temperature. Assignments were aided by COSY experiments. ^{13}C NMR spectra were recorded at 100.6 MHz with a Bruker DRX 400 spectrometer for solutions in $CDCl_3$ or pyridine-d_5 adopting 77.00 ppm for the central line of $CDCl_3$. Assignments were aided by J-mod technique and HMQC experiments. Optical rotations were measured on a Perkin Elmer 241 digital polarimeter with a path length of 1 dm. Reactions were monitored by thin-layer chromatography (TLC) on a precoated plate of silica gel 60 F_{254} (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh, E. Merck).

4.1.1. Perbenzylated duplex (6). Grubbs catalyst (9 mg, 11 μmol) was added to a stirred solution of **5** (547 mg, 106 μmol) in degassed dichloromethane (100 ml), under argon at room temperature. The reaction mixture was heated under reflux for 3 h. $Pb(OAc)_4$ (8 mg, 1.5 equiv/Ru) was added to the cooled solution (room temperature). The reaction mixture was stirred overnight at room temperature and concentrated. Chromatography of the residue (cyclohexane–ethyl acetate 5:1) on silica gel afforded the transient unsaturated duplex (470 mg, 87%) as a white foam: R_f 0.4 (cyclohexane–ethyl acetate 3:1). MS (MALDI-TOF): *m/z* (%) 5067.3 (100) $[M+Na]^+$. The solution of the obtained unsaturated duplex (470 mg, 87 μmol) with PtO_2 (20 mg, 87 μmol) in ethyl acetate (20 ml) was stirred overnight under the atmosphere of hydrogen. After filtration and concentration the residue was purified by flash chromatography, eluting with cyclohexane–ethyl acetate (6:1) to give compound **6** (456 mg, 97%) as a white foam: R_f 0.5 (cyclohexane–ethyl acetate 4:1); $[\alpha]_D$ +43 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.07 (160H, arom. H), 5.63 (4H, d, $J_{1,2}$= 3.8 Hz, 4×H-1), 5.51 (4H, AB, *J*=11.7 Hz, PhCH_2), 5.37 (4H, AB, *J*=11.6 Hz, PhCH_2), 5.08 (4H, d, $J_{1,2}$=3.0 Hz, 4×H-1), 5.01 (4H, AB, *J*=10.6 Hz, PhCH_2), 5.37 (8H, AB, *J*=10.6 Hz, PhCH_2), 4.94 (8H, m, 4×H-1, 4×PhCH_2), 4.82 (4H, AB, *J*=12.2 Hz, PhCH_2), 4.65–4.45 (24H, m, PhCH_2), 4.36 (12H, m, 4×H-3, 4×H-6, 4×PhCH_2), 4.19 (20H, m, 4×H-3, 4×H-4, 4×H-5, 4×H-6), 4.09 (4H, m, H-5), 3.97 (12H, m, 4×H-4, 8×H-5), 3.83 (4H, m, H-6), 3.74 (4H, m, H-6), 3.67 (8H, m, H-2, H-6), 3.59 (12H, m, 4×H-2, 8×H-6), 3.45 (12H, m, 4×H-2, 4×OCH_2, 4×PhCH_2), 3.30 (8H, m, 4×OCH_2, 4×PhCH_2), 1.55 (8H, m, OCH_2CH_2), 1.26 (16H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.2, 139.1, 138.5, 138.3, 138.2, 138.1, 138.0, 137.9 (32×arom. C), 128.1, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 126.9, 126.5 (160×arom. CH), 98.4, 98.2, 98.0 (12×C-1), 81.2 (12×C-3), 80.8, 80.6, 79.6 (12×C-4), 79.6, 78.8, 78.3 (12×C-2), 76.3, 75.6, 74.3, 73.3, 73.1, 72.9, 72.0 (32×PhCH_2), 71.8, 71.3, 71.0 (12×C-5), 69.9, 69.0 (12×C-6), 29.8 (CH_2CH_2O), 26.0 (CH_2); MS (MALDI-TOF): *m/z* (%) 5068.8 (100) $[M+Na]^+$.

4.1.2. Octaacetyl duplex (7). The perbenzylated duplex **6** (185 mg, 36.7 μmol) was dissolved in acetic anhydride (9 ml) and the solution was cooled to −30 °C. TMSOTf (85 μl, 50% in DCM, 1.5 equiv/6-OBn) was added to the solution, which was stirred for 30 min at the same temperature. The reaction mixture was poured into a mixture of saturated $NaHCO_3$ solution (5 ml) and DCM (50 ml), and the mixture was stirred hard for 30 min. The organic phase was dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography, eluting with cyclohexane–ethyl acetate (3:1) to give compound **7** (89 mg, 52%) as a white foam: R_f 0.4 (cyclohexane–ethyl acetate 3:2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.13 (120H, arom. H), 5.47 (4H, AB, *J*=10.5 Hz, PhCH_2), 5.39 (4H, d, $J_{1,2}$= 3.7 Hz, 4×H-1), 5.19 (4H, AB, *J*=10.9 Hz, PhCH_2), 5.08 (4H, m, 4×H-6), 4.98–4.84 (16H, m, 8×H-1, 8×PhCH_2), 4.78 (8H, m, 4×H-6, 4×PhCH_2), 4.53–4.37 (24H, m, 4×H-3, PhCH_2), 4.29 (4H, m, 4×H-3), 4.21 (4H, m, 4×H-4), 4.10 (20H, m, 4×H-3, 4×H-4, 4×H-5, 4×H-6), 3.84 (12H, m, 4×H-4, 8×H-5), 3.65 (4H, m, 4×H-6), 3.53 (4H, m, 4×H-6), 3.47 (12H, m, 8×H-2, 4×H-6), 3.40 (12H, m, 4×H-2, 4×OCH_2, 4×PhCH_2), 3.30 (8H, m, 4×OCH_2, 4×PhCH_2), 2.16 (12H, s, 4×$COCH_3$), 2.05 (12H, s, 4×$COCH_3$), 1.55 (8H, m, OCH_2CH_2), 1.26 (16H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (8×CO), 139.3, 139.2, 139.1, 138.6, 138.5, 138.3, 138.1, 137.9 (24× arom. C), 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 127.2, 127.1, 126.8, 126.5 (120×arom. CH), 98.9, 98.7, 98.5 (12×C-1), 81.6, 81.1, 80.8 (12×C-3), 80.7, 80.6, 80.4 (12×C-4), 79.6, 79.2, 79.1 (12×C-2), 76.0, 74.5, 73.4, 73.1, 72.4, 71.7, 69.0 (24×PhCH_2), 71.4, 69.9, 68.5 (12×C-5), 69.0, 63.7, 63.6 (12×C-6), 29.6, 29.4, 29.2 (CH_2CH_2O), 25.7 (CH_2), 20.9, 20.8 (8×COCH_3); MS (ESI^+): *m/z* (%) 4686.05 (100) $[M+Na]^+$.

4.1.3. Octapentenylated duplex (8). To the solution of octaacetyl duplex **7** (164 mg, 35.2 μmol) in dichloromethane (10 ml) was added the solution of $NaOCH_3$–CH_3OH (5 ml, 0.05 M). The reaction mixture was stirred overnight and neutralized with Amberlite IR120-H^+. After filtration and concentration the residue was purified by flash chromatography, eluting with cyclohexane–ethyl acetate (2:3) to give an octaol (144 mg, 95%) as a white foam: R_f 0.5 (cyclohexane–ethyl acetate 1:3); ^1H NMR (400 MHz, $CDCl_3$): the spectrum indicates the disappearance of the signals of the acetyl protons ($COCH_3$); MS (ESI^+): *m/z* (%) 4349.99 (100) $[M-H+Na]^+$. The transient octaol (57 mg, 13.2 μmol) was dissolved in DMF (4 ml) under argon at room temperature, and NaH (8.5 mg, 210 μmol) and 5-bromopent-1-ene (26 μl, 210 mmol) were added to the solution one by one. The reaction mixture was stirred until the disappearance of the starting material and the appearance of a single product. The reaction mixture was neutralized by methanol (5 ml) and co-evaporated with toluene. The residue was then dissolved in dichloromethane and washed with saturated NaCl solution and water. The organic phase was dried over $MgSO_4$, filtrated and concentrated. The residue was purified by flash chromatography, eluting with cyclohexane–ethyl acetate (5:1) to give compound **8** (64 mg, 98%) as a white foam: R_f 0.5 (cyclohexane–ethyl acetate 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.08 (120H, arom. H), 5.80 (8H, m, 8×CH=CH_2), 5.51 (4H, d, $J_{1,2}$=3.7 Hz, 4×H-1), 5.42 (4H, AB, *J*=10.7 Hz, PhCH_2), 5.31 (4H, AB, *J*=10.6 Hz, PhCH_2), 5.05–4.92 (20H, m, 4×H-1, 16×CH_2=CH), 4.87 (20H, m, 4×H-1, 16× PhCH_2), 4.73 (4H, AB, *J*=12.2 Hz, PhCH_2), 4.58 (8H, AB, *J*=12.7 Hz, PhCH_2), 4.43 (4H, AB, *J*=12.6 Hz, PhCH_2), 4.35 (4H, AB, *J*=12.8 Hz, PhCH_2), 4.26 (8H, m, 4×H-5, 4×PhCH_2), 4.12 (8H, m, 8×H-3), 4.03 (8H, m, 4×H-3, 4×H-6), 3.84 (16H, m, 12×H-4, 4×H-6), 3.78 (8H, m, 8×H-5), 3.60–3.40 (32H, m, 12×H-6, 16×H-6, 4×CH_2CH=CH_2, 4×OCH_2), 3.34 (8H, m, CH_2CH=CH_2, 4×OCH_2), 2.25–1.98 (8H, m, 8×OCH_2CH_2), 1.65 (8H, m, CH_2), 1.29 (24H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 139.2, 138.6, 138.3 (24×arom. C), 138.0, 137.9 (8×CH=CH_2), 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3, 127.1, 127.0, 126.9, 126.8, 126.5 (120×arom. CH), 114.8, 114.7 (8×CH=CH_2), 98.6, 98.3, 98.2 (12×C-1), 81.3, 80.9, 80.8 (12×C-3), 80.9, 80.8, 79.7 (12×C-4), 79.4, 78.8, 78.2 (12×C-2), 76.4, 75.7, 74.3, 74.1, 73.1, 73.0, 72.8, 72.1, 72.0, 71.0, 70.7 (24×PhCH_2), 71.6, 71.0, 70.7 (12×C-5), 69.5, 69.4, 69.3 (12×C-6), 30.3, 30.0 (CH=CH_2CH_2, CH_2CH_2O), 29.7, 29.6, 29.3, 28.9, 28.7 (CH_2); MS (ESI^+): *m/z* (%) 4894.86 (100) $[M-H+Na]^+$.

4.1.4. Octapentanylated duplex (9). To a solution of octaene **8** (58 mg, 11.8 μmol) in a mixture of methanol–acetic acid (5 ml:5 ml) was added Pd–C (20 mg, 10%). After being stirred for 12 h under the atmosphere of hydrogen at room temperature, the reaction mixture was filtrated and concentrated to give compound **9** (32 mg, 95%) as a white foam: $[\alpha]_D$ +63 (*c* 1.0, pyridine); ^{1}H NMR (400 MHz, pyridine-d_5) δ 5.51 (4H, m, 4×H-1), 5.42 (4H, d, $J_{1,2}$=3.5 Hz, 4×H-1), 5.40 (4H, d, $J_{1,2}$=3.5 Hz, 4×H-1), 4.67 (12H, m, 12×H-3), 4.43 (12H, m, 12×H-5), 4.19 (12H, m, 12×H-4), 4.11 (12H, m, 12×H-2), 3.75 (48H, m, 24×OCH_2, 24×H-6), 1.78 (24H, m, 24×OCH_2CH_2), 1.44 (48H, m, $CH_2CH_2CH_2$), 0.95 (24H, m, CH_3); ^{13}C NMR (100 MHz, pyridine-d_5) δ 104.7, 104.4, 104.3, 104.2, 104.1 (12×C-1), 83.9, 83.8, 83.7 (C-4), 75.7, 75.6, 75.5, 75.4 (C-3), 74.5, 74.4 (C-5), 73.1, 73.0, 72.9, 72.8 (C-2), 72.5, 72.4, 72.3 (C-6), 30.9, 30.8 (CH_2CH_2O), 29.4, 29.1, 27.4, 23.5 (CH_2), 14.9, 14.8 (CH_3); MS (MALDI-TOF): *m*/*z* (%) 2748.36 (100) $[M+Na]^+$.

4.1.5. Preparation of vesicles. The procedure was adapted from the electroformation method developed by Angelova and Dimitrov to produce liposomes.[11] CD **9** (6 μl) or egg yolk L-α-phosphatidylcholine (Egg PC, Avanti Polar Lipids) solution (10 mg/ml in 9:1 chloroform–methanol) was spread onto two ITO-coated glass slides over a total surface area of ca. 12 cm^2 (6 cm^2/ITO electrode). The CD **9** (resp. Egg PC) films were then dried under vacuum for 1 h. Thus obtained ITO electrodes coated by the CD **9** (resp. Egg PC) film were separated by 1 mm and the intervening space was filled by a sucrose solution (ca. 0.1 M in pure water with a measured osmotic pressure of 104 mOsmol/l). An AC field (2 V, 10 Hz) was applied between the two ITO electrodes for 14 h, which resulted in the electroswelling of the CD **9** (resp. Egg PC) film and the formation in the sucrose solution of vesicles containing sucrose. The suspension of vesicles was removed carefully (under low shear) from the electroswelling cell. One part was directly observed by phase contrast microscopy while the other part was mixed with an equal volume of glucose (ca. 0.1 M in pure water with an osmotic pressure adjusted at 104 mOsmol/l). The vesicles mixed with the glucose solution were then collected by gravity on a microscope glass slide after 2 h of decantation due to the density difference between inner (sucrose) and outer medium (sucrose–glucose) of vesicles. Vesicles were observed by phase contrast microscopy with an inverted microscope (DMIL, Leica) equipped with a 10× objective lens and a CCD camera (PL-A741, Pixelink).

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