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Dioxamethylene intramolecular bridging of *p-tert*-butylcalix[8]arene

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Abstract—The first examples of dioxamethylene bridged calix[8]arenes **2**–**6** have been obtained by Cs_2CO_3-promoted direct *O*-alkylation of *p-tert*-butylcalix[8]arene with $BrCH_2Cl$. Assignment of the 1,2-, 1,2:3,4-, 1,2:3,4:6,7-, 1,4:2,3:5,6:7,8-, and 1,2:3,4:5,6:7,8-bridging pattern of **2**–**6**, respectively, was mainly based on chemical shift of OH groups and chemical correlations. Dynamic ^1H NMR studies and MM3 calculations indicated that in these compounds the dioxocine subunit adopts a boat–chair conformation.

The intramolecular bridging of calix[*n*]arenes has been widely investigated as an effective tool to preorganize the parent macrocycle or to modify its conformational preferences.[1] Among the large variety of structural elements used as bridging groups, a particular interest has been devoted to the simple dioxamethylene bridge, originally introduced by Cram in the synthesis of cavitands and related compounds.[2]

In particular, the bridging with OCH_2O groups of *p-tert*-butylcalix[4]arene has led to the preparation of singly[3] and doubly bridged[4] derivatives, whose conformational properties have been investigated by means of detailed molecular mechanics and VT-NMR studies. Analogous mono-,[5] bis-,[6] and tris(dioxamethylene)[4] derivatives have been described for *p-tert*-butylcalix[6]arene, in addition to an example of monobridged calix[7]arene derivative.[7]

The observation that no examples of intramolecular bridging with OCH_2O groups of calix[8]arene macrocycle have been reported,[8] induced us to investigate the alkylation of *p-tert*-butylcalix[8]arene **1** with $BrCH_2Cl$ in the presence of a base. In this letter, we wish to report on the results of this study and on the conformational features of the first dioxamethylene-bridged calix[8]arenes thus obtained.

The treatment of **1** with 16 equiv of bromochloromethane and 8 equiv of Cs_2CO_3 as base, in DMF (80 °C), afforded 1,2-dioxamethylene-bridged calix[8]arene **2** in 15% yield, and 1,2:3,4-bis(dioxamethylene)-bridged calix[8]arene **3** in 18% yield (Scheme 1), besides to unreacted **1** (20%), after column chromatography of the crude reaction mixture.[9] Analogous treatment of **1** with a large excess of $BrCH_2Cl$ and 80 equiv of Cs_2CO_3 as base, in DMF (80 °C), led to the complete consumption of the starting material and to the isolation of 1,2:3,4:6,7-tris(dioxamethylene)-bridged calix[8]arene **4** (5%), 1,4:2,3:5,6:7,8-tetrakis(dioxamethylene)-bridged calix[8]arene **5** (13%), and 1,2:3,4:5,6:7,8-tetrakis(dioxamethylene)-bridged calix[8]arene **6** (27%) (Scheme 1).[9]

Structure assignment for bridged calix[8]arene derivatives **2**–**6** was mainly based on spectral data coupled to chemical correlations.[9] In particular, elemental analysis and ESI(+) MS confirmed the molecular formula, while ^1H and ^{13}C NMR spectroscopy was used to determine the bridging pattern.

As concerns the structure of conformationally mobile **2**, the presence of four *t*-Bu signals in a 1:1:1:1 ratio, five $ArCH_2Ar$ signals in 1:2:2:2:1 ratio, and three 1:1:1 OH signals in its ^1H NMR spectrum (Fig. 1 and vide infra) pointed to a 1,2- or 1,4-bridging, both characterized by a 2-fold symmetry element bisecting opposite $ArCH_2Ar$ groups (CH_2–CH_2 symmetry), among the four possible singly bridged regioisomers.[8] To discriminate between the two bridging patterns, we used the chemical shift of OH groups,[7,10] which can be classified as 'isolated'

Keywords: Calixarenes; Calix[8]arenes; Intramolecular bridging; Dioxamethylene-bridged; Lower rim; Alkylation.

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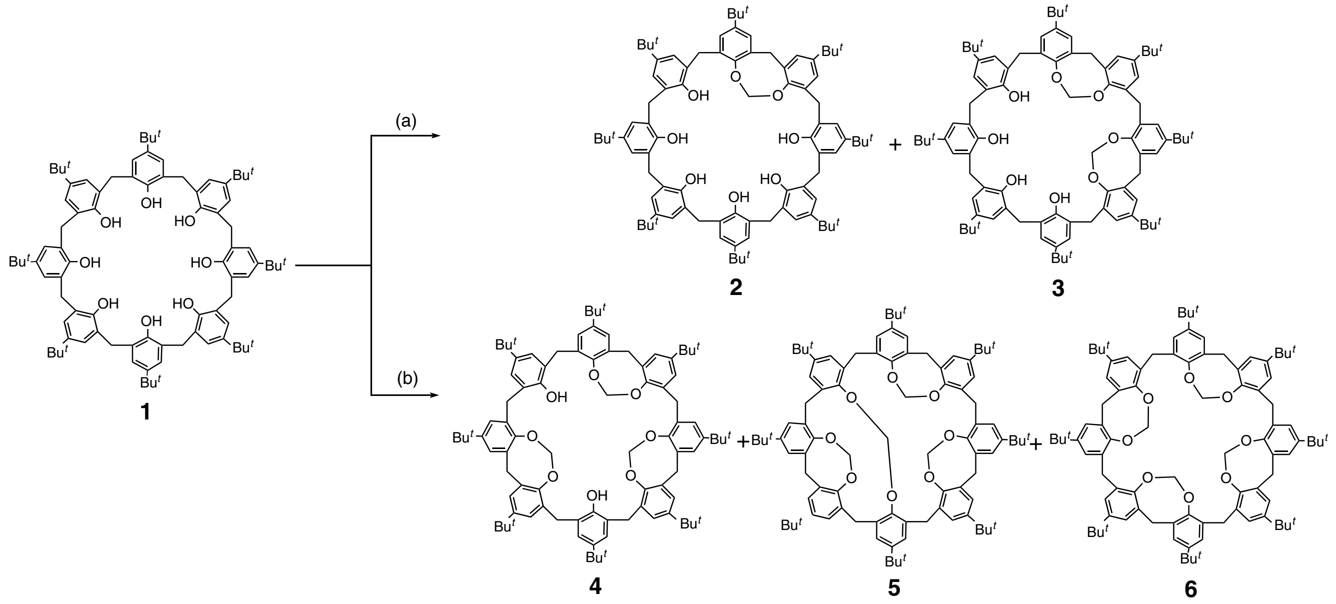

Scheme 1. Reagents and conditions: (a) $BrCH_2Cl$ (16 equiv), Cs_2CO_3 (8 equiv), DMF 80 °C, 48 h; (b) $BrCH_2Cl$ (200 equiv), Cs_2CO_3 (80 equiv), DMF 80 °C, 48 h.

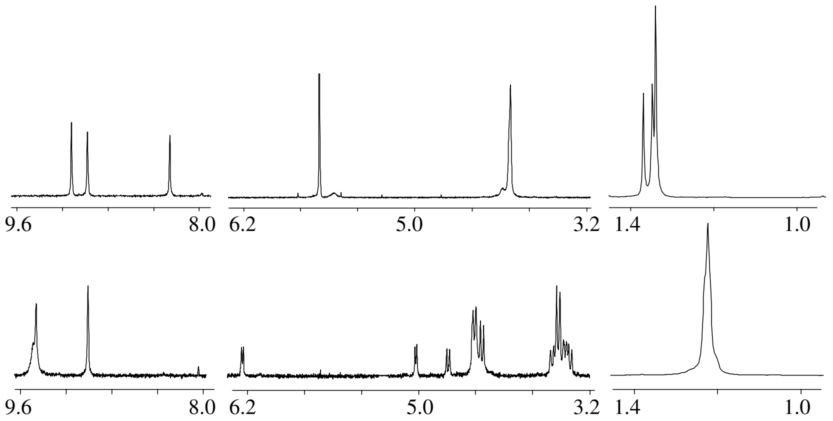

Figure 1. Significant portions of the ^1H NMR spectrum (400 MHz) of 1,2-monobridged calix[8]arene **2** at 213 K ($CDCl_3$, bottom) and 373 K ($C_2Cl_2D_4$, top) (different scales are used).

(i), 'singly H-bonded' (s), and 'doubly H-bonded' (d), based on their ^1H NMR chemical shift.[11] Thus, a 1,2-bridged derivative should show three 's,d,d' OH signals, whereas the 1,4-bridged isomer should give rise to three 's,s,d' OH resonances. The ^1H NMR spectrum of **2** (at 378 K) shows three OH resonances at 8.10, 8.80, and 8.94 ppm (Fig. 1), fully consistent with an 's,d,d' OH pattern, and consequently the 1,2-bridging can be confidently assigned to **2**.

In principle, 22 regioisomers are possible for calix[8]arene **3** bridged with two dioxamethylene elements.[12] The equivalence of the dioxamethylene bridges and the CH_2–CH_2 symmetry, evidenced by its ^1H NMR spectrum,[9] reduce the number of compatible bridging patterns to four, namely 1,2:3,4, 1,3:2,4, 1,3:4,6, and 1,4:3,6. The finding that alkylation of a pure sample of **2** with $BrCH_2Cl$ (10 equiv), in presence of Cs_2CO_3 (8 equiv), afforded **3** (15%), clearly demonstrated the presence of a 1,2-bridge in its structure and constituted a definitive proof of its 1,2:3,4-bridging. The chemical shift of OH groups was fully consistent with this pattern because two 's,d' OH resonances at 8.08 and 8.88 ppm were present in the ^1H NMR spectrum of **3** (at 353 K).

The most direct proof of the structure of **4** was obtained by alkylation of pure 1,2:3,4-bis-bridged calix[8]arene **3** with $BrCH_2Cl$ (40 equiv) and Cs_2CO_3 (20 equiv), which afforded a mixture of triply and quadruply bridged derivatives **4**, **5**, and **6** (30%, 10%, and 20%, respectively). This result is compatible with four possible bridging patterns for **4**, namely 1,2:3,4:5,6 (CH_2–CH_2 symmetry), 1,2:3,4:5,7 (asymmetric), 1,2:3,4:5,8 (CH_2–CH_2 symmetry), and 1,2:3,4:6,7 (CH_2–CH_2 symmetry). The presence in the ^1H NMR spectrum of **4** (353 K)[9] of four 1:1:1:1 *t*-Bu signals, indicating a CH_2–CH_2 symmetry, and of one 'i' OH resonance at 6.44 ppm allowed the confident assignment of its 1,2:3,4:6,7-bridging pattern.

The ^{1}H NMR spectrum of **5** at 373 K shows[9] four *t*-Bu singlets at 1.20, 1.25, 1.28, and 1.29 ppm (18H each), while its 2D COSY-45 spectrum contains 5 AX or AB systems for ArCH$_2$Ar groups (δ 3.46/4.58, J = 14.2 Hz, 2H; 3.67/4.35, J = 15.2 Hz, 4H; 3.82/4.16, J = 15.8 Hz, 2H; 3.90–4.20 overlapping 8H) and three AB systems for OCH$_2$O protons (δ 4.83/5.09, br d, 2H; 4.95/5.01, br d, 4H; 5.12/5.40, br d, 2H) clearly indicating a CH$_2$–CH$_2$ symmetry and a reduced conformational mobility. These data in conjunction with the finding that **5** was also obtained by alkylation of 1,2:3,4:6,7-triply-bridged derivative **4** proved the assigned structure.

The consecutive proximal tetrabridging pattern[13] of calix-[8]arene **6** was easily assigned because of the high symmetry evidenced by ^{1}H and ^{13}C NMR spectra (Fig. 2). In fact, its ^{1}H NMR spectrum (TCDE, 353 K) shows one *t*-Bu resonance (1.07 ppm, 72H), two broad ArCH$_2$Ar singlets (3.69 and 3.83 ppm, 8H each), one broad OCH$_2$O singlet (5.14 ppm, 8H), and one AB system for aromatic protons (6.76/7.02 ppm, J = 2.1 Hz, 16H) in agreement with a C_{4v}-symmetry. In accordance, the high conformational mobility of **6** excludes the presence of transannular or intercrossing bridges.[12]

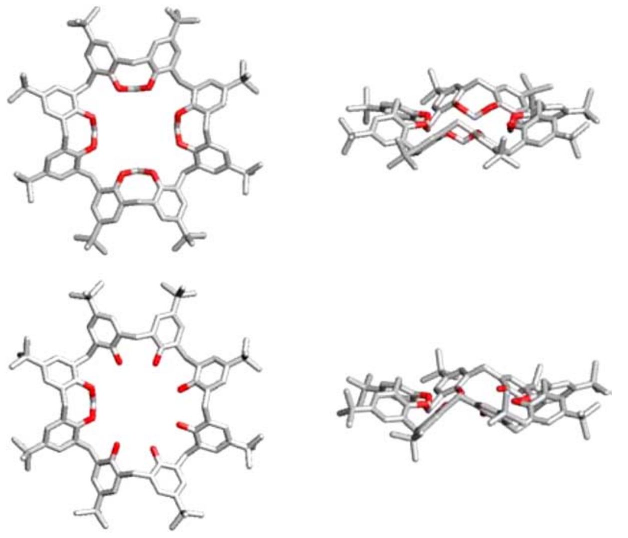

Figure 3. Top- (left) and side-view (right) of the lowest MM3-energy conformation (CHCl$_3$, GB/SA implicit model solvent) of mono- and tetrabridged calix[8]arenes **2** (bottom) and **6** (top), respectively.

Dynamic NMR studies (400 MHz, TCDE) evidenced that monobridged derivative **2** is conformationally mobile at temperatures above 330 K (Fig. 1), as indicated by the presence of a broad singlet for dioxamethylene protons at 5.65 ppm, while below 300 K a single conformer is present. In fact, its ^{1}H NMR spectrum at 213 K (CDCl$_3$) shows (Fig. 1) one AX system for OCH$_2$O protons (4.96/6.79 ppm, J = 6.5 Hz), three AX and one AB systems for ArCH$_2$Ar groups (4.61/3.35, J = 11.1 Hz, 2H; 4.34/3.48, J = 13.3 Hz, 8H; 4.24/3.48, J = 13.3 Hz, 4H; 3.54/3.40, J = 12.9 Hz, 2H). In accordance with the data reported by Biali,[3b] the large $\Delta\delta$ value for the dioxamethylene protons ($\Delta\delta$ = 1.83 ppm) suggests a boat–chair (BC) conformation of the dioxocine subunit, while the low-field OH resonances indicate a quasi-circular H-bond typical of a pleated-loop conformation.[14] MM3 calculations (CHCl$_3$, GB/SA implicit model solvent)[15] confirmed this structure (Fig. 3) as the lowest energy conformation in comparison with the other possible geometries for dioxocine ring (distorted-boat, twist-boat, and twist),[3b] which caused severe macrocycle distortions. From VT-^{1}H NMR a coalescence at 328 K was ascertained for OCH$_2$O signals, which led to an energy barrier of 16.2 kcal/mol for dioxocine conformational interconversion. This value is larger than those previously obtained for mono- and bis-(dioxamethylene)-bridged calix[4]arenes,[3b,4] probably due to unfavorable macrocycle distortions produced by the dioxocine transitions.

Similar dynamic NMR studies on 1,2:3,4-bis-bridged calix[8]arene **3** indicated again a conformationally averaged symmetrical structure at high temperatures

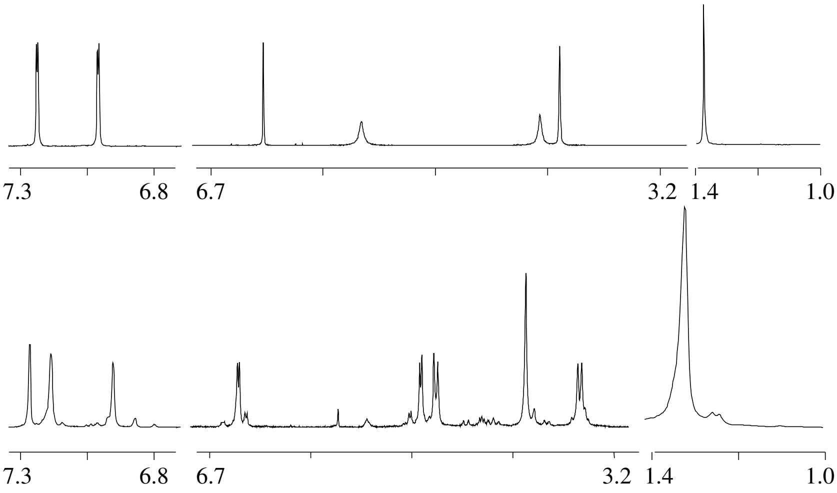

Figure 2. ^{1}H NMR spectrum (400 MHz) of symmetrically tetrabridged calix[8]arene **6** at 213 K (CDCl$_3$, bottom) and 373 K (C$_2$Cl$_2$D$_4$, top) (different scales are used).

(TCDE, 373 K), whereas below 253 K a complex pattern emerged, which was compatible with a mixture of conformers.

The high temperature ^{1}H NMR spectrum (TCDE, 373 K)[9] of 1,2:3,4:6,7-triply-bridged calix[8]arene **4** is also fully compatible with a mobile, averaged symmetrical structure as indicated by the presence of two 2:1 OCH$_2$O singlets at 4.99 and 5.12 ppm. Interestingly, cooling below 243 K caused the splitting of all the resonances, indicating that a single asymmetrical conformer had frozen out predominantly. In fact, three 1:1:1 OCH$_2$O AX systems (6.32/4.76 ppm, $J = 7.2$ Hz; 6.32/4.73 ppm, $J = 7.2$ Hz; 6.18/4.85 ppm, $J = 7.0$ Hz) and 8 *t*-Bu singlets were present in its ^{1}H NMR spectrum at 233 K (CDCl$_3$). The large $\Delta\delta$ values for OCH$_2$O protons indicate a BC conformation for all the three dioxocine subunits. An energy barrier of 15.5 kcal/mol was estimated for their conformational interconversion from the coalescence temperature (313 K).

The presence of a 1,4-bridge in the structure of tetrabridged calix[8]arene **5** implies an impeded conformational interconversion as indicated by the presence of AX systems for ArCH$_2$Ar groups up to 363 K.[9] However, a residual mobility give rise to complex spectra at low temperatures.

Symmetrical tetrabridged calix[8]arene **6** is also in a fast exchange regime at 373 K as indicated by one broad OCH$_2$O singlet at 5.30 ppm (Fig. 2). At 218 K this signal split into one AX system at 6.12/4.66 ppm corresponding to a predominant conformer with BC dioxocine subunits ($\Delta\delta = 1.46$ ppm). MM3 calculations confirmed the higher stability of this conformation (Fig. 3), which is perfectly compatible with the pleated-loop geometry of the calix[8]arene skeleton. From the coalescence temperature of 308 K an energy barrier of 15.3 kcal/mol was deduced for dioxocine conformational interconversion. Interestingly, ArCH$_2$Ar groups non-involved in dioxocine rings give rise to a singlet even at the lowest temperature reached (213 K, Fig. 2) indicating a residual mobility at this level.

In conclusion, we have described the first examples of mono- to tetra-dioxamethylene bridged calix[8]arene derivatives whose bridging pattern was determined by means of chemical correlations and NMR spectroscopy. Dynamic NMR studies and MM3 calculations showed a marked preference for a boat–chair conformation of dioxocine ring, which perfectly matches the geometrical requirements of a calix[8]arene pleated-loop conformation. The possibility to obtain a consecutive proximal tetrabridging suggests the use of benzal halides as alkylating agents,[16] which may give rise to new kind of preorganized calix[8]arenes with interesting stereochemical features.

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   Procedure for the preparation of 2 and 3. A solution of bromochloromethane (0.80 mL, 12.30 mmol) in DMF (64 mL) was added dropwise over 30 min, under stirring, to a solution of **1** (0.77 mmol) and Cs$_2$CO$_3$ (6.16 mmol) in DMF (120 mL) at 80 °C. The mixture was kept at 80 °C under stirring for 48 h. After concentration under vacuum, the residue was taken with CH$_2$Cl$_2$ (100 mL), washed with 1 N HCl (3 × 100 mL), dried (Na$_2$SO$_4$), and the solvent was evaporated under reduced pressure. The crude product was subjected to flash column chromatography on silica gel (petroleum ether/CH$_2$Cl$_2$, 6:4 v/v) to give the isolated compounds **2** and **3**.
   Compound **2** (153 mg, 15%): ESI(+) MS m/z 1309 (MH$^+$); ^{1}H NMR (400 MHz, TCDE, 378 K) δ 1.14 [s, C(CH$_3$)$_3$, 36H], 1.15 [s, C(CH$_3$)$_3$, 18H], 1.17 [s, C(CH$_3$)$_3$, 18H], 3.79 (s, ArCH$_2$Ar, 14H), 3.88 (s, ArCH$_2$Ar, 2H), 5.65 (br s, OCH$_2$O, 2H), 6.80–7.20 (overlapped, ArH, 14H), 7.10 (d, ArH, $J = 2.2$ Hz, 2H), 8.10 (s, OH, 2H), 8.80 (s, OH, 2H), 8.94 (s, OH, 2H). Anal. Calcd for C$_{89}$H$_{112}$O$_8$: C, 81.61; H, 8.62. Found: C, 81.54; H, 8.70.
   Compound **3** (180 mg, 18%): ESI(+) MS m/z 1321 (MH$^+$); ^{1}H NMR (400 MHz, TCDE, 353 K) δ 1.07 [s, C(CH$_3$)$_3$, 18H], 1.10 [s, C(CH$_3$)$_3$, 18H], 1.11 [s, C(CH$_3$)$_3$, 18H], 1.14 [s, C(CH$_3$)$_3$, 18H], 3.74 (s, ArCH$_2$Ar, 8H), 3.78 (s, ArCH$_2$Ar, 4H), 3.86 (br s, ArCH$_2$Ar, 4H), 5.38 (br s, OCH$_2$O, 4H), 6.78 (d, ArH, $J = 1.8$ Hz, 2H), 6.92 (br d, ArH, 4H), 7.03 (br d, overlapped, ArH, 8H), 7.05 (d, ArH, $J = 1.8$ Hz, 2H), 8.08 (br s, OH, 2H), 8.88 (br s, OH, 2H).

Anal. Calcd for $C_{90}H_{112}O_8$: C, 81.78; H, 8.54. Found: C, 81.70; H, 8.60.

Procedure for the preparation of 4, 5, and 6. *p-tert*-Butylcalix[8]arene **1** (0.77 mmol) in DMF (120 mL) was treated with $BrCH_2Cl$ (10 mL, 154 mmol) and Cs_2CO_3 (61.6 mmol) as described above, to give after flash column chromatography on silica gel (petroleum ether/diethyl ether, 96:4 v/v) the isolated compounds **4**, **5**, and **6**.

Compound **4** (50 mg, 5%): ESI(+) MS *m*/*z* 1333 (MH^+); ^{1}H NMR (400 MHz, TCDE, 353 K) δ 1.03 [s, $C(CH_3)_3$, 18H], 1.06 [s, $C(CH_3)_3$, 18H], 1.08 [s, $C(CH_3)_3$, 18H], 1.10 [s, $C(CH_3)_3$, 18H], 3.64 (s, $ArCH_2Ar$, 2H), 3.69 (s, $ArCH_2Ar$, 4H), 3.71 (s, $ArCH_2Ar$, 4H), 3.81 (s, $ArCH_2Ar$, 6H), 5.07 (br s, OCH_2O, 4H), 5.19 (br s, OCH_2O, 2H), 6.44 (s, OH, 2H), 6.75 (br d, ArH, 2H), 6.81 (br d, ArH, 2H), 6.89 (br d, ArH, 2H), 6.92 (br d, ArH, 2H), 6.96 (br d, ArH, 2H), 7.00 (d, ArH, $J = 2.1$ Hz, 4H), 7.02 (d, ArH, $J = 2.2$ Hz, 2H). Anal. Calcd for $C_{91}H_{112}O_8$: C, 81.94; H, 8.46. Found: C, 81.88; H, 8.54.

Compound **5** (136 mg, 13%): ESI(+) MS *m*/*z* 1345 (MH^+); ^{1}H NMR (400 MHz, TCDE, 373 K) δ 1.20 [s, $C(CH_3)_3$, 18H], 1.25 [s, $C(CH_3)_3$, 18H], 1.28 [s, $C(CH_3)_3$, 18H], 1.29 [s, $C(CH_3)_3$, 18H], 3.46/4.58 (AX, $ArCH_2Ar$, $J = 14.2$ Hz, 2H), 3.67/4.35 (AX, $ArCH_2Ar$, $J = 15.2$ Hz, 4H), 3.82/4.16 (AX, $ArCH_2Ar$, $J = 15.8$ Hz, 2H), 3.90–4.20 (overlapping, $ArCH_2Ar$, 8H), 4.83/5.09 (AB br, OCH_2O, 2H), 4.95/5.01 (AB br, OCH_2O, 4H), 5.12/5.40 (AB br d, OCH_2O, 2H), 6.94 (d, Ar*H*, $J = 2.1$ Hz, 2H), 6.98 (s, ArH, 4H), 7.01 (br d, ArH, 2H), 7.06 (d, Ar*H*, $J = 1.5$ Hz, 2H), 7.14 and 7.15 (d, Ar*H*, $J = 1.7$ Hz, 4H), 7.18 (d, Ar*H*, $J = 1.8$ Hz, 2H). Anal. Calcd for $C_{92}H_{112}O_8$: C, 82.10; H, 8.39. Found: C, 82.06; H, 8.45.

Compound **6** (283 mg, 27%): ESI(+) MS *m*/*z* 1345 (MH^+); ^{1}H NMR (400 MHz, TCDE, 353 K) δ 1.07 [s, $C(CH_3)_3$, 72H], 3.69 (s, $ArCH_2Ar$, 8H), 3.83 (br s, $ArCH_2Ar$, 8H), 5.14 (br s, OCH_2O, 8H), 6.76/7.02 (AB, ArH, $J = 2.1$ Hz, 16H); Anal. Calcd for $C_{92}H_{112}O_8$: C, 82.10; H, 8.39. Found: C, 82.17; H, 8.32.

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