A Calix[6]arene Dimer Linked Through Amino Acid Hydrogen Bond Interactions

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Dedicated to the memory of Professor Jesús H. Rodríguez-Ramos

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A calix[6]arene containing three leucine residues at the lower rim dimerizes in apolar solvents with the formation of up to eighteen hydrogen bonds, giving rise to a self-assembled molecular capsule. The dimerization in chloroform was conformed by NMR spectroscopy and gel permeation chromatography, as well as by molecular mechanics and dynamics calculations. The highly flexible structure is unable to encapsulate guests of complementary size, probably because six methoxy groups and one of the leucyl residues permanently occupy the cavity.

Introduction

Structures with designed cavities or networks may be formed by self-assembly when two or more identical subunits are geometrically and functionally complementary.[1,2]

A number of calixarene-based capsular structures, in which calixarene subunits are self-assembled through hydrogen bonds,[3] metal coordination[4] or assembled by covalent bonds have been described.[5] Only a few examples of calixarenes functionalized with amino acids or peptides are known,[6] most of them having been designed for molecular recognition purposes. When L-valine or L-isoleucine are linked to a tetra-*N*-ureidocalix[4]arene a dimeric cavity is formed, where sizeable molecules such as nopinone or norcamphor can be accommodated.[7] A similar urea-urea dimer is formed when four dipeptide H-Leu-D-Leu-OMe groups are attached to the ureas of the *N*-ureidocalix[4]arene, with an additional seam of peripheral hydrogen bonds forming a second coordination sphere.[8]

Isolated β-strands rarely occur in proteins, and their edges are usually hydrogen bonded to each other to form β-sheets, which are structurally and functionally relevant in many peptides and proteins. Since Kelly's pioneering work in the synthesis and study of artificial β-sheets,[9] the efforts of scientists have concentrated on understanding the factors that influence the β-sheet conformation in peptides.[10] Currently, a number of examples have been described.[11] Recently, supramolecular β-barrel models have been described and β-carotene encapsulation has been demonstrated.[12]

Here we describe the synthesis and association properties of the *p*-(*tert*-butyl)calix[6]arene **1a** with leucines linked to three acetate groups attached to the lower rim of alternate rings. In general, calix[6]arenes display a much higher conformational freedom than their tetramer analogues. However, the 1,3,5-trimethoxy-*p*-(*tert*-butyl)calix[6]arene platform employed here displays a considerable amount of rigidity and a much slower macrocycle inversion rate.[13a,13c]

Molecular modeling shows that a dimer with a cavity could be obtained by association through eighteen intermolecular hydrogen bonds between the amide groups of the two subunits (Figure 1). Most of the hydrogen bonding network arises from the antiparallel β-sheet structure (six bonds involving NH_a protons and six involving NH_b protons), although additional contacts can be established between the terminal NH_c protons and the methoxy groups (Figure 1c).

Leucine was selected because of its hydrophobic and branched structure that could facilitate an extended conformation and the solubility of the resulting compound in apolar solvents. For control purposes, compound **1b** was prepared, since for steric reasons it cannot dimerize as the *N*-octyl groups face the aromatic rings of the opposite subunit.

Results and Discussion

Compounds **1a−b** were synthesized in three steps from the easily available 1,3,5-trimethoxy-*p*-(*tert*-butyl)calix[6]arene (**2**).[13a][13b] First, the free hydroxy groups were alkylated to give **3**. Basic hydrolysis of the ester **3** afforded **4**, which was obtained in a higher overall yield than by a previously described method.[13c] Finally, coupling of **4** with the leuc-

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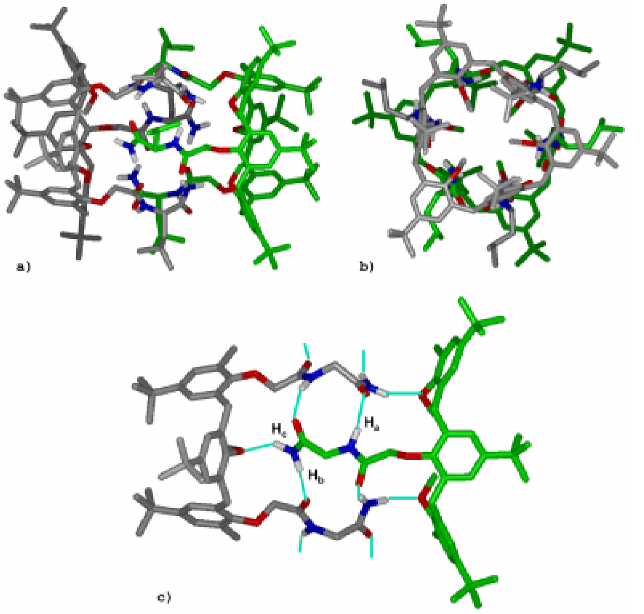
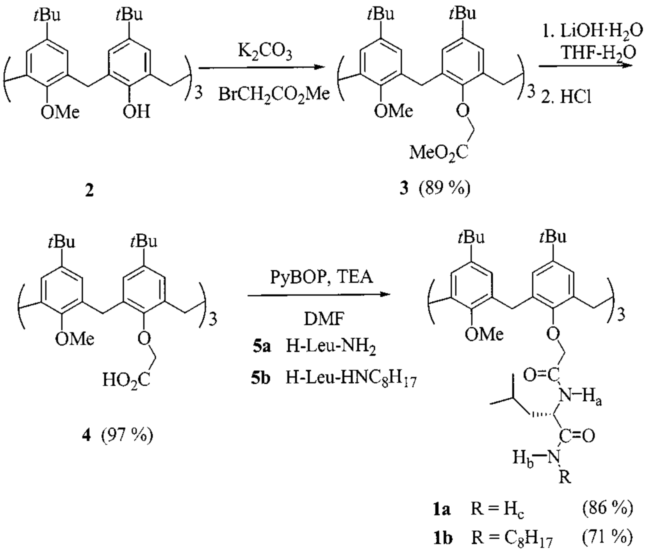


Figure 1. Optimized structure of **1a** dimer; a) side view; b) top view; c) partial view of the hydrogen bonding network

ine derivatives **5a** or **5b**[8] afforded compounds **1a**−**b** in good yields (Scheme 1).

Compounds **1a** and **1b** show dramatic differences in their ^{1}H NMR spectra recorded in $CDCl_3$ or [D$_4$]methanol. While the spectra of both compounds in [D$_4$]methanol display the expected pattern consistent with a C_3 symmetry (Figure 2, a and b), in $CDCl_3$ each compound gives rise to a totally different NMR spectrum. The spectrum of model **1b** indicates that the macrocycle inversion is restricted, as shown by the AX system observed for the methylene bridges, although a rapid rotation of the amino acid backbone is observed (Figure 2c). This rotation is restricted in **1a**, whose spectrum shows two signals for the aromatic protons of the rings containing the amino acids, two AX systems for the methylene protons, and two well-separated doublets assigned to the diastereotopic *O*-methylene protons, in agreement with a C_3 symmetry. The NH$_a$ signal is shifted much further downfield than the same signal in **1b** ($\Delta\delta$ = 0.64 ppm), indicating its participation in a strong hydrogen bond (Figure 2d). Similarly, NH$_b$ is shifted downfield, although to a smaller extent ($\Delta\delta \approx$ 0.3 ppm). Since the signals for NH$_b$ and NH$_c$ appear at similar chemical shifts, it is likely that the NH$_c$ protons are also involved in weak hydrogen bonds. All ^{1}H NMR signals were unequivocally assigned from COSY and ROESY spectra.



Scheme 1

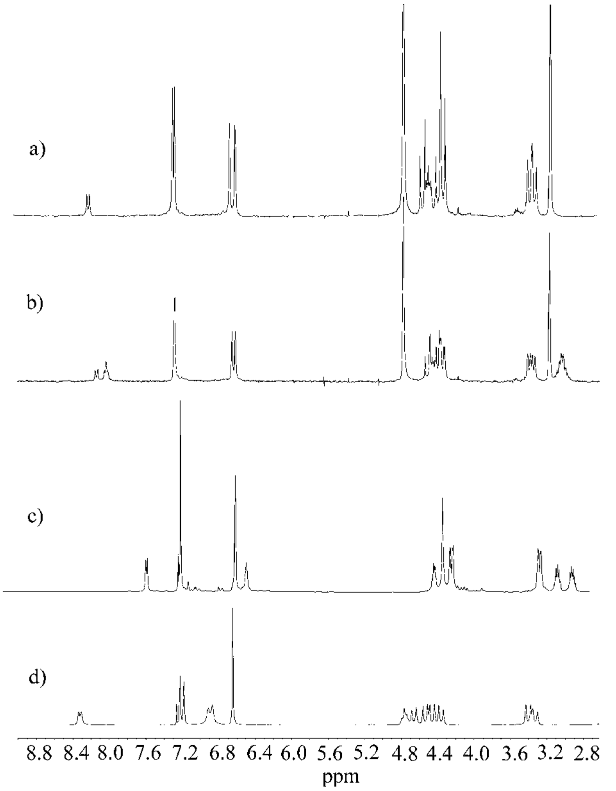


Figure 2. ^{1}H NMR spectra of calixarenes **1a** and **1b**; a: spectrum of **1a** in [D$_4$]CH_3OH (300 MHz, 25 °C); b) spectrum of **1b** in [D$_4$]CH_3OH (300 MHz, 25 °C); c) spectrum of **1b** in $CDCl_3$ (500 MHz, 25 °C); d) spectrum of **1a** in $CDCl_3$ (500 MHz, 25 °C)

In both cases a $J_{CH_\alpha-NH}$ coupling constant of greater than 8 ppm (8.7 and 8.1 Hz for **1a** and **1b**, respectively) was measured, indicating that the amino acids adopt an extended conformation,[14] necessary for dimerization.

The dimerization of **1a** in apolar solvents was additionally supported by gel permeation chromatography (GPC) in chloroform.[15] A peak was observed at 2750 Da, (calcd. 3050 Da), in good agreement with the dimer mass, while **1b** showed a peak at 1790 Da, corresponding to the monomer mass (calcd. 1861 Da) (Figure 3).

Concentration-dependent chemical shifts for the NH protons of compound **1a** allowed the determination of the dimerization constant by dilution experiments (K_{as} = 640 ± 30 M^{-1} in $CDCl_3$).[16] In agreement with a monomeric structure, no changes in the spectrum of **1b** were dis-

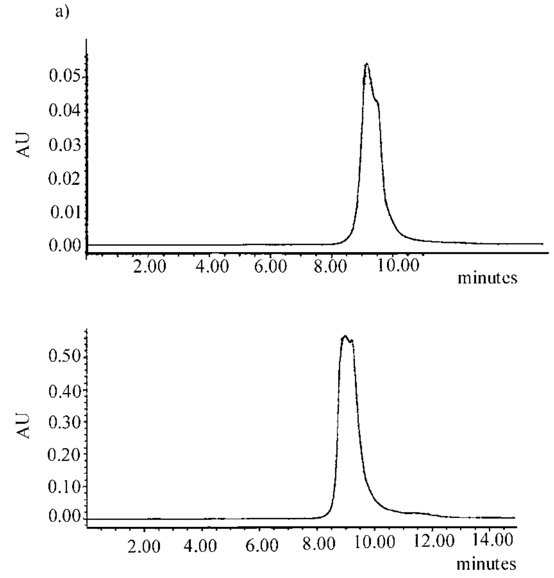


Figure 3. GPC chromatograms in $CDCl_3$ (1×10^{-3} M); a) **1a** (8.99 min); b) **1b** (9.51 min)

cernible upon dilution. The same effect was observed in the IR spectra in chloroform, where two absorbance bands at 3487 and 3313 cm^{-1} appeared for **1a**. The first one increased with dilution (3×10^{-2} to 1×10^{-3} M) while the second decreased. No changes in the intensity of these bands were observed for **1b** upon changing concentration.

^1H NMR spectra were recorded for **1a** in the aromatic solvents [D_6]benzene, [D_8]toluene, and [D_{10}]-*p*-xylene (Figure 4a) as these solvents have been found to be good guests for dimers of tetra-*N*-ureidocalix[4]arenes.[17] In all cases spectra less defined than in $CDCl_3$ were observed, probably indicating that these solvents are poor guests for the **1a** dimer. No changes in the ^1H NMR spectra ([D_{10}]-*p*-xylene or $CDCl_3$) were observed upon addition of different guest candidates,[18] except for ethylenediamine, which showed a more defined spectrum in [D_{10}]-*p*-xylene (Figure 4b). This could indicate encapsulation, although no definitive evidence has been obtained so far.

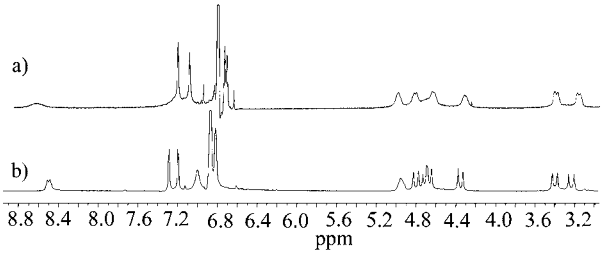


Figure 4. 500 MHz ^1H NMR spectra in [D_{10}]*p*-xylene; a) **1a**; b) **1a** + ethylenediamine (2:1)

To understand the reasons for the apparent lack of encapsulation a 500 ps molecular dynamics trajectory was generated at 300 K from the initial optimized structure (Figure 1). In the calculations, no solvent was added in order to have a better insight into the conformational behavior of the leucine chains in the unperturbed dimer. A rather stable structure develops along the trajectory (Figure 5) in which one of the chains partly occupies the cavity, thus preventing added guests from entering. Hydrogen bonds with NH_a permanently involve four out of the six potential H-donors, whereas those arising from NH_b or NH_c involve two or three, and are usually longer (see Supporting Information; see also footnote on the first page of this article). This is in good agreement with the observed NMR chemical shifts for these protons, which correspond to averaged values in the rather flexible structure.

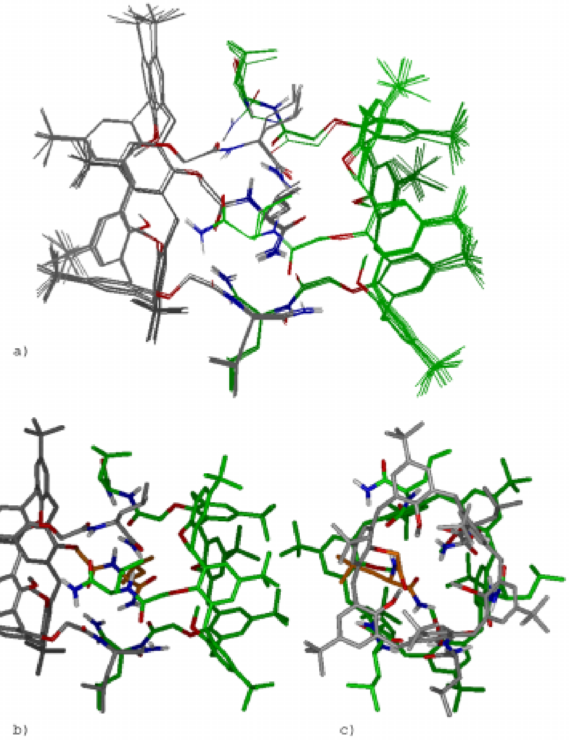


Figure 5. a) Superposition of nine optimized structures of **1a** from averaged coordinates taken for each 50 ps in a 500 ps molecular dynamics trajectory; b) and c) side and top views, respectively, of one representative structure showing a peptide chain partly occupying the capsule cavity

Conclusions

In conclusion, a dimer has been obtained for **1a** through multiple hydrogen bonds between the amide groups of leucine amino acids. The capsule formed by the **1a** dimer is quite small because the calixarene cavity is partly occupied by the methoxy groups. Furthermore, one of the flexible leucine chains tends to fold inwards into the capsule, permanently occupying the free space and thus preventing the encapsulation of suitable guests.

This is the first example of a calix[6]arene dimer based solely on interactions between amino acids, without participation of other functionalities such as urea groups. This opens a new perspective for calix[6]arene dimerization as an alternative to the association based on urea interactions.

Enlargement of the cavity could be envisaged by the addition of new amino acids to the lower rim chains. In that case formation of a β-sheet could allow dimerization of the calixarene with the peptide in an extended conformation, and the cavity size would then be directly dependent on the peptide length.

Experimental Section

General: Solvents were dried before use by standard methods. Analytical thin-layer chromatography was carried out on silica gel plates (SiO_2, MN Alugram SIL G/UV_{254}). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-300 and DRX-500 spectrometers. Chemical shifts are reported as δ values relative to the residual solvent H peak. Mass spectra were performed with a VG AutoSpec instrument by using the FAB^+ technique (NBA: *m*-nitrobenzyl alcohol). For MALDI-TOF a Reflex 3 instrument was used. IR spectra were recorded in chloroform with an FT-IR Bruker IFS 60v instrument. Elemental analyses were obtained with a Perkin−Elmer 2400 CHN analyzer. Melting points were obtained on a Gallenkamp apparatus. Specific rotations were measured with a Perkin−Elmer 241 MC polarimeter.

Molecular Modeling: INSIGHT-II/Discover packages were used for the calculations of the structure of the **1a** dimer. Standard potentials and atomic charges, as provided by the cvff force field, were employed without modifications. Calculations were performed in vacuo, with a dielectric constant $\varepsilon = 1$, and the initial structure was slowly relaxed by 300 steepest descent iterations, followed by full optimization with enough conjugate gradient iterations to reach an energy RMS gradient of less than 0.001 kcal mol^{-1} $Å^{-1}$. Minimized structures were subjected to a molecular dynamics protocol through 500 ps (50 ps heating to equilibration at 300 K). Coordinates were saved each 500 fs. Average coordinates taken for each 50 ps were minimized again obtaining a set of nine final representative structures.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-trimethoxy-38,40,42-tris(methoxycarbonylmethoxy)calix[6]arene (3): A suspension of **2** (400 mg, 0.4 mmol) and K_2CO_3 (3.20 g, 23 mmol) in CH_3CN (40 mL) was stirred under argon at 60 °C. After 30 min $BrCH_2CO_2CH_3$ (0.5 mL, 5.4 mmol) was added. The mixture was stirred for 18 h, and quenched with 25% NH_4OH (0.5 mL), acidified with HCl (1 N) and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue was triturated with MeOH to afford pure **3** (440 mg, 89%), m.p. 217−218 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (s, 6 H, ArH), 6.79 (s, 6 H, ArH), 4.36 (br, 6 H, OCH_2), 3.94 (br, 12 H, $ArCH_2Ar$), 3.64 (s, 9 H, OCH_3), 2.55 (s, 9 H, OCH_3), 1.32 [s, 27 H, $C(CH_3)_3$], 0.94 [s, 27 H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 169.8 (CO), 154.5, 151.6, 146.3, 145.8, 133.4, 132.9 (ArC), 127.7, 124.5 (ArCH), 69.4 (OCH_2), 60.6, 51.7 (OCH_3), 34.1, 34.0 [$\mathit{C}(CH_3)_3$], 31.5 [$C(\mathit{C}H_3)_3$], 31.3 ($ArCH_2Ar$), 31.1 [$C(\mathit{C}H_3)_3$]. MS (FAB^+): *m/z* (%) = 1232.0 (100) $[M + 1]^+$. $C_{78}H_{102}O_{12}\cdot CH_2Cl_2$ (1315.7): calcd. C 72.06, H 7.96; found C 72.40, H 8.07.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,39,41-tri(hydroxycarbonylmethoxy)-38,40,42-trimethoxycalix[6]arene (4): A solution of **3** (200 mg, 0.16 mmol) and $LiOH\cdot H_2O$ (60 mg, 1.44 mmol) in THF/H_2O (5:1, 6 mL) was stirred at room temperature for 16 h. The mixture was acidified with HCl (1 N) and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and the solvent was evaporated to give **4** (186 mg, 97%), m.p. 290−291 °C (ref.[13c] m.p. 292−294 °C). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 171.7 (CO), 153.0, 151.4, 146.5, 146.2, 133.0, 132.7 (ArC), 125.9, 125.7 (ArCH), 68.9 (OCH_2), 60.8 (OCH_3), 34.0 [$\mathit{C}(CH_3)_3$], 31.3 [$C(\mathit{C}H_3)_3$], 29.9 ($ArCH_2Ar$).

General Procedure for the Synthesis of 1a and 1b: Et_3N (0.12 mL, 0.86 mmol), $PyBOP\cdot PF_6$ (226 mg, 0.43 mmol) and leucine **5** (0.43 mmol) were added to a solution of **4**[13c] (150 mg, 0.13 mmol) in DMF (7 mL) and the resulting mixture was stirred at room temperature for 18 h. The solvent was evaporated, the residue was dissolved in diethyl ether and washed sequentially with NaOH (1 N), water, HCl (1 N) and water. The solution was dried ($MgSO_4$) and the solvents evaporated to give compounds **1a−b**.

1a: 86% yield, m.p. 175−176 °C. $[\alpha]_D^{25} = -20.0$ ($c = 0.1$, in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, $J = 8.7$ Hz, 3 H, NH), 7.22 (d, $J = 2.3$ Hz, 3 H, ArH), 7.18 (d, $J = 2.3$ Hz, 3 H, ArH), 6.91 (br, 3 H, NH_2), 6.87 (br, 3 H, NH_2), 6.64 (s, 6 H, ArH), 4.73 (m, 3 H, CH_α), 4.65 (d, $J = 14.8$ Hz, 3 H, OCH_2), 4.53 (d, $J = 15.1$ Hz, 3 H, $ArCH_2Ar$), 4.45 (d, $J = 15.2$ Hz, 3 H, $ArCH_2Ar$), 4.35 (d, $J = 14.8$ Hz, 3 H, OCH_2), 3.40 (d, $J = 15.1$ Hz, 3 H, $ArCH_2Ar$), 3.33 (d, $J = 15.2$ Hz, 3 H, $ArCH_2Ar$), 2.27 (s, 9 H, OCH_3), 1.77−1.61 (m, 9 H), 1.36 [s, 27 H, $C(CH_3)_3$], 0.91 (d, $J = 5.7$ Hz, 9 H, CH_3), 0.83 (d, $J = 5.7$ Hz, 9 H, CH_3), 0.78 [s, 27 H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 175.1, 169.1 (CO), 154.2, 150.5, 146.7, 146.1, 133.5, 133.2, 132.4 (ArC), 128.1, 128.0, 123.9 (ArCH), 71.5 (OCH_2), 60.3 (OCH_3), 51.1 (CH_α), 41.4 (CH_2), 34.2, 34.0 [$\mathit{C}(CH_3)_3$], 31.6, 31.0 [$C(\mathit{C}H_3)_3$], 30.0, 29.6 ($ArCH_2Ar$), 24.9 (CH), 23.0, 22.0 (CH_3). MS (MALDI-TOF): *m/z* (%) = 1548.7 (100) $[M + Na]^+$, 1526.7 $[M + 1]^+$. $C_{93}H_{132}N_6O_{12}\cdot H_2O$ (1543.0): calcd. C 72.33, H 8.75, N 5.44; found C 72.01, H 8.72, N 5.39.

1b: 71% yield, m.p. 122−124 °C. $[\alpha]_D^{25} = -27.0$ ($c = 0.1$, in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, $J = 8.1$ Hz, 3 H, NH), 7.25 (s, 6 H, ArH), 6.68 (s, 6 H, ArH), 6.58 (br, 3 H, NH), 4.57 (m, 3 H, CH_α), 4.49 (s, 6 H, OCH_2), 4.40 (d, $J = 15.0$ Hz, 6 H, $ArCH_2Ar$), 3.45 (d, $J = 15.0$ Hz, 6 H, $ArCH_2Ar$), 3.27 (m, 3 H, NCH_2), 3.12 (m, 3 H, NCH_2), 2.49 (s, 9 H, OCH_3), 1.80 (m, 3 H), 1.71 (m, 12 H), 1.44 (m, 30 H), 1.25 [s, 27 H, $C(CH_3)_3$], 0.94 (d, $J = 5.6$ Hz, 18 H, CH_3), 0.88 (t, $J = 6.4$ Hz, 9 H, CH_3), 0.83 [s, 27 H, $C(CH_3)_3$]. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT): δ = 171.3, 169.0 (CO), 154.3, 150.5, 146.7, 146.2, 133.1, 132.5 (ArC), 128.0, 124.0 (ArCH), 71.3 (OCH_2), 60.3 (OCH_3), 51.7 (CH_α), 40.6, 39.5 (CH_2), 34.2, 33.9 [$\mathit{C}(CH_3)_3$], 31.7 (CH_2), 31.5, 31.0 [$C(\mathit{C}H_3)_3$], 30.1, 29.4, 29.2, 26.8 (CH_2), 24.8 (CH), 22.7 (CH_3), 22.6 (CH_2), 22.0, 14.0 (CH_3). MS (FAB^+): *m/z* (%) = 1863.0 (100) $[M + 1]^+$. $C_{117}H_{180}N_6O_{12}\cdot H_2O$ (1879.3): calcd. C 74.71, H 9.76, N 4.47; found C 74.70, H 9.47, N 4.55.

Acknowledgments

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