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Wide Rim Urethanes Derived from Calix[4]arenes: Synthesis and Self-Assembly

Yudong Cao, Myroslav O. Vysotsky, and Volker Böhmer*

Fachbereich Chemie, Pharmazie und Geowissenschaften, Abteilung Lehramt Chemie, Johannes Gutenberg-Universität Mainz, Duesbergweg 10-14, D-55099 Mainz, Germany

vboehmer@mail.uni-mainz.de

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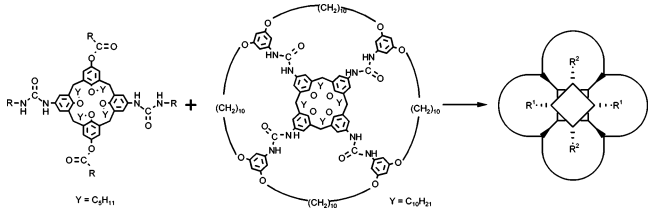

Calix[4]arenes **4**, substituted at the wide rim by four *N*-tolyl-urethane groups, were synthesized, as well as derivatives **10a**,**b** bearing two or three tolyl-urea groups beside of one or two urethane group(s). In contrast to tetra-tolyl urea **11**, the urethane derivatives do not form hydrogen-bonded, dimeric capsules in $CDCl_3$ or benzene-d_6, but the dimerization can be induced for the triurea **10b** by tetraethylammonium cations as guests. The quantitative formation of heterodimers is observed for all urethanes **4** and **10a**,**b** in benzene-d_6 in mixtures with a "tetra-loop" tetraurea **14**, while "bisloop" tetraureas **13** require di- or triurea derivatives **10a**,**b** for a clean heterodimerization.

Introduction

Calix[4]arenes bearing four urea functions at their wide rim form dimeric capsules in aprotic, apolar solvents,[1] which are held together by a seam of hydrogen bonds between the interdigitating urea functions of the two calixarenes. The structure of these S_8-symmetrical dimers (Figure 1) was first deduced from their ^{1}H NMR spectra,[2] which typically show two *m*-coupled doublets for the aromatic protons of the calix[4]arene skeleton ($\Delta\delta = \sim 1.2-1.7$ ppm) and two singlets for the NH protons,[3] which are usually found around 9.3 and 7.0 ppm for aryl urea residues (R = −Ar−X) in $CDCl_3$.

This difference in their chemical shift suggests already two −NH···O═C hydrogen bonds of different strengths,[3] although the values for the aromatic protons show that shielding and deshielding effects may have a strong influence, which is difficult to predict. The first X-ray structure of a dimeric capsule[4] revealed, however, that the N···O distance for the calixarene bound nitrogen is distinctly longer (3.10−3.16 Å) than that of the nitrogen attached to the urea residue R (2.84−2.85 Å).[5] Further X-ray structures confirmed this difference and showed, in agreement with MD simulations, that some of these weaker hydrogen bonds may not be present if a large cation (e.g., tetraethylammonium) is included as a guest.[6]

These results led to the idea of studying the association of tetraurethanes in which the NH_β group is replaced by an oxygen.[7] Even if these tetraurethanes would not form homodimers as a result of the lower number of hydrogen bonds, heterodimers with tetraureas might be possible. This would add an interesting novel selectivity to the self-organization of such systems.

Results and Discussion

Syntheses. Tetraurethanes **4** were obtained in three steps from the well-known tetraether, **1**, unsubstituted in the para position (Scheme 1). Tetra formylation by hexamethylenetetramine[8] and

(1) Rebek, J., Jr. *Chem. Commun.* **2000**, 637−643.
(2) Shimizu, K.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 12403−12407. Hamann, B. C.; Shimizu, K.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1326−1329.
(3) Vysotsky, M. O.; Böhmer, V. *Org. Lett.* **2000**, *2*, 3571−3574.
(4) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534.
(5) One of the referees of ref 4 even suggested that there is no hydrogen bond because the NH group must be in this distance as a result of the overall geometry of the capsule.
(6) Thondorf, I.; Broda, F.; Rissanen, K.; Vysotsky, M. O.; Böhmer, V. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1796−1800.
(7) *p*-Nitrophenyl urethanes of calix[4]arenes, in which the other NH group is replaced by O, were prepared and used for the synthesis of tetraureas. They do not show self-association to dimers.

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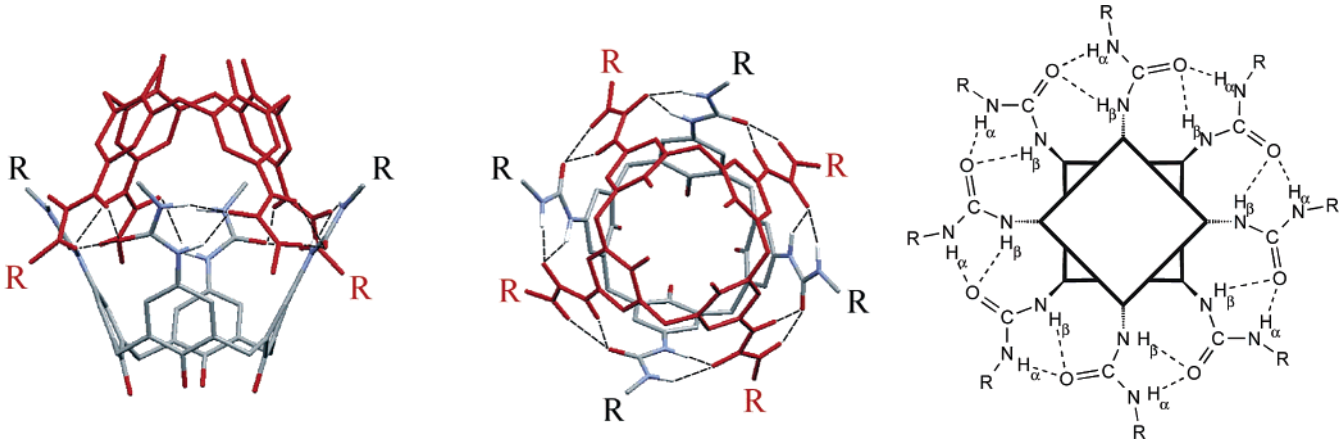
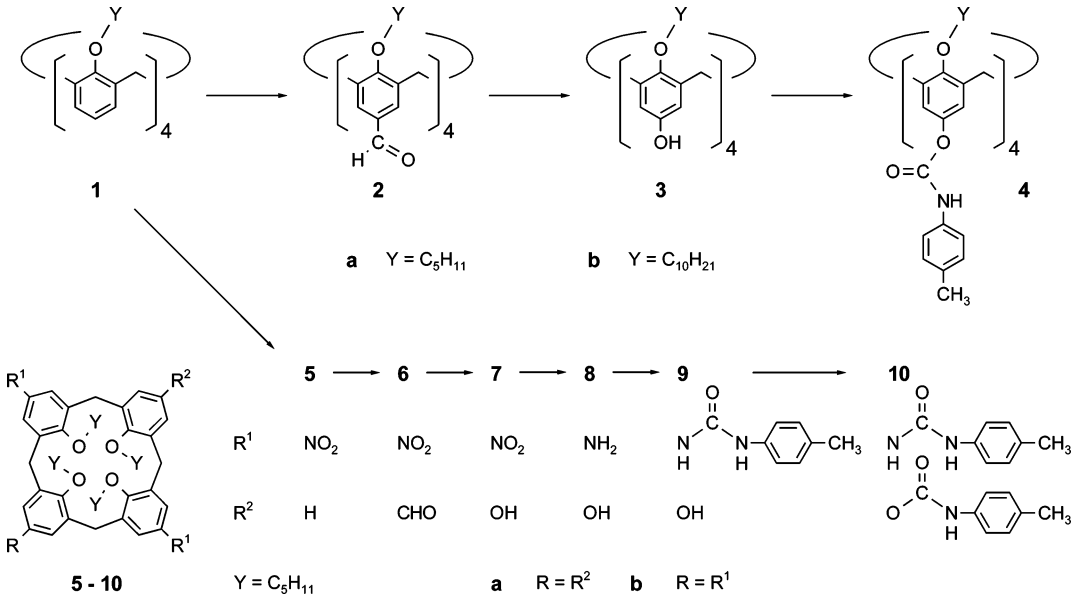


FIGURE 1. Molecular shape of a dimeric capsule (MD simulations are in agreement with X-ray structures) and schematic representation of the hydrogen-bonded belt. As indicated by shorter distances, $NH_\alpha\cdots O{=}C$ hydrogen bonds are stronger than $NH_\beta\cdots O{=}C$ hydrogen bonds.

SCHEME 1. Synthesis of Calix[4]arenes Substituted at the Wide Rim by Urethane Functions, Alone or in Combination with Urea Functions



Baeyer−Villiger oxidation[9] with *m*-chloroperbenzoic acid in analogy to literature procedures furnished the calix[4]arenes **3** in about 40−50% overall yield. They were reacted in the last step with *p*-tolyl isocyanate in acetone in the presence of potassium carbonate (35−40% of **4**, not optimized).

In addition to **4**, calix[4]arenes were synthesized, in which urethane functions are combined with urea functions at the wide rim. In these cases, the reaction sequence (Scheme 1) starts with the (unspecific) partial nitration of the tetraether **1**,[10] followed by formylation and oxidation, as described above. Hydrogenation of the nitro groups with the use of Pd/C as catalyst leads to compounds **8** bearing at their wide rim a combination of two[11] or three amino groups with one or two[11] hydroxy group(s). A reaction with an appropriate isocyanate finally should give the mixed urea/urethanes **10**. As a result of the different reactivities of amino and hydroxy groups, it was advantageous to do this last acylation in two steps. First the amino groups were converted to urea groups in $CHCl_3$ at room temperature. After purification of the intermediate ureas **9**, the remaining hydroxy groups were acylated in acetone in the presence of sodium/potassium carbonate. It is evident that by this sequence (in principle) easily two different carbamoyl residues could be introduced.[12]

All compounds described in Scheme 1 were unambiguously characterized by NMR- and mass spectra. Only some typical features will be discussed below.

(8) Komori, T.; Shinkai, S. *Chem. Lett.* **1992**, 901−904.

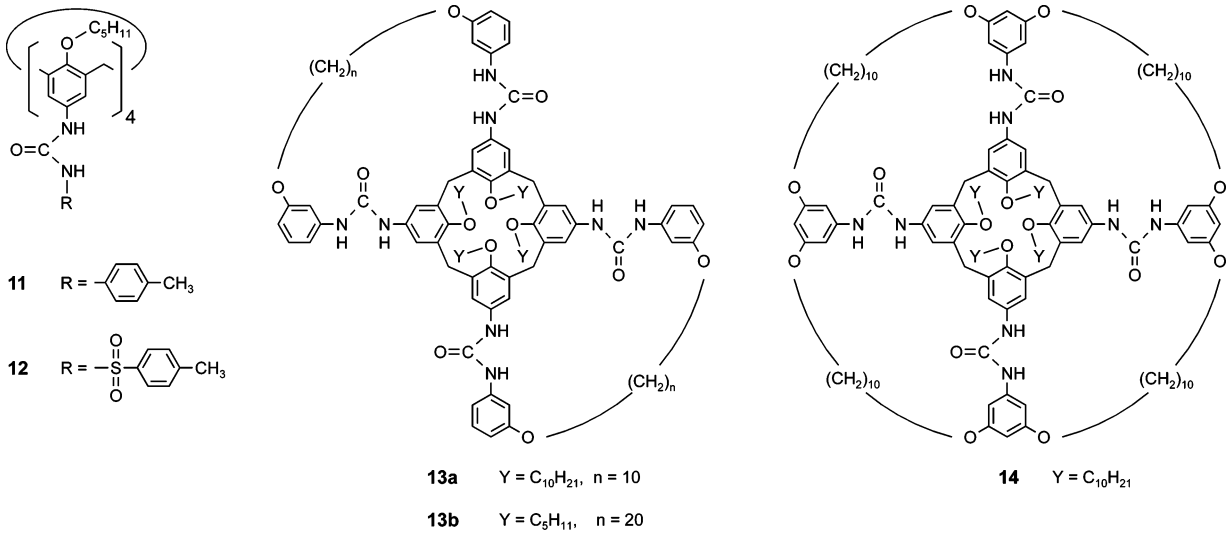
(9) Mascal, M.; Warmuth, R.; Naven, R. T.; Edwards, R. A.; Hursthouse, M. B.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 3435−3441. Arduini, A.; Mirone, L.; Paganuzzi, D.; Pinalli, A.; Pochini, A.; Secchi, A.; Ungaro, R. *Tetrahedron* **1996**, *52*, 6011−6018. Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361−9364.

(10) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640−1644. Kenis, P. J. A.; Noordman, O. F. J.; Schönherr, H.; Kerver, E. G.; Snellink-Rüel, B. H. M.; van Hummel, G. J.; Harkema S.; van der Vorst, C. P. J. M.; Hare, J.; Picken, S. J.; Engbersen, J. F. J.; van Hulst, N. F.; Vancso, G. J.; Reinhoudt, D. N. *Chem.—Eur. J.* **1998**, *4*, 1225−1234. Budka, J.; Lhoták, P.; Michlová, V.; Stibor, I. *Tetrahedron Lett.* **2001**, *42*, 1583−1586.

(11) Only the 1,3-isomer was synthesized and studied here, but the 1,2-isomer could be prepared analogously, as well as a mononitro-tri-hydroxy derivative.

(12) Alternatively, it should be possible to acylate the hydroxy groups before the nitro groups are hydrogenated.

CHART 1



The formylation, for instance, is easily controlled by the appearance of a signal at 9.55 ppm. Aromatic protons appear as one singlet (8 H) for the C_{4v}-symmetrical compounds **2**−**4**, as two singlets (4 H each) for the C_{2v}-symmetrical compounds **6a**−**10a**, while two singlets (2 H each) and two *m*-coupled doublets (2 H each) should be seen for the C_s-symmetrical compounds **6b**−**10b**, a pattern which is characteristic even if in routine spectra the *m*-coupling often is not resolved. The symmetry is also reflected by the pattern of the methylene protons, which appear as a pair of doublets with geminal coupling for C_{4v}- and C_{2v}-symmetrical compounds (**1**−**4** and **5a**−**10a**), while two pairs of doublets are seen for the C_s-symmetrical compounds (**5b**−**10b**).

For all compounds, the molecular peak was found in the FD or ESI mass spectrum, and because these compounds are prepared stepwise, according to the indicated synthetic strategy, this information cannot be improved by high-resolution mass spectrometry.

Dimerization Studies. While the ^{1}H NMR spectra of **4**, **10a**, and **10b** in DMSO-d_6 are sharp and in total agreement with the expected structure of a "monomeric" calix[4]arene with C_{4v}, C_{2v}, and C_s symmetry, respectively, broad unresolved spectra are observed in $CDCl_3$ or benzene-d_6. This can be explained by interactions via inter- and intramolecular hydrogen bonds, but there is no indication for the formation of a dimeric capsule or of any other well-defined species.

Attempts to induce the dimerization by adding a favorable guest such as 1,4-difluorobenzene were also unsuccessful; for tetraethylammonium cations, see below. Thus, we have to conclude that not only do tetraurethanes **4** not form homodimers, but that the usual dimerization is also impossible when just a single urea group is replaced by an analogous urethane like in **10b**. Obviously the "formalistic" picture that only two of the eight weaker NH···O═C hydrogen bonds are lacking in such a dimer **10b**·**10b** in comparison with the dimer **11**·**11** of the corresponding tetraurea **11** is too simple. Potential explanations (small differences in bond lengths and bond angles between —NH— and —O—, lower basicity of the carbonyl group in urethanes or repulsion between Ar—O—C and O═C oxygens) necessarily must be tentative.

Heterodimerization. We, therefore, turned our attention to the potential formation of heterodimers with tetraurea calix[4]-arenes. However, stoichiometric mixtures of **4**, **10a**, or **10b** with the tetratolyl urea **11** or the tetratosyl urea **12** (known to form exclusively heterodimers[13] with tetraarylureas such as **11**) showed only sharp NMR signals for the homodimers **11**·**11** and **12**·**12**, respectively, in benzene-d_6 but no indication of heterodimers. The situation changes if the bis-loop compound **13** or the tetra-loop compound **14** are offered as a partner, which cannot form homodimers for sterical reasons (Chart 1).[14] In the latter case, all urethane derivatives form heterodimers completely in benzene-d_6, but only the di- and triurea derivatives **10a** and **10b** do so in $CDCl_3$. In benzene-d_6, **10a** and **10b** form heterodimers with **13b**, and **10b** will also form heterodimers with **13a**, which has smaller loops. From the number of NH signals and from their relative intensity, we conclude that both possible regioisomers with the urethane group(s) penetrating the loops or being placed between the loops can be formed in nearly equal quantity (see Figure 2). No definite species with bisloop compounds are formed by **4**, which contains no urea

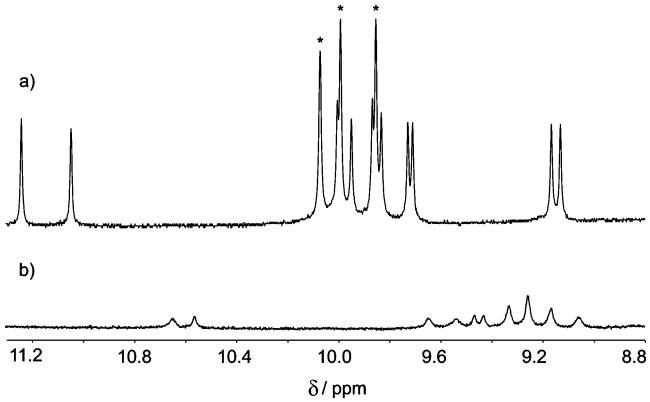


FIGURE 2. Section of the ^{1}H NMR spectra of a mixture of **10b** and **13a** (ratio 1:1.1) in (a) benzene-d_6 and (b) $CDCl_3$. Low field signals for 16 protons (peaks marked by an asterisk have the double intensity) indicate the formation of two regioisomeric heterodimers (two times eight $-NH_\alpha-$ groups) in nearly equal quantity (a).

(13) Castellano, R. K.; Kim, B. H.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12671−12672. Castellano, R. K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3657−3663.

(14) For the synthesis of **13** and **14**, see: Bogdan, A.; Vysotsky, M. O.; Wang, L.; Böhmer, V. *Chem. Commun.* **2004**, 1268−1269.

TABLE 1. Heterodimerization Studies of Urethane Derivatives 4, 10a, and 10b with Bis- and Tetra-loop Tetraureas 13 and 14[a]

	4	10a	10b
13a		((**B**))[b]	**B**[b]/(**C**)[b]
13b		**B**[b]	**B**[b]/(**C**)[b]
14	**B**	**B**/**C**	**B**/**C**

[a] **B** and **C** indicate the formation of dimers in benzene-d_6 or $CDCl_3$, respectively. Weak ( ) and very weak (( )) signals for heterodimers are indicated by parentheses. [b] Two regioisomers are possible.

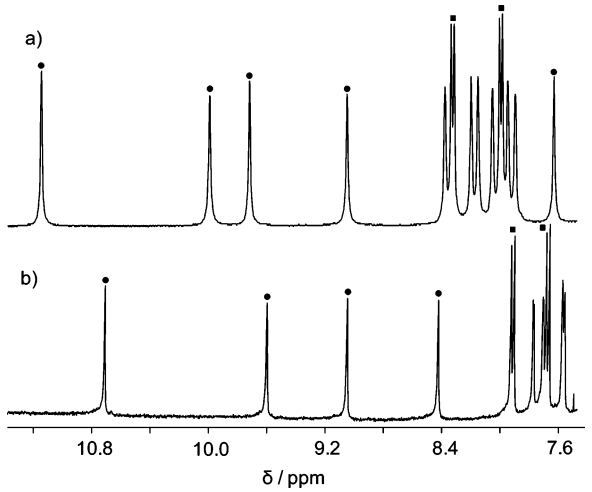


FIGURE 3. Section of the ^{1}H NMR spectra of a mixture of **10a** and **14** (ratio 1:1.1) in (a) benzene-d_6 and (b) $CDCl_3$. Assignment of peaks: filled circles, N−H (5 or 4 of 7 singlets); filled squares, tolyl Ar−H (2 of 4 doublets); remaining peaks, calixarene Ar−H.

group at all. These results are summarized in Table 1, which also contains some "borderline" cases. The low field section of some typical ^{1}H NMR spectra of such heterodimers is shown in Figures 2 and 3.

The results show, that the tendency to form heterodimers with multimacrocyclic tetraureas increases with the number of the loops and with the number of urea functions in mixed urea−urethanes. Benzene is more favorable for the dimerization than chloroform, while the influence of the size of the loops in bisloop compounds is less clear. Under the conditions studied, the tetraurethane **4** is able to form dimers only with the tetraloop tetraurea **14** and only in benzene.

Cationic Guests. Triurea-monoacetamide derivatives form hydrogen-bonded, noncapsular tetramers in chloroform or benzene,[15] which can be "reorganized" to form the usual dimeric capsules if tetraethylammonium cations are offered as guests. Similar studies with compounds **4**, **10a**, and **10b** in $CDCl_3$ in the presence of $Et_4N^+PF_6^-$ show that the dimerization of the monourethane **10b** can also be induced. The ^{1}H NMR spectrum suggests that only one of the two possible regioisomers is formed, but it is not possible to deduce if the urethane functions are adjacent or in distal position. In the case of diurethane **10a**, a guest signal at approximately −1.5 ppm indicates encapsulation, but the total spectrum remains rather broad, while no significant spectral change is observed for tetraurethane **4** upon addition of $Et_4N^+PF_6^-$.

The inclusion of the Et_4N^+ cations follows from the highfield shift of its CH_3 signal (see Figure 4), which appears as a broad

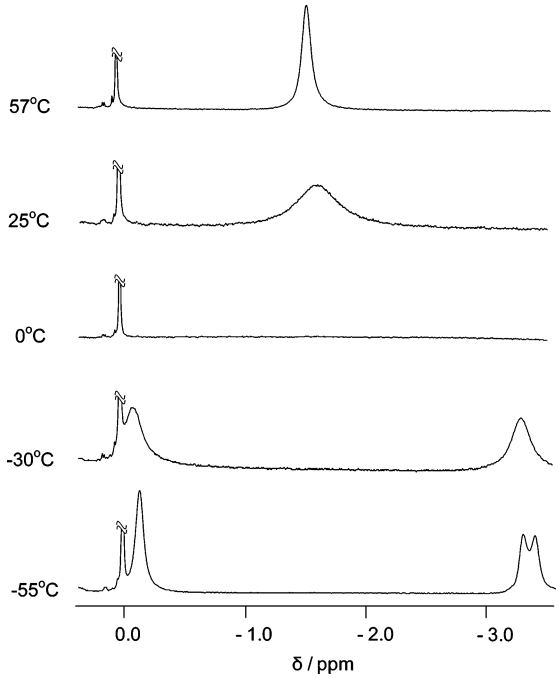


FIGURE 4. Section of the methyl signals of the guest in the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of [**10b**·Et_4N^+·**10b**] PF_6^- at different temperatures.

singlet ($\delta = -1.51$ ppm) at 57 °C and splits into two signals ($\delta = -0.06$ ppm and $\delta = -3.28$ ppm) at −30 °C. This splitting[16] is due to the fact that the exchange between methyl groups in the "equatorial plane" of the hydrogen-bonded belt and methyl groups oriented toward the aromatic rings of the calixarenes is now slow on the NMR time scale. When the coalescence temperature of 0 °C is used, an energy barrier of $\Delta G = 48.6$ kJ mol^{-1} can be estimated.[17] This value is lower than the energy barrier observed for Et_4N^+, included in dimers of **11** ($\Delta G = 54.8$ kJ mol^{-1} at 305 K under analogous conditions[18]), but corresponds to the value found for triurea−monoacetamides ($\Delta G = 48.1$ kJ mol^{-1}).

Conclusions

Although the strength of the two NH···O═C hydrogen bonds formed by the urea functions in dimeric capsules of tetraurea calix[4]arenes is quite different, urethanes obtained by the (partial) replacement of the less strongly binding ─NH─ attached to the calixarene part by ─O─ are not able to form dimers under the usual conditions. Only in the case of monourethane **10b** can the dimerization be induced by tetraethylammonium cations, known as favorable guests. The higher mobility of the included cation, indicated by a lower energy barrier $\Delta G^{\ddagger}$, shows that the capsule is less tightly bound in this case. Heterodimers are also not formed with partners, for example, **11** or **12**, which are also able to form homodimers. Heterodimers are observed, however, with bis- or tetraloop tetraureas **13** and **14**, which are not able to homodimerize for sterical reasons. Subtle effects due to the number and the size

(15) Shivanyuk, A.; Saadioui, M.; Broda, F.; Thondorf, I.; Vysotsky, M. O.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Chem.—Eur. J.* **2004**, *10*, 2138−2148.

(16) A further splitting at lower temperature as a result of the directionality of the hydrogen-bonded belt is not discussed.

(17) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228−1234.

(18) Vysotsky, M. O.; Pop, A.; Broda, F.; Thondorf, I.; Böhmer, V. *Chem.—Eur. J.* **2001**, *7*, 4403−4410.

of the loops and the number of urea groups in mixed urea−urethanes further demonstrate the delicate balance of weak forces holding together such self-assembled dimers.

Experimental Section

5,11,17,23-Tetra-formyl-25,26,27,28-tetra-pentyloxy-calix[4]-arene, 2a: A mixture of **1a**[19] (1.06 g, 1.5 mmol) and hexamethylenetetramine (6.3 g, 45 mmol) was stirred in 60 mL CF_3COOH under reflux for 2 days. The pink solution was cooled to rt, diluted with 1 M HCl (50 mL) and CH_2Cl_2 (50 mL), and vigorously stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 (50 mL) and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford **2a** as a white solid (0.9 g, 73%): mp 186−188 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 4H), 7.14 (s, 8H), 4.49, 3.34 (2 d, ^2J = 14 Hz, 2 × 4H), 3.96 (t, ^3J = 7.4 Hz, 8H), 1.87 (m, 8H), 1.39 (m, 16H), 0.94 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{52}H_{64}O_8$, 816.46; found, 816.5.

5,11,17,23-Tetra-formyl-25,26,27,28-tetra-decyloxy-calix[4]-arene, 2b: A mixture of **1b**[20] (1.97 g, 2 mmol) and hexamethylenetetramine (8.4 g, 60 mmol) was stirred in 80 mL CF_3COOH under reflux for 2 days. The crude product was purified as described above to afford **2b** (1.24 g, 57%): mp 128−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.57 (s, 4H), 7.14 (s, 8H), 4.48, 3.33 (2 d, ^2J = 13.6 Hz, 2 × 4H), 3.95 (t, ^3J = 7.4 Hz, 8H), 1.87 (m, 8H), 1.36 (m, 56H), 0.87 (t, ^3J = 6.3 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{72}H_{104}O_8$, 1096.77; found, 1096.9.

5,11,17,23-Tetra-hydroxy-25,26,27,28-tetra-pentyloxy-calix-[4]arene, 3a: Compound **2a** (816 mg, 1 mmol) and *m*-chloroperoxobenzoic acid (MCPBA, 2.4 g, 10.9 mmol) were stirred with 80 mL of chloroform at rt for 3 days until the starting material disappeared. The solution was washed first with 2 M $NaHSO_3$ to remove the residual MCPBA and then twice with brine and dried over $MgSO_4$. The solvent was evaporated, the residue was dissolved in 40 mL of methanol, and sodium hydroxide (400 mg, 10 mmol) was added. The mixture was stirred at rt for 3 h. The solution was concentrated, 1 M HCl (20 mL) was added, and the precipitate was filtered and washed with water. The crude product was finally purified by column chromatography ($CHCl_3$/MeOH = 30:1) to afford **3a** (520 mg, 68%) as a white solid: mp >300 °C (slow decomposition). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (s, 4H), 6.11 (s, 8H), 4.20, 2.91 (2 d, ^2J = 12.2 Hz, 2 × 4H), 3.70 (t, ^3J = 7.4 Hz, 8H), 1.86 (m, 8H), 1.37 (m, 16H), 0.91 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{64}O_8$, 768.46; found, 770.0. HRMS (ESI): $[M + Na]^+$ calcd for $C_{48}H_{64}O_8Na$, 791.4499; found, 791.4487.

5,11,17,23-Tetra-hydroxy-25,26,27,28-tetra-decyloxy-calix[4]-arene, 3b: A mixture of **2b** (548 mg, 0.5 mmol) and MCPBA (1.2 g, 5.44 mmol) in 50 mL of chloroform was stirred at rt for 3 days until the starting material disappeared. The crude product was purified as described above to afford **3b** (390 mg, 74%): mp 269−271 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (s, 4H), 6.16 (s, 8H), 4.24, 2.95 (2 d, ^2J = 12.5 Hz, 2 × 4H), 3.73 (t, ^3J = 7.4 Hz, 8H), 1.91 (m, 8H), 1.38 (m, 56H), 0.89 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{68}H_{104}O_8$, 1048.77; found, 1050.9. HRMS (ESI): $[M + Na]^+$ calcd for $C_{68}H_{104}O_8Na$, 1071.7629; found, 1071.7645.

5,11,17,23-Tetra-tolylcarbamoyloxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 4a: Tolyl-isocyanate (80 mg, 0.6 mmol) was added to a suspension of **3a** (80 mg, 0.1 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in dry acetone (40 mL) under nitrogen. The reaction mixture was stirred at rt overnight and evaporated. CH_2Cl_2 (40 mL) was added, the suspension was filtered, and the filtrate was washed with saturated NH_4Cl and dried (Na_2SO_4). After evaporation, the residue was purified by column chromatography (hexane/ethyl acetate = 4:1) to afford **4a** (50 mg, 37%): mp 152−154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24, 7.08 (2 d, ^3J = 8.0 Hz, 16H), 6.99 (br s, 4H), 6.49 (s, 8H), 4.44, 3.14 (2 d, ^2J = 13.7 Hz, 2 × 4H), 3.83 (t, ^3J = 7.4 Hz, 8H), 2.29 (s, 12H), 1.87 (m, 8H), 1.37 (m, 16H), 0.94 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{80}H_{92}N_4O_{12}$, 1300.67; found, 1301.6. HRMS (ESI): $[M + H]^+$ calcd for $C_{80}H_{93}N_4O_{12}$, 1301.6790; found, 1301.6746.

5,11,17,23-Tetra-tolylcarbamoyloxy-25,26,27,28-tetra-decyloxy-calix[4]arene, 4b: Compound **4b** was prepared and purified analogously to **4a**: yield 36%; mp 112−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24, 7.09 (2 d, ^3J = 8.6 Hz, 16H), 6.83 (br s, 4H), 6.51 (s, 8H), 4.44, 3.15 (2 d, ^2J = 13.7 Hz, 2 × 4H), 3.86 (t, ^3J = 7.0 Hz, 8H), 2.29 (s, 12H), 1.89 (m, 8H), 1.30 (m, 56H), 0.89 (t, ^3J = 6.7 Hz, 12H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 4H), 7.31, 7.06 (2 d, ^3J = 8.1 Hz, 16H), 6.60 (s, 8H), 4.32, 3.32 (2 d, ^2J = 13.0 Hz, 2 × 4H), 3.84 (br t, 8H), 2.21 (s, 12H), 1.92 (m, 8H), 1.25 (m, 56H), 0.85 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{100}H_{132}N_4O_{12}$, 1580.98; found, 1584.9. HRMS (ESI): $[M + Na]^+$ calcd for $C_{100}H_{132}N_4O_{12}Na$, 1603.9739; found, 1603.9772.

5,17-Di-nitro-25,26,27,28-tetra-pentyloxy-calix[4]arene, 5a: To a solution of **1a** (1.06 g, 1.5 mmol) in a mixture of CH_2Cl_2 (100 mL) and glacial acetic acid (14 mL) was added 65% HNO_3 (7 mL), and the reaction mixture was stirred at rt. After 15 min, the solution became black (if not, a few drops of 100% HNO_3 should be added). The reaction was monitored by TLC and quenched after 2 h by the addition of 100 mL of water. The organic layer was washed with water and brine and finally dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography (hexane/ethyl acetate = 10:1) to afford **5a** (490 mg, 41%) as yellow powder: mp 141−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 4H), 6.72 (s, 6H), 4.46, 3.24 (2 d, ^2J = 13.7 Hz, 2 × 4H), 3.94, 3.89 (2 t, ^3J = 7.4 Hz, 2 × 4H), 1.87 (m, 8H), 1.37 (m, 16H), 0.94 (t, ^3J = 7.0 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{62}N_2O_8$, 794.45; found, 795.4.

5,11,17-Tri-nitro-25,26,27,28-tetra-pentyloxy-calix[4]arene, 5b: To a solution of **1a** (0.7 g, 1 mmol) in a mixture of CH_2Cl_2 (60 mL) and glacial acetic acid (9.4 mL) was added 65% HNO_3 (4.7 mL), and the reaction mixture was stirred at rt for 3 days. The crude product was purified as described above to afford **5b** (490 mg, 41%) as a yellow powder by column chromatography (hexane/ethyl acetate = 8:1): mp 139−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, 4H), 7.23 (s, 2H), 6.35 (s, 3H), 4.50, 4.45 (2 d, ^2J = 14.1 Hz, 2 × 2H), 4.08−4.00 (m, 4H), 3.89, 3.78 (2 t, ^3J = 7.0 Hz, 2 × 2H), 3.34, 3.29 (2 d, ^2J = 14.1 Hz, 2 × 2H), 1.85 (m, 8H), 1.37 (m, 16H), 0.93 (m, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{61}N_3O_{10}$, 839.44; found, 839.4.

5,17-Di-nitro-11,23-di-formyl-25,26,27,28-tetra-pentyloxy-calix[4]arene, 6a: A mixture of **5a** (670 mg, 0.84 mmol) and hexamethylenetetramine (1.76 g, 12.6 mmol) was stirred in 80 mL CF_3COOH under reflux for 5 h. The solution was cooled to rt, diluted with aqueous 1 M HCl (30 mL) and CH_2Cl_2 (30 mL), and vigorously stirred at rt for 1 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by column chromatography (hexane/ethyl acetate = 3:1) to afford **6a** (640 mg, 89%) as a white solid: mp 206−208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 2H), 7.62, 7.09 (2s, 8H), 4.49, 3.36 (2 d, ^2J = 13.7 Hz, 2 × 4H), 3.99−3.91 (br t, 8H), 1.85 (m, 8H), 1.38 (m, 16H), 0.93 (br t, 12H). MS (FD) *m*/*z*: calcd for $C_{50}H_{62}N_2O_{10}$, 850.44; found, 852.3.

5,11,17-Tri-nitro-23-formyl-25,26,27,28-tetra-pentyloxy-calix-[4]arene, 6b: A mixture of **5b** (340 mg, 0.4 mmol) and hexamethylenetetramine (420 mg, 3 mmol) was stirred in 20 mL CF_3-

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COOH under reflux for 6 h. The crude product was purified as described above to afford **6b** (340 mg, 98%) as a white solid: mp 226−229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.60 (s, 1H), 7.65 (s, 2H), 7.58 (br s, 4H), 7.29 (s, 2H), 4.37, 4.35 (2 d, ^2J = 14.1 Hz, 2 × 2H), 4.00 (m, 8H), 3.68, 3.61 (2 d, ^2J = 14.1 Hz, 2 × 2H), 1.85 (m, 8H), 1.38 (m, 16H), 0.91 (t, ^3J = 6.6 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{49}H_{61}N_3O_{11}$, 867.43; found, 867.5.

5,17-Di-nitro-11,23-di-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 7a: A mixture of **6a** (300 mg, 0.35 mmol) and MCPBA (425 mg, 1.89 mmol) in 40 mL of chloroform was stirred at rt for 3 days until **6a** disappeared. Additional chloroform (20 mL) was added, and the solution was washed with 2 M $NaHSO_3$ to remove the residual MCPBA and twice with brine and dried ($MgSO_4$). After evaporation, the residue was dissolved in methanol (20 mL) and water (4 mL), NaOH (280 mg, 7 mmol) was added, and the mixture was stirred at rt for 3 h. The solution was concentrated in vacuo, 1 M HCl (20 mL) was added, and the resulting precipitate was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford **7a** (220 mg, 75%): mp 202−205 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89, 5.70 (2s, 8H), 4.70 (s, 2H), 4.42, 3.21 (2 d, ^2J = 13.6 Hz, 2 × 4H), 4.09, 3.70 (2 t, ^3J = 7.8 Hz, 2 × 4H), 1.85 (m, 8H), 1.38 (m, 16H), 0.90 (m, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{62}N_2O_{10}$, 826.44; found, 828.1. HRMS (ESI): $[M + Na]^+$ calcd for $C_{48}H_{62}N_2O_{10}Na$, 849.4302; found, 849.4296.

5,11,17-Tri-nitro-23-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 7b: A mixture of **6b** (360 mg, 0.42 mmol) and MCPBA (250 mg, 1.12 mmol) in 50 mL of chloroform was stirred at rt for 4 days until **6b** disappeared. The crude product was isolated and purified by column chromatography (hexane/ethyl acetate = 4:1) as described above to afford **7b** (250 mg, 70%): mp 195−197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, 4H), 7.18 (s, 2H), 5.64 (s, 2H), 4.51, 4.40 (2 d, ^2J = 14.1 Hz, 2 × 2H), 4.18−4.06 (m, 4H), 3.85, 3.69 (2 t, ^3J = 7.0 Hz, 2 × 2H), 3.36, 3.24 (2 d, ^2J = 14.1 Hz, 2 × 2H), 1.90 (m, 8H), 1.51 (m, 16H), 0.97 (m, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{61}N_3O_{11}$, 855.43; found, 855.5. HRMS (ESI): $[M + Na]^+$ calcd for $C_{48}H_{61}N_3O_{11}Na$, 878.4204; found, 878.4215.

5,17-Di-amino-11,23-di-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 8a: Pd/C (106 mg, 0.1 mmol) was added to a solution of **7a** (410 mg, 0.5 mmol) in toluene (30 mL), and the mixture was stirred at rt under H_2 overnight. The catalyst was filtered through Celite and washed with THF (2 × 30 mL), and the solvent was evaporated in vacuo to afford **8a** (310 mg, 81%): mp 276−278 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.31 (s, 2H), 6.14, 5.93 (2 s, 8H), 4.44 (br s, 4H), 4.18, 2.84 (2 d, ^2J = 12.1 Hz, 2 × 4H), 3.78, 3.58 (2 t, ^3J = 8.2 Hz, 2 × 4H), 1.83 (m, 8H), 1.38 (m, 16H), 0.91, 0.90 (2 t, ^3J = 7.0 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{66}N_2O_6$, 766.49; found, 767.9.

5,11,17-Tri-amino-23-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 8b: Compound **7b** (170 mg, 0.2 mmol) was hydrogenated with Pd/C (96 mg, 0.09 mmol) in toluene (30 mL) as described above to yield **8b** (130 mg, 85%): mp > 270 °C (partly decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (s, 1H), 6.04 (s, 4H), 6.02 (s, 2H), 5.87 (s, 2H), 4.36 (br s, 6H), 4.17 (m, 4H), 3.72−3.63 (m, 8H), 2.85, 2.79 (2 d, ^2J = 12.5 Hz, 2 × 2H), 1.88 (m, 8H), 1.37 (m, 16H), 0.90 (t, ^3J = 7.0 Hz, 12H). MS (FD) *m*/*z*: calcd for $C_{48}H_{67}N_3O_5$, 765.51; found, 766.7.

5,17-Di-tolylurea-11,23-di-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 9a: Tolyl-isocyanate (120 mg, 0.9 mmol) was added to a solution of **8a** (70 mg, 0.09 mmol) in chloroform (20 mL) under nitrogen. The mixture was stirred at rt overnight. The solvent was evaporated, and the residue was purified by column chromatography (hexane/ethyl acetate = 2:1) to afford **9a** (60 mg, 64%): mp 176−178 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.40 (s, 2H), 8.31, 8.22 (2s, 4H), 7.27, 7.05 (2 d, ^3J = 8.6 Hz, 8H), 6.92, 6.01 (2 s, 8H), 4.27, 3.01 (2 d, ^2J = 12.5 Hz, 2 × 4H), 3.86, 3.67 (2 t, ^3J = 7.4 Hz, 2 × 4H), 2.23 (s, 6H), 1.90 (m, 8H), 1.37 (m, 16H), 0.94, 0.91 (2 t, ^3J = 7.0 Hz, 12H). MS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{64}H_{80}N_4O_8Na$, 1055.59; found, 1055.67. HRMS (ESI): $[M + H]^+$ calcd for $C_{64}H_{81}N_4O_8$, 1033.6054; found, 1033.6088.

5,11,17-Tri-tolylurea-23-hydroxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 9b: Tolyl-isocyanate (665 mg, 5 mmol) was added to a solution of **8b** (380 mg, 0.5 mmol) in chloroform (30 mL) under nitrogen. The mixture was stirred at rt overnight and evaporated, and the residue was purified by column chromatography (hexane/THF = 2:1) to afford **9b** (290 mg, 50%): mp > 290 °C (partly decomposition). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.26 (s, 2H), 8.24 (s, 1H), 8.18 (s, 2H), 8.07 (s, 1H), 7.24, 7.03 (2 d, ^3J = 7.0 Hz, 12H), 6.89, 6.84, 6.72, 6.05 (4s, 8H), 4.32, 4.27 (2 d, ^2J = 12.9 Hz, 2 × 2H), 3.84 (t, ^3J = 7.4 Hz, 4H), 3.76, 3.71 (2 t, ^3J = 7.0 Hz, 4H), 3.09, 3.02 (2 d, ^2J = 12.5 Hz, 2 × 2H), 2.22 (s, 6H), 2.20 (s, 3H), 1.89 (m, 8H), 1.39 (m, 16H), 0.93 (t, ^3J = 6.6 Hz, 12H). MS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{72}H_{88}N_6O_8Na$, 1187.66; found, 1187.74. HRMS (ESI): $[M + Na]^+$ calcd for $C_{72}H_{88}N_6O_8Na$, 1187.6561; found, 1187.6542.

5,17-Di-tolylurea-11,23-di-tolylcarbamoyloxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 10a: Tolyl-isocyanate (51 mg, 0.39 mmol) was added to a suspension of **9a** (40 mg, 0.039 mmol) and K_2CO_3 (54 mg, 0.39 mmol) in dry acetone (20 mL) under nitrogen. The reaction mixture was stirred at rt overnight and evaporated. CH_2Cl_2 (20 mL) was added, the suspension was filtered, and the filtrate was washed with saturated NH_4Cl and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography (hexane/THF = 3:1) to afford **10a** (30 mg, 60%): mp 198−200 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.68 (s, 2H), 8.36 (s, 2H), 8.27 (s, 2H), 7.28, 7.03 (2 d, ^3J = 7.8 Hz, 16H), 7.06, 6.33 (2 s, 8H), 4.34, 3.18 (2 d, ^2J = 12.9 Hz, 2 × 4H), 3.92, 3.76 (2 t, ^3J = 8.2 Hz, 2 × 4H), 2.22 (s, 12H), 1.92 (m, 8H), 1.40 (m, 16H), 0.96, 0.93 (2 t, ^3J = 7.4 Hz, 12H). MS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{80}H_{94}N_6O_{10}Na$, 1321.69; found, 1321.78. HRMS (ESI): $[M + H]^+$ calcd for $C_{80}H_{95}N_6O_{10}$, 1299.7110; found, 1299.7150.

5,11,17-Tri-tolylurea-23-tolylcarbamoyloxy-25,26,27,28-tetra-pentyloxy-calix[4]arene, 10b: Tolyl-isocyanate (210 mg, 1.5 mmol) was added to a suspension of **9b** (175 mg, 0.15 mmol) and Na_2CO_3 (160 mg, 1.5 mmol) in dry acetone (20 mL) under nitrogen. The crude product was purified as described above to afford **10b** (100 mg, 51%), except using hexane/ethyl acetate (3:1) as eluent: mp 204−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 70 °C): δ 9.39 (s, 1H), 8.11 (s, 2H), 8.05 (br s, 3H), 7.90 (s, 1H), 7.24, 7.03 (2 d, ^3J = 8.2 Hz, 16H), 6.95, 6.91, 6.71, 6.45 (4 s, 8H), 4.40, 4.38 (2 d, ^2J = 12.9 Hz, 2 × 2H), 3.94 (m, 4H), 3.87, 3.81 (2 t, ^3J = 7.0 Hz, 4H), 3.18, 3.12 (2 d, ^2J = 13.3 Hz, 2 × 2H), 2.24 (s, 9H), 2.22 (s, 3H), 1.94 (m, 8H), 1.41 (m, 16H), 0.96 (m, 12H). MS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{80}H_{95}N_7O_9Na$, 1320.71; found, 1320.87. HRMS (ESI): $[M + H]^+$ calcd for $C_{80}H_{96}N_7O_9$, 1298.7270; found, 1298.7278.

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Supporting Information Available: General experimental information. Signal assignment for ^{1}H NMR spectra of heterodimers. Selected ^{1}H NMR spectra of newly synthesized compounds and homo-and heterodimers. This material is available free of charge via the Internet at http://pubs.acs.org.

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