Guest exchange in dimeric capsules formed by tetra-urea calix[4]arenes†

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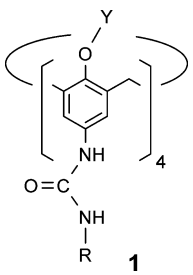
Ten tetra-urea calix[4]arene derivatives with different ether residues (methyl, pentyl, benzyl, all combinations of methyl and pentyl, 1,3-dibenzyl-2,4-dipentyl), including also the tetrahydroxy compound and the 1,3-dipentyl ether, were synthesised. Their urea groups were substituted with a lipophilic residue to ensure sufficient solubility in cyclohexane. Thus, kinetics for the exchange of the included guest (benzene) against the solvent (cyclohexane) could be followed by ^{1}H NMR spectroscopy. The apparent first order rate constants decrease with increasing size of the ether residues from methyl to benzyl by more than three orders of magnitude. This can be understood by a decreasing flexibility/mobility of the calixarene skeleton. In line with this explanation is the rather slow exchange for the tetrahydroxy compound, where the cone conformation is stabilised by a cyclic array of intramolecular OH · · · OH hydrogen bonds.

Introduction

The inclusion of guest molecules into the cavity of self-assembled capsules is a topic of steadily growing interest, since the first example of a hydrogen bonded capsule was reported nearly 15 years ago.[1] Calix[4]arenes substituted at their wide rim by four urea functions (**1**) form dimeric capsules held together by a seam of intermolecular hydrogen bonds between the urea groups.[2,3] The internal volume of about 190–200 Å^3 is large enough to host suitably sized (neutral or cationic) guests. Although larger capsules are known, including examples composed of more than two molecular building blocks,[4–6] dimers formed by **1** are attractive and challenging due to their special geometry. The two calixarene molecules are turned by 45° around their common axis and the interdigitating urea groups of the two calixarenes point in opposite directions including angles of 25–30° with the S_4 axis of the dimer and of 120–130° between adjacent urea groups. Functional groups R attached to the urea residues are thus brought into a unique mutual position.[7,8] This has been used, for instance, to synthesise various topologically interesting molecules, such as multiple catenanes or rotaxanes.[9]



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† Electronic supplementary information (ESI) available: Experimental details for the preparation of new compounds **2–7**; ^{1}H NMR spectra of tetra-ureas **8** in cyclohexane-d_{12}; rate constants for separate kinetic runs. See DOI: 10.1039/b719053k

The guest included in a capsule can be exchanged with another guest and the mechanism of this guest exchange $\mathbf{1}\cdot\mathbf{G}^1\cdot\mathbf{1} \rightarrow \mathbf{1}\cdot\mathbf{G}^2\cdot\mathbf{1}$ is another challenging problem. A simple opening of a single flap as described for glycoluril based dimeric capsules[10] is surely not possible here. However, it seems at least possible that the hydrogen bonded belt is partly retained. Yet, early studies by a series of 2D NMR experiments suggested that the guest (benzene) included in a dimeric capsule is exchanged with the solvent (benzene) *via* a dissociation–recombination process.[11] Much deeper insight into the association and dissociation process was obtained by FRET techniques, using tetra-urea derivatives marked by covalently attached donor and acceptor dyes.[12] The rate for the guest release is lower if benzene is replaced by cyclohexane as solvent, allowing kinetic measurements for the decyl ether of the tetratolyl urea **1** (Y = $C_{10}H_{21}$, R = *p*-CH_3–C_6H_4) and various guests by "conventional" NMR spectroscopy.[13] To elucidate the influence of the ether residues on the kinetic stability, we have now conducted a detailed kinetic study of the exchange of included benzene against cyclohexane used as solvent.

Results and discussion

To ensure sufficient solubility for all combinations of ether residues we have chosen tetra-urea compounds **8** substituted by branched tetradecyloxy phenyl groups. As ether groups, Y, we considered initially methyl (small enough to pass the annulus) and pentyl in all possible combinations. The series was later completed by selected compounds with benzyl ether groups and free phenolic hydroxy groups. Again, all exchange reactions could be monitored by recording the NMR spectra as a function of time.

Syntheses

The main synthetic steps are summarised in Scheme 1.

All tetra-urea derivatives were obtained by acylation of the respective tetraamino calix[4]arene **4** with the isocyanate obtained *in situ* from the alkoxy aniline **7** with triphosgene. **7** was prepared by O-alkylation of *N*-(*p*-hydroxyphenyl)acetamide **5**, followed by alkaline hydrolysis. Tetraamino calix[4]arenes **4** were usually

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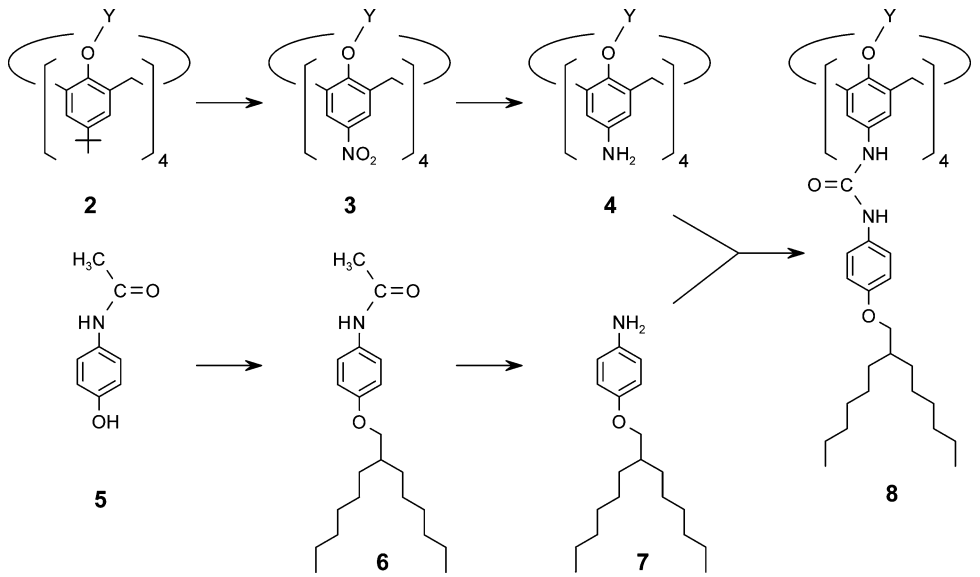

Scheme 1 Synthesis of tetra-urea derivatives, **8**, used for the kinetic studies. Ether residues Y are indicated by letters **M** (= methyl), **P** (= pentyl), **B** (= benzyl) and **H** (free OH group) as subscript, *e.g.* $\mathbf{8}_{\mathbf{MPPP}}$ = methyltripentyl ether, $\mathbf{8}_{\mathbf{BBBB}}$ = tetrabenzyl ether, $\mathbf{8}_{\mathbf{PHPH}}$ = 1,3-dipentyl ether.

synthesised by *ipso*-nitration (60–77%) of the corresponding tetraethers **2** of *tert*-butylcalix[4]arene and subsequent hydrogenation. Mixed pentyl/methyl ethers of *tert*-butylcalixarene were prepared *via* the mono-, di- and tripentyl ethers followed by exhaustive O-methylation.[14] This sequence is essential to ensure that all pentyl ether groups are in a *syn*-orientation.

Since all attempts to *ipso*-nitrate the tetrabenzyl ether of *tert*-butylcalix[4]arene ($\mathbf{2}_{\mathbf{BBBB}}$) failed, the respective tetraamine $\mathbf{4}_{\mathbf{BBBB}}$ was prepared as described.[2] The tetraamine $\mathbf{4}_{\mathbf{PBPB}}$ was synthesised analogously. The dibenzyldipentyl ether of *p-H*-calix[4]arene, obtained by 1,3-dibenzylation followed by exhaustive O-alkylation with pentylbromide, was iodinated, substituted by phthalimide and finally reacted with hydrazine.

The whole synthetic sequence was followed step-by-step by ^{1}H NMR spectroscopy, which in this case is the most appropriate analytical technique. Only partially methylated nitro- and amino-compounds could not be easily characterised due to their conformational flexibility. However, the dimeric capsule of the tetra-urea derivative showed a well resolved ^{1}H NMR spectrum. On the other hand, for tetra-urea derivatives with C_s-symmetry ($\mathbf{8}_{\mathbf{MMMP}}$, $\mathbf{8}_{\mathbf{MMPP}}$, $\mathbf{8}_{\mathbf{MPPP}}$) two regioisomeric capsules exist, which leads to rather complicated spectra.[15] Nevertheless, they could be analysed, showing that both capsules were formed with the same probability. (Kinetic data refer to this average).

Kinetics

The ^{1}H NMR spectra of the dimeric capsules containing benzene or cyclohexane-d_{12} are sufficiently different so as to enable a rapid identification as to the identity of the encapsulated guest. Thus, the exchange could be followed by NMR spectroscopy, using the more or less resolved signal(s) of the benzene-filled capsules (in most cases a urea NH signal). An example is shown in Fig. 1.

Intuitively it might be more reasonable to use the increasing signal of free benzene in cyclohexane. However, due to the long reaction times (often several weeks), the signals of a volatile compound (such as benzene) are much less reliably monitored, than those of non-volatile compounds. (For details see the experimental part).

As anticipated, clean first order reactions were observed for all compounds from 5% up to conversions of 70–80%. Plots are shown in Fig. 2, which show linearity during the course of the exchange reaction with the exception of the initial period of the reaction. Presently it is not clear if the slight but distinct deviations observed in the very beginning are due to an artefact. Fig. 2 contains plots for three examples from which the apparent first order rate constants are easily derived as the slopes of their linear parts. These values are collected in Table 1. Since they differ by a factor higher than 10^3 the respective half-life times are visualised in Fig. 3 using a logarithmic scale.

It can be easily shown, that the rate of the guest exchange increases upon addition of small amounts of water. Although the measurements were done under dry conditions (see experimental part), the available technique did not allow us to exclude traces of water completely. This may be the reason why a reproducibility of ±10% was observed for the rate constants within a period of

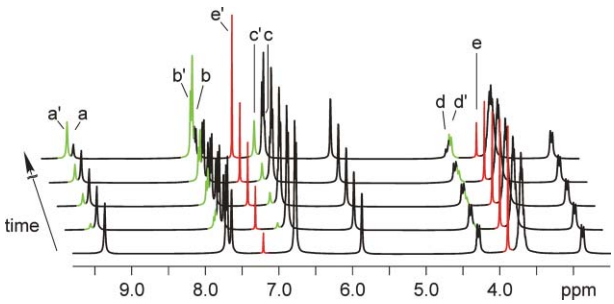

Fig. 1 Section of the NMR spectrum of $\mathbf{8}_{\mathbf{PPPP}}$ as a function of time, illustrating the exchange of encapsulated benzene by cyclohexane-d_{12}; red: signals for free (e′) and included (e) benzene, green: signals for the new complex (a′–d′), the respective signals of the initial complex are marked as a–d.

Table 1 Apparent first order rate constants for the exchange of benzene by cyclohexane-d_{12}

Tetra-urea	k/h^{-1}
$\mathbf{8}_{\mathbf{MMMM}}$	0.47 ± 0.03
$\mathbf{8}_{\mathbf{MMMP}}$	0.37 ± 0.02
$\mathbf{8}_{\mathbf{MPMP}}$	0.35 ± 0.02
$\mathbf{8}_{\mathbf{MMPP}}$	0.090 ± 0.008
$\mathbf{8}_{\mathbf{MPPP}}$	0.052 ± 0.003
$\mathbf{8}_{\mathbf{PPPP}}$	0.027 ± 0.003
$\mathbf{8}_{\mathbf{PBPB}}$	0.0082 ± 0.0001
$\mathbf{8}_{\mathbf{BBBB}}$	0.00026 ± 0.00007
$\mathbf{8}_{\mathbf{PHPH}}$	0.031 ± 0.002
$\mathbf{8}_{\mathbf{HHHH}}$	0.0039 ± 0.0003

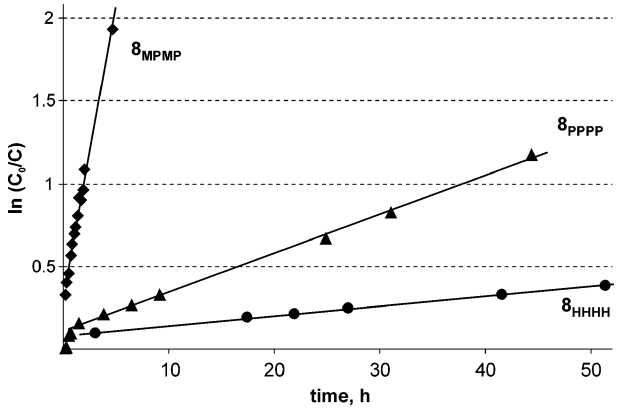

Fig. 2 Examples of first order plots for the exchange of encapsulated benzene by cyclohexane-d_{12}.

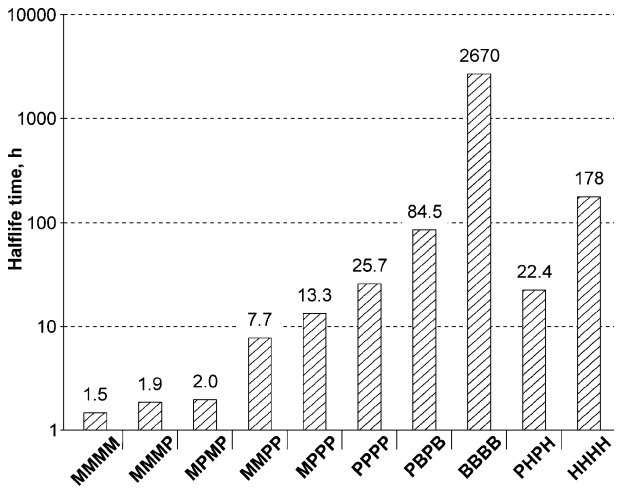

Fig. 3 Illustration of the half-life times for the exchange of encapsulated benzene by cyclohexane-d_{12} for the series of compounds **8**.

1–2 months (using also the same samples of cyclohexane-d_{12} and benzene) while the reproducibility is lower over a longer period. However, for the present discussion it is only important that the apparent rate constants can be compared within the set of data presented in Table 1.

Among the tetraether derivatives with identical ether residues Y ($\mathbf{8}_{\mathbf{MMMM}}$, $\mathbf{8}_{\mathbf{PPPP}}$ and $\mathbf{8}_{\mathbf{BBBB}}$) the rate of the guest release decreases drastically with increasing size of Y. The ratio of the rate constants for capsules formed by $\mathbf{8}_{\mathbf{MMMM}}$, $\mathbf{8}_{\mathbf{PPPP}}$ and $\mathbf{8}_{\mathbf{BBBB}}$ is 1808 : 104 : 1. Mixed tetraethers show intermediate rates.

Tentatively this may be explained by an increasing rigidity (decreasing flexibility) of the calixarene skeleton with increasing size of the ether groups. A tetraether with ether residues equal to or larger than propyl is kept in one of the basic conformations, *e.g.* the cone conformation, which however is "pinched" due to the repulsion of the ether residues. Methoxy groups still can pass the annulus of the calix[4]arene and for the same reason a tetramethyl ether normally prefers the partial cone conformation.[16] Within the dimeric capsule the calixarenes are kept in a regular (C_4-symmetrical) cone conformation. The opening of the capsule by bending one (or several) urea residues outwards, means that the corresponding ether residues must be bent inwards. And this is obviously more easily facilitated for small ether residues where the repulsion is lower.

This explanation is further corroborated by the whole series of compounds with methyl and pentyl ether groups $\mathbf{8}_{\mathbf{MMMM}}$ to $\mathbf{8}_{\mathbf{PPPP}}$, which show decreasing rate constants with increasing number of pentyl ether groups. Interestingly, the alternating arrangement in $\mathbf{8}_{\mathbf{MPMP}}$ leads to 3.9 times higher rates for the guest release than the adjacent position of identical ether groups Y in $\mathbf{8}_{\mathbf{MMPP}}$. In this alternating arrangement the inwards moving methyl group faces the opposite methyl group. An opposite pentyl ether group as in $\mathbf{8}_{\mathbf{MMPP}}$ might cause a stronger repulsion, which explains the lower exchange rate.

A slow exchange reaction is also observed for $\mathbf{8}_{\mathbf{HHHH}}$ and may be explained in a similar way, although in this case the main reason for the stabilisation of the cone conformation is the cyclic belt of intramolecular OH $\cdots$ OH hydrogen bonds between the phenolic hydroxyl groups. A lower stability for the capsule of $\mathbf{8}_{\mathbf{PHPH}}$ is in line with this but a further interpretation in comparison with the tetraether derivatives is not possible on the basis of the present results.

Conclusions

We have shown that the rate of guest exchange strongly depends on the size of the ether groups attached to the narrow rim of tetra-urea calix[4]arenes. This is in keeping with a mechanism where the opening of the capsule is connected with an outwards movement of the urea residues, necessarily accompanied by an inward motion of the alkoxy groups. This movement is sterically hindered by the repulsion of the ether residues, which increases with increasing size. Although other mechanisms for the guest exchange might be also possible, *e.g.* an opening by rotation around the aryl–urea–aryl axis, the proposed explanation is in agreement with the lower rate of guest exchange found for capsules where the calix[4]arenes are rigidified by two short crown ether groups.[17]

Experimental

Cyclohexane-d_{12} (Deutero GmbH, 99.5 atom% D) and benzene (Riedel-de Haën, p.a.) were treated as described below. All other solvents and commercially available chemicals were purchased from Acros and Aldrich, and used without further purification. NMR spectra were recorded on a Bruker Avance DRX400 spectrometer at 25 °C if not stated otherwise. FD- and ESI-mass spectra were measured on Finnigan MAT 8230 and Micromass QToF Ultima 3 instruments. Melting points were determined with a MEL TEMP 2 capillary melting point apparatus and

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are uncorrected. 1-Bromo-2-hexyloctane,[18] tetraamines $\mathbf{4}_{MMMM}$,[14] $\mathbf{4}_{PPPP}$,[19] $\mathbf{4}_{MPMP}$[11] and $\mathbf{4}_{BBBB}$,[2] and *p-H*-calix[4]arene 1,3-dibenzyl ether[20] were described previously. Synthesis and characterisation of the new compounds **2–7** are reported in the ESI.†

Synthesis

General procedure for the preparation of tetra-urea calixarenes 8 from tetraamines 4. Triphosgene (0.36 g, 1.2 mmol) was added to a stirred solution of 4-[(2-hexyloctyl)oxy]aniline **7** (0.37 g, 1.2 mmol) in toluene (70 ml). The solution was refluxed under nitrogen for 1 h, cooled and the solvent evaporated *in vacuo* at 70–80 °C. The resultant oil was dissolved in toluene (5 ml) and the solution of the respective calixarene **4** (0.2 mmol) in toluene (30 ml) was added. The reaction mixture was stirred overnight at room temperature and then concentrated *in vacuo.* The residue was finally purified by column chromatography (gradient from dichloromethane to dichloromethane–ethanol, 30 : 1).

Calix[4]arene $\mathbf{8}_{MMMM}$. Yield 62%, mp 192–194 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.68 (s, 8H, NH), 8.07 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 8.02 (d, *J* 2.2 Hz, 8H, ArH), 7.47 (s, 8H, NH), 6.87 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 6.30 (d, *J* 2.2 Hz, 8H, ArH), 4.27 (d, *J* 11.8 Hz, 8H, $ArCH_2Ar$), 3.61 (s, 24H, OCH_3), 3.57 (m, 16H, OCH_2CH), 3.17 (d, *J* 11.8 Hz, 8H, $ArCH_2Ar$), 1.69 (m, 8H, CH), 1.51–1.15 (m, 160H, CH_2), 0.91 (t, *J* 7.0 Hz, 24H. CH_3) and 0.90 (t, *J* 7.0 Hz, 24H, CH_3). *Monomer:* δ_H(400 MHz; THF-d_8) 7.57 (br s, 4H, NH), 7.40 (br s, 4H, NH), 7.26 (d, *J* 8.6 Hz, 8H, ArH_{Ph}), 6.87 (s, 8H, ArH), 6.73 (d, *J* 8.6 Hz, 8H, ArH_{Ph}), 4.32 (d, *J* 12.7 Hz, 4H, $ArCH_2Ar$), 3.77 (br s, 20H, OCH_3 + OCH_2), 3.09 (d, *J* 12.7 Hz, 4H, $ArCH_2Ar$), 1.57–1.21 (m, 84H, CH_2), 0.89 (m, 24H. CH_3) and 0.90 (t, *J* 7.0 Hz, 24H, CH_3). δ_C(100 MHz; THF-d_8) 154.01 (C=O), 152.53, 151.97, 134.22, 133.80, 132.80 (C_{Ar}), 118.94, 117.74, 113.67 (CH_{Ar}), 70.11 (OCH_2CH), 60.35 (OCH_3), 37.63 (CH), 31.30, 30.84 (CH_2), 30.12 br s ($ArCH_2Ar$), 29.16, 26.26, 22.03 (CH_2) and 12.92 (CH_3). ESI-MS *m/z* 1889.26 (100%), 1888.26 (64), 1890.26 (46) $[M + Na]^+$ for $C_{116}H_{168}NaN_8O_{12}$ (1888.27).

Calix[4]arene $\mathbf{8}_{MMMP}$. Yield 62%, mp 190–192 °C.[21] δ_H(400 MHz; THF-d_8; 0 °C) 8.00–7.47 (m, 6H, NH), 7.46–7.07 (m, 14H, NH + ArH_{Ph} + ArH), 6.84–6.60 (m, 8H, ArH_{Ph}), 6.47 (br s, 4H, ArH), 4.31 (br d, 3H, $ArCH_2Ar$), 4.03 (br s, 1H, $ArCH_2Ar$), 3.95–3.60 (m, 19H, OCH_2 + OCH_3 + OCH_2CH), 3.09 (m, 4H, $ArCH_2Ar$), 1.90 (m, 2H, CH_2), 1.61 (m, 2H, CH), 1.53–1.16 (m, 86H, CH + CH_2), 0.96 (t, *J* 7.1 Hz, 3H, CH_3) and 0.88 (m, 24H, CH_3). δ_C(100 MHz; THF-d_8) 155.56, 155.52 (C=O), 154.49, 153.68, 153.59, 152.48, 137.38, 137.32, 135.81, 134.78, 134.60, 134.43, 134.35, 134.20 (C_{Ar}), 120.55, 120.47, 119.42 br s, 115.23, 115.15 (CH_{Ar}), 75.93 (OCH_2), 71.66 (OCH_2CH), 62.55, 61.30 (OCH_3), 39.16 (CH), 32.83, 32.39, 32.36, 31.80, 31.64, 31.18, 30.69 (CH_2), 29.55 ($ArCH_2Ar$), 27.79, 23.55 (CH_2) and 14.45 (CH_3). ESI-MS *m/z* 1945.37 (100%), 1944.37 (63), 1946.37 (58) $[M + Na]^+$ for $C_{120}H_{176}NaN_8O_{12}$ (1944.33).

Calix[4]arene $\mathbf{8}_{MPMP}$. Yield 43%, mp 193–195 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.90 (s, 2H, NH), 9.88 (s, 2H, NH), 9.81 (s, 2H, NH), 9.79 (s, 2H, NH), 8.46 (d, *J* 2.2 Hz, 2H, ArH), 8.27 (br s, 2H, ArH), 8.25 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.18 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.17 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 8.07 (br s, 2H, ArH), 8.05 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 7.78 (d, *J* 2.2 Hz, 2H, ArH), 7.70 (s, 2H, NH), 7.67 (s, 2H, NH), 7.35 (s, 2H, NH), 7.34 (s, 2H, NH), 7.03 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 6.95 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.92 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.82 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 6.54 (d, *J* 2.2 Hz, 2H, ArH), 6.47 (d, *J* 2.2 Hz, 2H, ArH), 6.40 (d, *J* 2.2 Hz, 2H, ArH), 6.38 (d, *J* 2.2 Hz, 2H, ArH), 4.53 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 4.47 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 4.44 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 4.41 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 3.92 (s, 12H, OCH_3), 3.71–3.47 (m, 24H, OCH_2), 3.43 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 3.31 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 3.29 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 3.20 (d, *J* 12.1 Hz, 2H, $ArCH_2Ar$), 1.97 (m, 8H, CH_2), 1.74 (m, 8H, CH), 1.57–1.16 (m, 176H, CH_2) and 1.09–0.90 (m, 60H, CH_3). *Monomer:* δ_H(400 MHz; DMSO-d_6–$CDCl_3$) 8.31 (s, 2H, NH), 8.22 (s, 2H, NH), 7.88 (s, 2H, NH), 7.78 (s, 2H, NH), 7.31 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 7.21 (s, 4H, ArH), 7.09 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.77 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.68 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.48 (s, 4H, ArH), 4.26 (d, *J* 11.4 Hz, 4H, $ArCH_2Ar$), 3.88 (s, 6H, OCH_3), 3.75 (d, *J* 5.4 Hz, 4H, OCH_2CH), 3.70 (d, *J* 5.4 Hz, 4H, OCH_2CH), 3.63 (br s, 4H, OCH_2), 3.09 (d, *J* 11.4 Hz, 4H, $ArCH_2Ar$), 1.87 (m, 4H, CH_2), 1.68 (m, 4H, CH), 1.55 (m, 4H, CH_2), 1.47–1.11 (m, 84H, CH_2), 0.92 (t, *J* 7.3 Hz, 6H, CH_3) and 0.88–0.76 (m, 24H, CH_3). δ_C(100 MHz; DMSO-d_6–$CDCl_3$) 154.03, 153.87 (C=O), 152.96, 152.78, 152.44, 150.72, 136.08, 134.25, 132.86, 132.67, 132.56, 132.45 (C_{Ar}), 119.70, 119.49, 118.49, 117.39, 114.31, 114.19 (CH_{Ar}), 75.07 (OCH_2), 70.53 (OCH_2CH), 60.21 (OCH_3), 37.30 (CH), 31.20, 31.18, 30.76, 30.73 (CH_2), 29.70 ($ArCH_2Ar$), 29.05, 29.02, 27.91, 26.15, 26.13, 22.04, 22.01 (CH_2), 13.76, 13.74 and 13.72 (CH_3). ESI-MS *m/z* 2001.45 (100%), 2000.46 (57), 2002.46 (57) $[M + Na]^+$ for $C_{124}H_{184}NaN_8O_{12}$ (2000.39).

Calix[4]arene $\mathbf{8}_{MMPP}$. Yield 47%, mp 198–200 °C.[21] δ_H(400 MHz; THF-d_8) 7.61 (br s, 4H, NH), 7.51 (br s, 4H, NH), 7.25 (br d, 8H, ArH_{Ph}), 6.84 (br s, 8H, ArH), 6.72 (br d, 8H, ArH_{Ph}), 4.34 (br s, 4H, $ArCH_2Ar$), 3.75 (br d, 8H, OCH_2CH), 3.73 (br s, 4H, OCH_2), 3.57 (s, 6H, OCH_3), 3.04 (br d, 4H, $ArCH_2Ar$), 1.93 (br s, 4H, CH_2), 1.73 (br s, 4H, CH), 1.53–1.20 (m, 88H, CH_2), 0.95 (br s, 6H, CH_3) and 0.88 (br s, 24H, CH_3). δ_C(100 MHz; THF-d_8) 155.54 (C=O), 153.85 br s, 153.76, 152.83, 135.90 br s, 135.60 br s, 135.24 br s, 135.01 br s, 134.30 (C_{Ar}), 120.55, 119.63 br s, 115.20 (CH_{Ar}), 76.01 (OCH_2), 71.66 (OCH_2CH), 61.66 (OCH_3), 39.16 (CH), 32.82, 32.37, 30.68 (CH_2), 29.44 ($ArCH_2Ar$), 27.79, 23.68, 23.55 (CH_2), 14.60 and 14.45 (CH_3). ESI-MS *m/z* 2001.44 (100%), 2000.44 (60), 2002.45 (60) $[M + Na]^+$ for $C_{124}H_{184}NaN_8O_{12}$ (2000.39).

Calix[4]arene $\mathbf{8}_{MPPP}$. Yield 54%, mp 200–202 °C.[21] δ_H(400 MHz; THF-d_8; 0 °C) 7.95 (s, 1H, NH), 7.94 (s, 1H, NH), 7.80 (s, 2H, NH), 7.50 (s, 2H, NH), 7.44–7.19 (m, 10H, NH + ArH_{Ph} + ArH), 7.14 (br d, *J* 7.8 Hz, 4H, ArH_{Ph}), 6.77 (br d, *J* 7.8 Hz, 4H, ArH_{Ph}), 6.65 (br d, *J* 8.3 Hz, 4H, ArH_{Ph}), 6.40 (m, 4H, ArH), 4.42 (d, *J* 12.2 Hz, 2H, $ArCH_2Ar$), 4.30 (d, *J* 12.2 Hz, 2H, $ArCH_2Ar$), 4.06 (m, 2H, OCH_2), 3.89–3.60 (m, 15H, OCH_2 + OCH_3 + OCH_2CH), 3.06 (d, *J* 12.2 Hz, 4H, $ArCH_2Ar$), 2.07 (m, 2H, CH_2), 1.89 (m, 4H, CH), 1.63–1.16 (m, 96H, CH_2), 0.96 (t, *J* 7.1 Hz, 9H, CH_3) and 0.87 (m, 24H, CH_3). δ_C(100 MHz; THF-d_8) 155.54, 155.52 (C=O), 154.54, 153.91, 153.66, 153.58, 152.23, 137.51, 137.40, 135.71, 135.38, 134.58, 134.47, 134.44, 134.16, 134.09 (C_{Ar}), 120.59, 120.47, 120.44, 119.66, 119.57, 115.23, 115.14 (CH_{Ar}), 75.98 (OCH_2), 71.66 (OCH_2CH), 61.27 (OCH_3), 39.18, 39.15 (CH), 32.83, 32.40, 32.35 (CH_2), 31.97 (br s, $ArCH_2Ar$), 31.16 (CH_2), 30.69, 29.62 (CH_2), 29.27 (br s,

$ArCH_2Ar$), 27.80, 23.80, 23.62, 23.56 (CH_2), 14.52 and 14.46 (CH_3). ESI-MS *m/z* 2057.44 (100%), 2058.45 (61), 2056.44 (57) $[M + Na]^+$ for $C_{128}H_{192}NaN_8O_{12}$ (2056.46).

Calix[4]arene 8_{PPPP}. Yield 71%, mp 202–204 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.92 (s, 8H, NH), 8.15 (d, *J* 2.2 Hz, 8H, ArH), 8.13 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 7.41 (s, 8H, NH), 6.85 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 6.49 (d, *J* 2.2 Hz, 8H, ArH), 4.61 (d, *J* 11.8 Hz, 8H, $ArCH_2Ar$), 3.76 (m, 16H, OCH_2), 3.53 (d, *J* 5.7 Hz, 16H, OCH_2CH), 3.33 (d, *J* 11.8 Hz, 8H, $ArCH_2Ar$), 2.12 (m, 16H, CH_2), 1.68 (m, 8H, CH), 1.52–1.16 (m, 192H, CH_2), 1.02 (t, *J* 7.3 Hz, 24H, CH_3), 0.91 (t, *J* 6.8 Hz, 24H, CH_3) and 0.90 (t, *J* 6.8 Hz, 24H, CH_3). *Monomer:* δ_H(400 MHz; THF-d_8) 7.51 (s, 4H, NH), 7.39 (s, 4H, NH), 7.25 (d, *J* 8.6 Hz, 8H, ArH_{Ph}), 6.81 (s, 8H, ArH), 6.72 (d, *J* 8.6 Hz, 8H, ArH_{Ph}), 4.44 (d, *J* 13.0 Hz, 4H, $ArCH_2Ar$), 3.87 (t, *J* 6.7 Hz, 8H, OCH_2), 3.78 (d, *J* 5.1 Hz, 8H, OCH_2CH), 3.07 (d, *J* 13.0 Hz, 4H, $ArCH_2Ar$), 1.95 (m, 8H, CH_2), 1.56–1.16 (m, 100H, CH + CH_2), 0.98 (t, *J* 6.7 Hz, 12H, CH_3) and 0.89 (m, 24H, CH_3). δ_C(100 MHz; THF-d_8) 153.96 (C=O), 151.96, 151.07, 134.34, 133.54, 132.86 (C_{Ar}), 118.86, 117.81, 113.63 (CH_{Ar}), 74.31 (OCH_2), 70.11 (OCH_2CH), 37.64 (CH), 31.29, 30.84 (CH_2), 30.62 ($ArCH_2Ar$), 29.36, 29.16, 27.98, 26.26, 22.25, 22.02 (CH_2), 13.09 and 12.92 (CH_3). ESI-MS *m/z* 2113.52 (100%), 2114.52 (69), 2112.52 (53) $[M + Na]^+$ for $C_{132}H_{200}NaN_8O_{12}$ (2112.52).

Calix[4]arene 8_{PBPB}. Yield 89%, mp 198–200 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.95 (s, 4H, NH), 9.90 (s, 2H, NH), 9.89 (s, 2H, NH), 8.26 (d, *J* 2.2 Hz, 2H, ArH), 8.21 (d, *J* 2.2 Hz, 2H, ArH), 8.18 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.17 (br d, 4H, ArH), 8.15 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.14 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.11 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 7.57 (s, 2H, NH), 7.54–7.45 (m, 12H, NH + ArH_{Bz}), 7.40 (s, 2H, NH), 7.39–7.33 (m, 12H, ArH_{Bz}), 6.92 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.89 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.88 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.87 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.53 (d, *J* 2.2 Hz, 4H, ArH), 6.47 (d, *J* 2.2 Hz, 2H, ArH), 6.45 (d, *J* 2.2 Hz, 2H, ArH), 4.70 (d, *J* 12.0 Hz, 2H, OCH_2Ph), 4.88 (d, *J* 12.0 Hz, 2H, OCH_2Ph), 4.77 (d, *J* 12.0 Hz, 2H, OCH_2Ph), 4.76 (d, *J* 12.0 Hz, 2H, OCH_2Ph), 4.54 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 4.53 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 4.40 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 4.38 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 3.72–3.50 (m, 24H, OCH_2), 3.27 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 3.23 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 3.11 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 3.06 (d, *J* 12.0 Hz, 2H, $ArCH_2Ar$), 1.76 (m, 16H, CH + CH_2), 1.55–1.15 (m, 176H, CH_2), 1.10 (m, 12H, CH_3) and 1.00–0.89 (m, 48H, CH_3). *Monomer:* δ_H(400 MHz; THF-d_8) 7.66 (s, 2H, NH), 7.54 (s, 2H, NH), 7.50 (m, 4H, ArH_{Bz}), 7.41 (s, 2H, NH), 7.36–7.27 (m, 10H, ArH_{Ph} + ArH_{Bz}), 7.25 (s, 2H, NH), 7.17 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 7.07 (s, 4H, ArH), 6.76 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.68 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.56 (s, 4H, ArH), 4.80 (s, 4H, OCH_2Ph), 4.41 (d, *J* 13.2 Hz, 4H, $ArCH_2Ar$), 3.84 (m, 4H, OCH_2), 3.79 (d, *J* 5.9 Hz, 4H, OCH_2CH), 3.75 (d, *J* 5.9 Hz, 4H, OCH_2CH), 3.02 (d, *J* 13.2 Hz, 4H, $ArCH_2Ar$), 1.53–1.00 (m, 96H, CH + CH_2) and 0.92–0.82 (m, 30H, CH_3). δ_C(100 MHz; THF-d_8) 155.55, 155.47 (C=O), 153.66, 153.61, 153.13, 151.33, 139.20, 136.87, 135.16, 135.12, 134.40, 134.29 (C_{Ar}), 130.03, 128.86, 128.47, 120.47, 120.43, 119.51, 119.43, 115.22, 115.14 (CH_{Ar}), 77.85, 75.81 (OCH_2), 71.65 (OCH_2CH), 39.16 (CH), 32.82, 32.38, 32.36, 32.27, 30.67, 30.30 (CH_2), 29.06 ($ArCH_2Ar$), 27.79, 23.55, 23.52 (CH_2), 14.73 and 14.45 (CH_3). ESI-MS *m/z* 2153.56 (100%), 2154.56 (46), 2152.56 (27) $[M + Na]^+$ for $C_{136}H_{192}NaN_8O_{12}$ (2152.46).

Calix[4]arene 8_{BBBB}. Yield 75%, mp 182–184 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.77 (s, 8H, NH), 8.11 (d, *J* 2.2 Hz, 8H, ArH), 8.02 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 7.49 (s, 8H, NH), 7.50 (br t, *J* 7.2 Hz, 8H, ArH_{Bz}), 7.29 (br t, *J* 7.2 Hz, 16H, ArH_{Bz}), 7.21 (br d, *J* 7.2 Hz, 16H, ArH_{Bz}), 6.82 (d, *J* 9.2 Hz, 16H, ArH_{Ph}), 6.33 (d, *J* 2.2 Hz, 8H, ArH), 4.85 (d, *J* 12.1 Hz, 8H, OCH_2Ph), 4.58 (d, *J* 12.1 Hz, 8H, OCH_2Ph), 3.97 (d, *J* 12.1 Hz, 8H, $ArCH_2Ar$), 3.60 (m, 16H, OCH_2), 2.75 (d, *J* 12.1 Hz, 8H, $ArCH_2Ar$), 1.72 (m, 8H, CH), 1.45 (m, 16H, CH_2), 1.39–1.14 (m, 144H, CH_2) and 0.88 (t, *J* 6.5 Hz, 48H, CH_3). *Monomer:* δ_H(400 MHz; THF-d_8) 7.47 (s, 4H, NH), 7.38–7.33 (m, 12H, NH + ArH_{Bz}), 7.27–7.19 (m, 20H, ArH_{Ph} + ArH_{Bz}), 6.76 (s, 8H, ArH), 6.73 (d, *J* 9.2 Hz, 8H, ArH_{Ph}), 4.94 (s, 8H, OCH_2Ph), 4.21 (d, *J* 13.3 Hz, 4H, $ArCH_2Ar$), 3.78 (d, *J* 5.5 Hz, 8H, OCH_2CH), 2.84 (d, *J* 13.3 Hz, 4H, $ArCH_2Ar$), 1.53–1.24 (m, 84H, CH + CH_2) and 0.89 (m, 24H, CH_3). δ_C(100 MHz; THF-d_8) 153.96 (C=O), 151.89, 149.87, 137.57, 134.67, 133.79, 132.85 (C_{Ar}), 129.14, 127.17, 126.87, 118.86, 117.68, 113.63 (CH_{Ar}), 75.73 (OCH_2), 70.10 (OCH_2CH), 37.63 (CH), 31.30 (CH_2), 31.06 ($ArCH_2Ar$), 30.84, 29.15, 26.26, 22.02 (CH_2) and 12.92 (CH_3). ESI-MS *m/z* 1108.23 (100%), 1108.73 (63), 1107.72 (34) $[M + 2Na]^{2+}$ for $C_{140}H_{184}Na_2N_8O_{12}$ (2215.38) and 2193.45 (28), 2194.42 (20) $[M + Na]^+$ for $C_{140}H_{184}NaN_8O_{12}$ (2192.39).

Calix[4]arene 8_{PHPH}. Pd/C (10%, 0.048 g, 0.045 mmol) was added to a solution of $\mathbf{8_{PBPB}}$ (0.096 g, 0.045 mmol) in THF (30 ml) and the mixture was stirred at room temperature under H_2 for 14 h. The reaction mixture was filtered and the filtrate concentrated. The product was re-precipitated from dichloromethane–ethanol. Yield 51% (0.045 g), mp 220–222 °C. *Dimer:* δ_H(400 MHz; C_6D_6) 9.67 (s, 2H, NH), 9.66 (s, 2H, NH), 9.40 (s, 2H, NH), 9.38 (s, 2H, NH), 8.50 (s, 2H, OH), 8.49 (s, 2H, OH), 8.30 (d, *J* 2.2 Hz, 2H, ArH), 8.19 (d, *J* 2.2 Hz, 2H, ArH), 8.13 (br s, 2H, ArH), 8.11 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.07 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 8.03 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 7.99 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 7.98 (br s, 2H, ArH), 7.84 (s, 2H, NH), 7.81 (s, 2H, NH), 7.76 (s, 2H, NH), 7.71 (s, 2H, NH), 6.95 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.89 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.87 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.82 (d, *J* 8.9 Hz, 4H, ArH_{Ph}), 6.39 (d, *J* 2.2 Hz, 2H, ArH), 6.35 (d, *J* 2.2 Hz, 2H, ArH), 6.34 (d, *J* 2.2 Hz, 2H, ArH), 6.33 (d, *J* 2.2 Hz, 2H, ArH), 4.42 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 4.39 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 4.32 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 4.28 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 3.68–3.42 (m, 24H, OCH_2), 3.35 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 3.32 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 3.25 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 3.22 (d, *J* 12.6 Hz, 2H, $ArCH_2Ar$), 2.03 (m, 8H, CH_2), 1.71 (m, 4H, CH), 1.63 (m, 4H, CH), 1.55–1.09 (m, 176H, CH_2), 1.04 (t, *J* 7.0 Hz, 6H, CH_3), 1.03 (t, *J* 6.8 Hz, 6H, CH_3) and 0.90 (m, 48H, CH_3). *Monomer:* δ_H(400 MHz; DMSO-d_6–$CDCl_3$) 8.13 (s, 2H, NH), 8.08 (s, 2H, OH), 8.07 (s, 2H, NH), 8.06 (s, 2H, NH), 8.03 (s, 2H, NH), 7.25 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 7.16 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 7.12 (s, 4H, ArH), 7.02 (s, 4H, ArH), 6.72 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 6.69 (d, *J* 9.2 Hz, 4H, ArH_{Ph}), 4.19 (d, *J* 12.7 Hz, 4H, $ArCH_2Ar$), 3.91 (br t, *J* 6.5 Hz, 4H, OCH_2), 3.71 (d, *J* 5.7 Hz, 4H, OCH_2CH), 3.69 (d, *J* 5.7 Hz, 4H, OCH_2CH), 3.28 (d, *J* 12.7 Hz, 4H, $ArCH_2Ar$), 2.00 (m, 4H, CH_2), 1.67 (m, 8H, CH + CH_2), 1.47 (m, 4H, CH_2), 1.40–1.12 (m, 80H, CH_2), 0.97 (t, *J* 7.3 Hz, 6H, CH_3), 0.82 (t, *J* 6.8 Hz, 12H, CH_3) and 0.82 (t, *J* 6.5 Hz, 12H, CH_3). δ_C(100 MHz; DMSO-d_6–$CDCl_3$) 154.03, 153.97 (C=O), 152.85,

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152.53, 147.85, 147.46, 136.16, 133.49, 132.54, 130.98, 127.65, 126.32 (C_{Ar}), 119.74, 119.68, 119.38, 118.47, 114.23, 114.17 (CH_{Ar}), 76.34 (OCH_2), 70.54 (OCH_2CH), 37.29, 37.27 (CH), 31.18, 30.73, 30.71, 29.02, 29.01, 28.06, 27.49, 26.14, 26.12, 22.02, 21.92 (CH_2), 13.76 and 13.72 (CH_3). ESI-MS *m/z* 1973.44 (100%), 1972.44 (50), 1974.44 (41) $[M + Na]^+$ for $C_{122}H_{180}NaN_8O_{12}$ (1972.36).

Calix[4]arene $\mathbf{8}_{HHHH}$ was obtained from calixarene $\mathbf{8}_{BBBB}$ (0.271 g, 0.125 mmol) and Pd/C (10%, 0.133 g, 0.125 mmol) in THF (40 ml) as described for $\mathbf{8}_{PHPH}$. Yield 95% (0.22 g), mp 244–246 °C (decomp.). *Dimer:* δ_H(400 MHz; C_6D_6) 10.13 (s, 8H, OH), 9.19 (s, 8H, NH), 8.01 (d, *J* 2.2 Hz, 8H, ArH), 7.93 (d, *J* 8.9 Hz, 16H, ArH_{Ph}), 7.87 (s, 8H, NH), 6.90 (d, *J* 8.9 Hz, 16H, ArH_{Ph}), 6.11 (d, *J* 2.2 Hz, 8H, ArH), 4.00 (d, *J* 13.4 Hz, 8H, $ArCH_2Ar$), 3.62 (m, 16H, OCH_2), 3.18 (d, *J* 13.4 Hz, 8H, $ArCH_2Ar$), 1.71 (m, 8H, CH), 1.43 (m, 16H, CH_2), 1.37–1.16 (m, 144H, CH_2) and 0.90 (m, 48H, CH_3). *Monomer:* δ_H(400 MHz; DMSO-d_6–$CDCl_3$) 9.66 (s, 4H, OH), 8.08 (s, 4H, NH), 7.96 (s, 4H, NH), 7.16 (d, *J* 8.9, 8H, ArH_{Ph}), 7.10 (s, 8H, ArH), 6.67 (d, *J* 8.9 Hz, 8H, ArH_{Ph}), 4.14 (br s, 4H, $ArCH_2Ar$), 3.67 (br d, *J* 5.1 Hz, 8H, OCH_2CH), 3.37 (br s, 4H, $ArCH_2Ar$), 1.63 (m, 4H, CH), 1.41–1.05 (m, 80H, CH_2) and 0.79 (m, 24H, CH_3). δ_C(100 MHz; DMSO-d_6–$CDCl_3$) 154.15 (C=O), 152.74, 143.33, 133.38, 132.16, 128.18 (C_{Ar}), 119.83, 118.38, 114.17 (CH_{Ar}), 70.60 (OCH_2CH), 37.30 (CH), 31.18, 30.72, 29.02, 26.14, 22.01 (CH_2) and 11.66 (CH_3). ESI-MS *m/z* 1833.23 (100%), 1832.23 (56), 1834.23 (28) $[M + Na]^+$ for $C_{112}H_{160}NaN_8O_{12}$ (1832.21).

Kinetic studies

All the tetra-ureas **8** were dissolved in dichloromethane–ethanol (100 : 1, v/v) and then passed through a 1 cm layer of silica. The evaporated samples were solidified upon addition of methanol (p.a.) and then pre-dried with a rotary evaporator first at room temperature and then at 60 °C. The obtained powders of monomeric **8** were kept *in vacuo* over P_2O_5 and solid NaOH for 1 week. Cyclohexane-d_{12} was dried over molecular sieves 3 Å for at least 4 weeks. Benzene was passed through a 1 cm layer of basic Al_2O_3 and then kept over molecular sieves 3 Å for 2 days. NMR tubes, sample pipettes and flasks for kinetic runs were kept *in vacuo* over P_2O_5 and NaOH for 2 days.

A sample of the monomeric **8** was weighted in a flask to give finally a 2 mM solution of the respective dimer in the NMR tube (4.89–5.86 mg of **8**). Benzene (5 ml) was added and the solution was kept at room temperature for 1 h. The solvent was evaporated without heating, and the glassy mass of $\mathbf{8}\cdot C_6H_6\cdot\mathbf{8}$ was dried *in vacuo* over P_2O_5 and NaOH for 2–3 days. Cyclohexane-d_{12} (0.675 ml) was added to the flask and, after 1 min, the clear solution was transferred in one portion to the NMR tube, containing one piece of molecular sieve 3 Å. The tube was stoppered with the cap and covered with PARAFILM. The first NMR measurement was performed exactly 10 min after the addition of cyclohexane-d_{12} to $\mathbf{8}\cdot C_6H_6\cdot\mathbf{8}$. Normal ^{1}H NMR spectra were acquired at 25 °C with 32 scans accumulation. The total duration of one kinetic measurement was 3 min 58 s, so for the rate calculations the middle of this time interval was used. Between kinetic measurements samples were thermostated at 25 °C. The guest exchange was monitored by the integration of the same signals from $\mathbf{8}\cdot C_6H_6\cdot\mathbf{8}$ and $\mathbf{8}\cdot C_6D_{14}\cdot\mathbf{8}$. For each tetra-urea **8** at least 3 independent kinetic runs were performed. Measurements at different concentrations (1.0 mM to 4.0 mM) did not show any significant deviation or trend in the rate constants, thus confirming the first order rate law. The individual exchange rate values for each run are given in the ESI.†

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21 NMR spectra of homodimers of $\mathbf{8}_{MMMP}$, $\mathbf{8}_{MMPP}$, $\mathbf{8}_{MPPP}$ in C_6D_6 or cyclohexane-d_{12} are too complicated for a description since mixtures of regioisomeric dimers exist. Still, the characteristic patterns in the NH region with the definite number of (partially overlapped) signals were obtained; see pictures in the ESI† and ref. 15 for symmetry notation. In THF-d_8 these tetra-ureas exist in monomeric form but as mixtures of conformers. ^{1}H NMR spectra in THF-d_8 were measured at +50, +25, 0, −25 and −50 °C and the data presented are taken from the best resolved spectra. Nevertheless, from the ratio between CH_3 signals of pentyl groups at the narrow rim and those of 2-hexyloctyl groups at the wide rim, the number of pentyl residues at the narrow rim can be unambiguously concluded.