

# Synthesis and computational study of two new glycoluril clips containing benzocrown ether side walls

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**Abstract** Two new glycoluril-derived molecular clips containing benzocrown ether side walls have been synthesized via reaction of a glycoluril scaffold with two bromomethylated benzocrown ethers. The molecular geometry of their most stable structures were investigated with density functional theory at the B3LYP level of theory using STO-3G, 6-31G, and 6-311G basis sets. Then based on the obtained computer-optimized structures, the binding properties of one clip with some 5-substituted resorcinols have been calculated.

**Keywords** Molecular clip · Geometry optimization · Glycoluril · Binding properties

## Abbreviation

STO Slater-type orbital

## Introduction

Molecular recognition continues to be a topic of great interest in supramolecular chemistry [1, 2]. Depending upon the function and the need of selectivity in the rec-

ognition process, several types of interactions can play a role. In aqueous solution the hydrophobic effect often is the main driving force for host–guest complex formation [3], which can lead to very high association constants for natural as well as synthetic systems. The selectivity of the binding can be improved if additional interactions are involved, such as hydrogen bonding, electrostatic interactions, van der Waals forces, and  $\pi$ – $\pi$  stacking interactions. When these interactions are highly complementary and directional, the binding process will be completely selective as in the case of the mutual recognition of DNA base pairs, primarily by hydrogen bonding, which has served as an example for the design of many synthetic hosts capable of binding guests according to the same complementarily principles [4–6].

In 1987, Nolte et al. [7] synthesized some organic receptors based on diphenylglycoluril commonly referred to as “molecular clips”. This molecule possesses a well-defined and rigid U-shaped cavity, which is formed by the glycoluril framework and two aromatic side walls. With its preorganized cleft, it is a good receptor for a 1,3-dihydroxybenzene guest molecule in a chloroform solution through hydrogen bond,  $\pi$ – $\pi$  stacking interactions, and a so-called “cavity effect” [8–10]. In addition, in the solid state, the molecule can form head-to-head dimeric structures, in which the cavity of one molecule is filled by one of the side walls of its dimeric partner and vice versa [11–14]. This property was applied to create well-defined nanosized materials [15–17]. In this paper, we present the synthesis, geometry optimization of two new glycoluril clips which possess defined cavities with two benzocrown ether moieties. Then, the binding behavior of one of these clips which has more suitable cavity for binding, has been computationally studied in detail and will be discussed.

**Electronic supplementary material** The online version of this article (doi:10.1007/s10847-012-0174-0) contains supplementary material, which is available to authorized users.

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## Results and discussion

### Synthesis

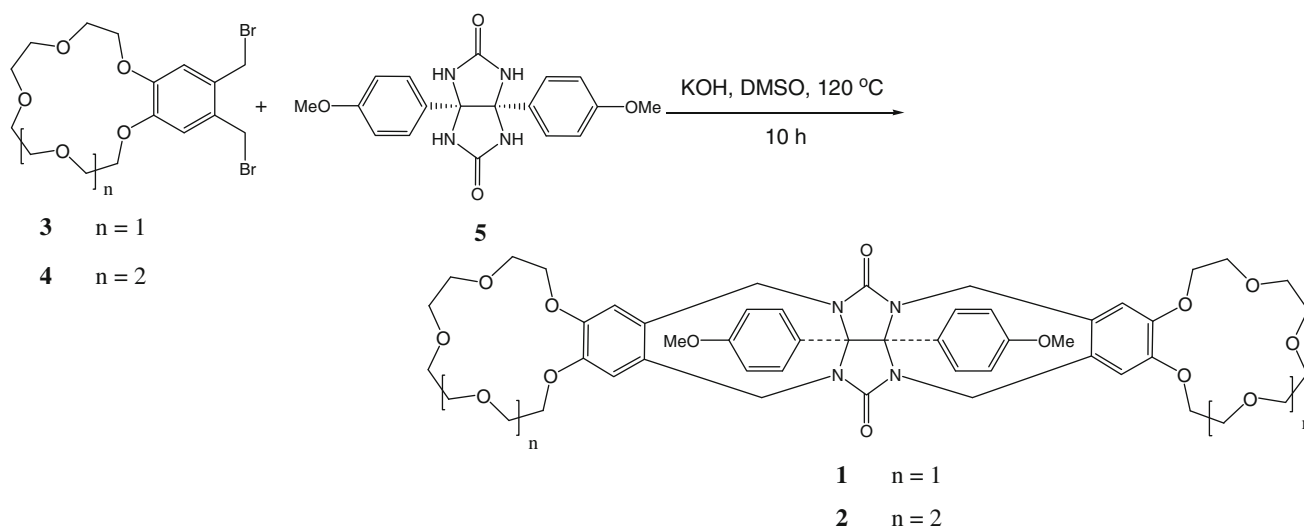
The synthesis of the clip (host) molecules **1** and **2** is outlined in Scheme 1. The glycoluril derivative **5** [18] was used as a scaffold for constructing of clips **1** and **2**. Double ring closure of **5** with 2 equivalent of compounds **3** and **4** under nucleophilic substitution conditions in DMSO with KOH as a base gave **1** and **2** respectively. The bromomethylated benzocrown ethers **3** [19] and **4** [20] were prepared from the corresponding benzocrown ether according to standard procedures.

Evidence for the alkylation reaction depicted in Scheme 1 was found in the IR spectrum of **1**. The spectrum showed no broad band for NH groups at nearly  $3,300\text{ cm}^{-1}$  and therefore confirmed N-alkylation. Furthermore, the protons of the  $\text{OCH}_2\text{CH}_2\text{O}$  units in the benzocrown ether side walls of compound **1** appeared as a multiplet in  $^1\text{H NMR}$  spectrum. In the case of compound **2**, it was initially obtained in a

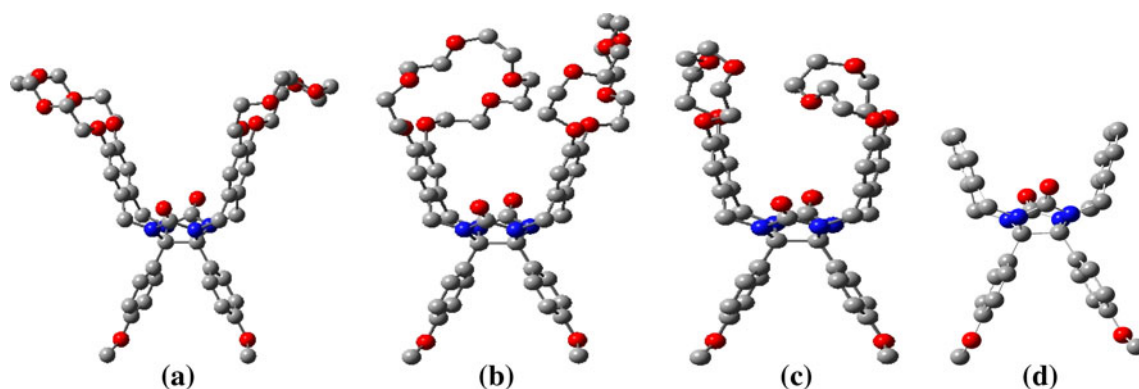
relatively impure status; but, it was purified by dry-column flash chromatography technique and fully characterized by elemental analysis and spectroscopic methods.

### Calculations

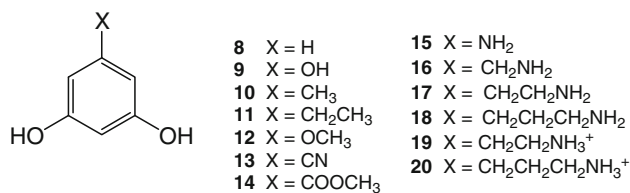
Density functional theory (DFT) calculations were employed in order to optimize the minimum-energy geometry of clips **1** and **2**. For comparison, the structure of clips **6**, having two benzo-12-crown-4 units (side walls), and **7**, lacking the crown ether moieties, were also optimized (Fig. 1). In this study, effects of the presence as well as the ring size of the mentioned crown ethers on clip geometry were investigated (Fig. 1). The calculations results showed that increasing of the number of oxygen atoms in the crown ether ring makes the clip more stable. Therefore, clip **2** with six oxygen atoms in each of its side walls, is the most stable (see Supplementary Information). One of the most important results has been revealed as the distance of “center-to-center” of two aromatic side walls.



**Scheme 1** Synthesis of clips **1** and **2**



**Fig. 1** Computer-optimized structures of **1** (a), **2** (b), **6** (c), and **7** (d)



**Chart 1** Schematic representation of the guests

Compound **6** has the least distance and therefore, has the tightest cavity (see Supplementary Information). Moreover, the calculations yielded some other data which have been indicated in Supplementary Information.

We also performed computational studies on their host–guest complexes using with DFT at the B3LYP level of theory using 6-31G basis set. The interaction energies were calculated by subtracting the energies of the host and guest from the minimum complex energy. The more electron withdrawing the substituent on the guest, the deeper it is bound in the clip cleft. On the other hand, the more electron-deficient the aromatic ring of the guest is, the smaller the repulsive electrostatic interaction between the walls and the guest becomes resulting in larger overall interaction energy with the electron rich side walls.

#### Binding properties of clip **1**

Regarding to the obtained computer-optimized structures, clip **2** is not a good host due to its cage-like structure. Hence, the calculations were performed on host–guest chemistry of clip **1**. A detailed computational study on the binding properties of clip **1** with several guests (Chart **1**) was accomplished. The calculated host–guest complexes for complexation of **1** with guests **8–17** are indicated in Fig. **2**. Moreover, the binding behavior of **7** towards the guests was calculated and compared with that of **1**.

The non-covalent interactions formed between clip **1** and the guests are hydrogen bonding and  $\pi$ – $\pi$  stacking. Thus, the hydroxyl groups of the guest form two hydrogen bonds with the carbonyl oxygens of the clip. First, we used some 5-substituted resorcinols with a diverse electron density on the aromatic ring as guest in the calculations. Like previous reports, the more electron-deficient resorcinols formed the stronger host–guest complexes (Table **1**). In the next step, we chose some 5-aminoalkyl resorcinols varying the length of the alkyl chain, as guest and computed their interaction energy with clip **1** (Table **1**). These guests (**16–18**) because of containing an amino group plus hydroxyl groups in their structures may form the more stable host–guest complexes with clip **1**. Since, they are potentially capable of forming three hydrogen bonds with the clip. When guest **16**, **17** or **18** locates into the clip cavity, probably three hydrogen bonds (HBs) including two HBs between hydroxyl groups and the

carbonyl oxygens, and one HB between NH<sub>2</sub> group and the ethereal oxygens are created. We supposed with a given length of the alkyl chain, the resorcinol guest attains a condition that it can more effectively binds to the clip. This assumption was actually demonstrated by the calculations. So that, when the aminoalkyl substituent was aminoethyl (i.e., in the case of guest **16**), NH<sub>2</sub> group was able to position in an ideal place for the strongest interaction with the crown ether rings (Table **1**). Also for comparison, the formed complexes between clip **7** and guests **15–20** were optimized (Fig. **3**). The interaction energy of this host with the mentioned guests **15–20** was calculated (Table **2**). By comparing the values of the interaction energy in Tables **1** and **2**, it is concluded in the case of guest **17**, the presence of the crown ether moieties in host **1** causes an enhancement in the interaction energy. Therefore, in the basis of data in Tables **1** and **2**, host **1** shows a “molecular recognition” phenomenon and unusual interaction energy with guest **17** and it is predicted to be an ideal host for guest **17** and probably other structurally-similar 5-substituted resorcinols.

## Experimental

### General

Silica gel 60 (0.040–0.063  $\mu$ m, Merck) was used for column chromatography. Benzo-15-crown-5, benzo-18-crown-6, HBr in acetic acid (30%, w/w), and 4,4'-dimethoxybenzil were purchased from Merck company. Compounds **3** [19], **4** [20], and **5** [18] were prepared according to literature procedures. Melting points were recorded on a Bamstead electrothermal type 9200 melting point apparatus and are uncorrected. The IR spectra were obtained on a 8400 Shimadzu spectrometer and only noteworthy absorptions are listed. The <sup>1</sup>H NMR spectra were recorded on a Bruker DRX-500 AVANCE spectrometer. Elemental analysis was performed on a ThermoFinnigan Flash EA microanalyzer.

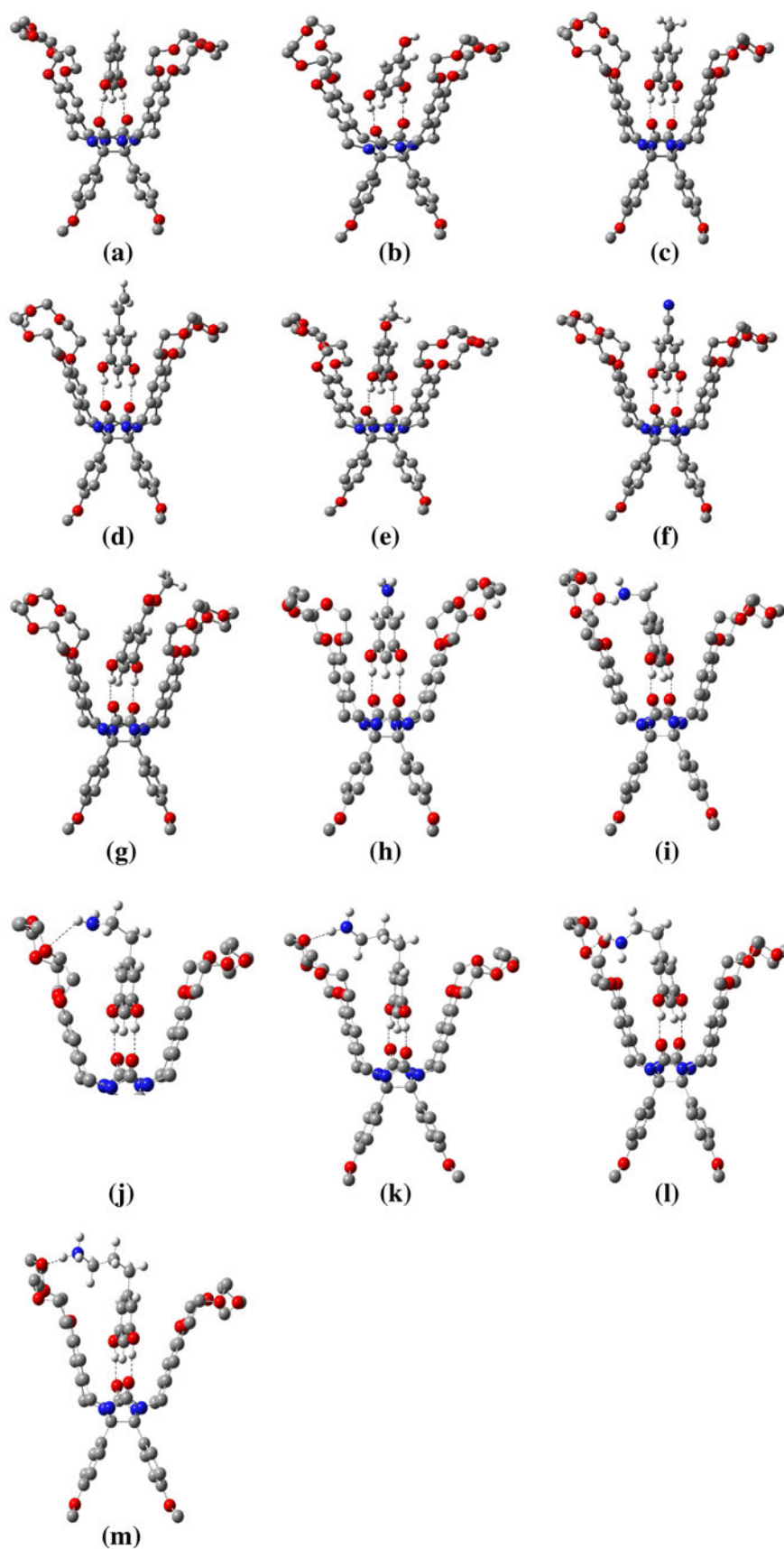
### Computational details

All of the present calculations have been performed with the B3LYP [21–23] hybrid density functional level using the Gaussian 98 package [24]. The STO-3G, 6-31G, and 6-311G basis sets were employed.

### Clip **1**

4,4'-bis(methoxyphenyl)glycoluril (0.49 g, 1.4 mmol) and freshly ground KOH (0.8 g, 14 mmol) were heated in DMSO (10 ml) at 120 °C for 20 min. with vigorous stirring. 4,5-bis(bromomethyl)benzo-15-crown-5 (**3**) (1.3 g,

**Fig. 2** The calculated host–guest complex of clip **1** with guest **8** (a), **9** (b), **10** (c), **11** (d), **12** (e), **13** (f), **14** (g), **15** (h), **16** (i), **17** (j), **18** (k), **19** (l), **20** (m). Hydrogen atoms in clip **1** have been omitted for clarity. *Dashed lines* indicate hydrogen bonds



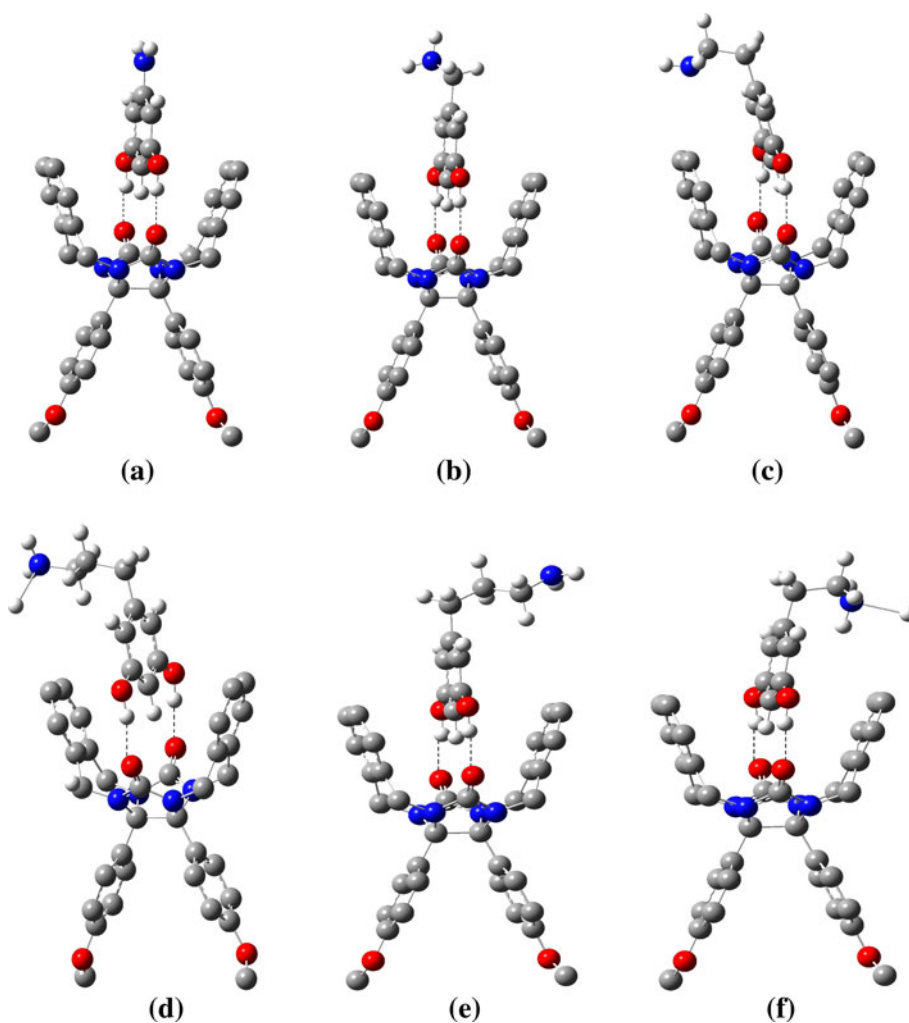
**Table 1** Calculated interaction energies (kJ/mol) between clip **1** and guests **8–20** using 6-31G basis set

| Guest     | Interaction energy (kJ/mol) |
|-----------|-----------------------------|
| <b>8</b>  | –101.423                    |
| <b>9</b>  | –110.036                    |
| <b>10</b> | –99.100                     |
| <b>11</b> | –102.698                    |
| <b>12</b> | –100.872                    |
| <b>13</b> | –114.842                    |
| <b>14</b> | –108.515                    |
| <b>15</b> | –96.526                     |
| <b>16</b> | – <sup>a</sup>              |
| <b>17</b> | –1923.283                   |
| <b>18</b> | –243.629                    |
| <b>19</b> | –314.082                    |
| <b>20</b> | –246.000                    |

Values were obtained by subtracting of the energies of the host (clip) and guest from the minimum complex energy

<sup>a</sup> A positive value

**Fig. 3** The calculated host–guest complex of clip **7** with guest **15** (a), **16** (b), **17** (c), **18** (d), **19** (e), **20** (f). Hydrogen atoms in clip **7** have been omitted for clarity. *Dashed lines* indicate hydrogen bonds



3 mmol) was added in one portion and stirring was then continued at this temperature for 10 h. After cooling, the reaction mixture was added to water (100 ml) and stirred for 30 min. The light brown precipitate was collected by filtration, washed with water ( $3 \times 100$  ml), and reduced to dryness under vacuum to yield 0.75 g (57 %).

Mp = 222–226 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  3.65–3.77 (m, 22 H,  $2 \times \text{Me}$ ;  $2 \times -\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$ ), 3.82–3.92 (m, 8 H,  $4 \times -\text{OCH}_2\text{CH}_2-\text{OAr}$ ), 4.04–4.21 (m, 12 H,  $4 \times -\text{OCH}_2\text{CH}_2-\text{OAr}$ ;  $4 \times \text{NCHHAr}$ ), 4.63 (d,  $J = 16$  Hz, 4 H,  $4 \times \text{NCHHAr}$ ), 6.79 (s, 4 H), 6.67 (d,  $J = 8.5$  Hz, 4 H), 6.99 (d,  $J = 8.5$  Hz, 4 H) ppm; IR (KBr disc,  $\text{cm}^{-1}$ ) 542, 604, 762, 843, 882, 964, 1052, 1305, 1184, 1263, 1471, 1522, 1615, 1692, 2871, 2892; Anal. Cald for ( $\text{C}_{50}\text{H}_{58}\text{N}_4\text{O}_{14}$ ): C 63.95, H 6.23, N 5.97; Found: C 64.17, H 6.37, N 5.71.

#### Clip 2

4,4'-Bis(methoxyphenyl)glycoluril (0.49 g, 1.4 mmol) and freshly ground KOH (0.8 g, 14 mmol) were heated in

**Table 2** Calculated interaction energies (kJ/mol) between clip **7** and guests **15–20** using 6-31G basis set

| Guest     | Interaction energy (kJ/mol) |
|-----------|-----------------------------|
| <b>15</b> | –65.940                     |
| <b>16</b> | –69.476                     |
| <b>17</b> | 70.445                      |
| <b>18</b> | –55.820                     |
| <b>19</b> | –389.947                    |
| <b>20</b> | –398.888                    |

Values were obtained by subtracting of the energies of the host (clip) and guest from the minimum complex energy

DMSO (10 ml) at 120 °C for 20 min. with vigorous stirring. 4,5-bis(bromomethyl)benzo-18-crown-6 (**4**) (1.49 g, 3 mmol) was added in one portion and stirring was then continued at this temperature for 10 h. After cooling, the reaction mixture was added to water (100 ml) and stirred for 30 min. The light brown precipitate was collected by filtration, washed with water (3 × 100 ml). Then, the crude product was purified by dry-column flash chromatography (eluent CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 96:4 v/v) to yield 0.75 g (57 %).

Mp = 96–100 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 3.65–3.80 (m, 30 H, 2 × Me; 2 × –CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>–CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>O–), 3.82–3.92 (m, 8 H, 4 × –OCH<sub>2</sub>CH<sub>2</sub>–OAr), 4.04–4.21 (m, 12 H, 4 × –OCH<sub>2</sub>CH<sub>2</sub>–OAr; 4 × NCHHAr), 4.63 (d, *J* = 16 Hz, 4 H, 4 × NCHHAr), 6.79 (s, 4 H), 6.67 (d, *J* = 8.5 Hz, 4 H), 6.99 (d, *J* = 8.5 Hz, 4 H) ppm; IR (KBr disc, cm<sup>–1</sup>) 550, 599, 762, 853, 935, 1042, 1106, 1198, 1269, 1291, 1474, 1522, 1604, 1725, 2844, 2892; Anal. Cald for (C<sub>54</sub>H<sub>66</sub>N<sub>4</sub>O<sub>14</sub>): C 65.18, H 6.69, N 5.63; Found: C 65.57, H 6.91, N 5.31.

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