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A New Class of C_3-Symmetrical Hemicryptophane Hosts: Triamide- and Tren-hemicryptophanes

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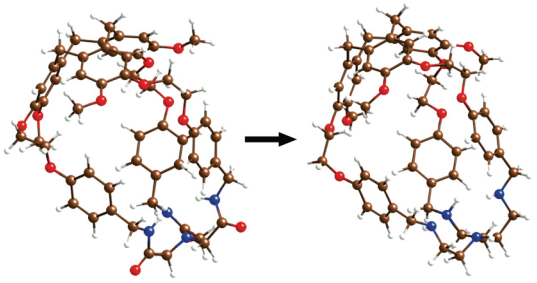

3 4

The first hemicryptophanes derived from tris(*N*-alkylcarbamoylmethyl)amine and tris(2-aminoethyl)amine (tren) have been synthesized following a single synthetic pathway that allows the subsequent formation of the two heteroditopic hosts **3** and **4**. X-ray crystal structures show a well-defined cavity encapsulating a solvent guest for both compounds emphasizing their complexation properties.

The use of molecular containers for the design of metalloreceptors is very attractive, as they can act as supramolecular catalysts and can mimic biological entities such as enzymes.[1] The cryptophane hosts, which are constructed from cyclotriveratrylene (CTV) units, have remarkable binding properties toward neutral or charged guests[2] and are efficient in chiral recognition.[3] The related hemicryptophanes, introducing dissymmetry at the molecular cavity level, are ditopic host molecules with all ingredients to produce catalytic and recognition properties.[4,5] We have previously reported the synthesis of the diastereomeric hemicryptophanes **1** and **2** (C_3 symmetry), which contain a CTV unit, providing a rigid scaffold with a lipophilic cavity, and a chiral C_3-symmetrical trialkanolamine moiety, a potential metalloreceptor with catalytic properties if proper metal and reactant(s) are used (Chart 1).[6] The related oxidovanadium(V) complexes, including the vanatrane structure, have been synthesized. They showed interesting stereochemical properties[7] and were found to be a novel class of efficient supramolecular catalysts.[8] These promising results led us to investigate the design of new hemicryptophane hosts by varying the nature of the tripodal amino group. The replacement of the trialkanolamine unit in **1** and **2** by C_3-symmetrical ligands derived from tris(*N*-alkylcarbamoyl-methyl)-amine and from tris(2-aminoethyl)-amine (tren), was expected to give rise to original derivatives exhibiting complexation properties related to the triamide or the tren structures. Indeed, these structures have been widely used to recognize, respectively, anions[9] and cations.[10] They have been also used to complex metal ions such as cobalt, zinc,[11] and copper.[12] For instance, the calix[6]arenes capped with a C_{3v}-symmetrical azacrown bridge[13] were designed to reinforce the complexation ability toward ammonium cations,[14] as well as neutral molecules.[14,15] They were found to be efficient in recognition and metal complexation, opening the way to interesting and unexpected reactivity. Herein, we wish to report the synthesis of the first C_3-symmetrical triamide- and tren-hemicryptophane derivatives **3** and **4**, the first members of a new class of hemicryptophane hosts (Chart 1).

The amide functions in hemicryptophane **3** should be easily reduced to afford derivative **4**. It was thus convenient to envision a general synthetic pathway for the subsequent synthesis of compounds **3** and **4** (Scheme 1). Starting from

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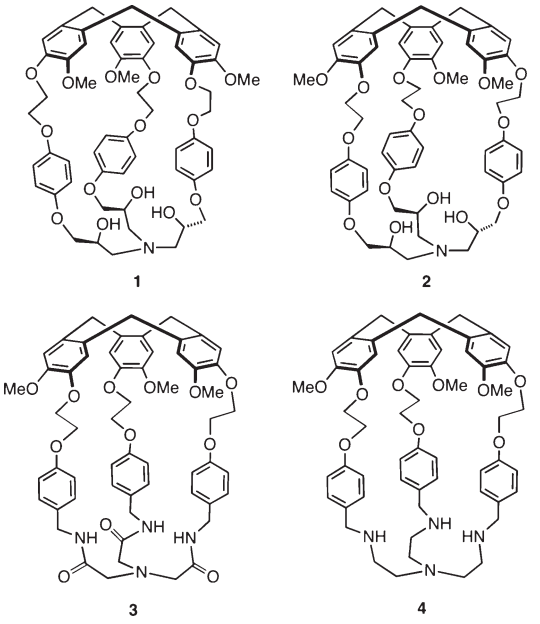
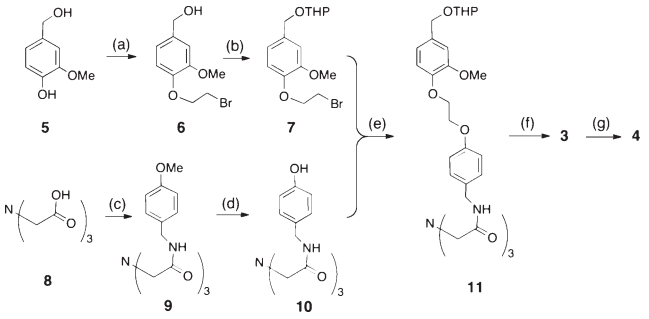
CHART 1. Structures of Hemicryptophanes 1−4



SCHEME 1[a]



[a]Reagents and conditions: (a) $BrCH_2CH_2Br$, K_2CO_3, EtOH, 80°C, 21 h, 34%; (b) DHP, pyridinium *p*-toluenesulfonate, THF/CH_2Cl_2, rt, 3 d, 79%; (c) *p*-methoxybenzylamine, $P(OPh)_3$, pyridine, 110°C, 15 h, 70%; (d) BBr_3, CH_2Cl_2, −78°C → rt, 18 h, 87%; (e) Cs_2CO_3, DMF, 80°C, 18 h, 58%; (f) HCOOH, rt, 24 h, 30%; (g) $BH_3 \cdot SMe_2$, THF, 30%.

vanillyl alcohol **5**, compound **6** was obtained and protected with THP to give **7** in 27% overall yield, according to a well-known two-step sequence.[16] Nitrilotriacetic acid **8** was condensed at 100 °C with 3 equiv of *p*-methoxy benzylamine in the presence of $P(OPh)_3$ using pyridine as solvent to give the tripodal triamidoamine derivative **9**.[17] Compound **9** was purified by crystallization from $CHCl_3$/pentane (70% yield). The amide functions act as amine protecting groups so that both protection and skeleton construction are performed during this step. Deprotection, i.e., amide reduction, will be performed only in the last step, thus avoiding side reactions during the next sequences of the synthesis. The methoxy groups in compound **9** were then removed by using BBr_3 (1 M solution in CH_2Cl_2) to give the triphenol derivative **10**. The preparation of the hemicryptophane precursor **11** was

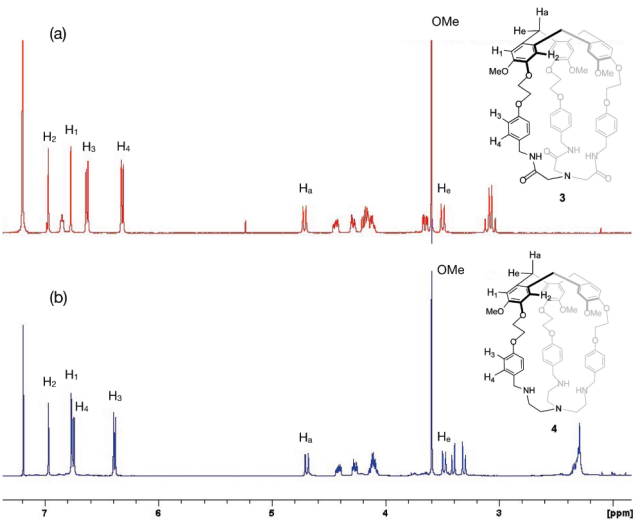


FIGURE 1. ^1H NMR spectra (497.8 MHz, $CDCl_3$, 293 K) of hemicryptophanes **3** (a) and **4** (b).

conducted under standard conditions by reacting **7** with **10** in DMF in presence of Cs_2CO_3. Compound **11** was obtained in 58% yield after selective precipitation in diethyl ether.

The formation of the cup-shaped cyclotriveratrilene unit was first investigated using $Sc(OTf)_3$ as Lewis acid, following the synthetic procedure reported for the synthesis of CTVs, cryptophane,[18] and hemicryptophane derivatives.[6] Therefore, the intramolecular cyclization of the tripodal triamide **11** was first attempted by using a stoichiometric amount of $Sc(OTf)_3$ in CH_3CN. Although standard dilution conditions for the hemicryptophane and cryptophane syntheses were used (10^{-3} M) to favor intramolecular reactions, only polymeric products were obtained. Changing the solvent to CH_2Cl_2 or the temperature conditions did not allow the formation of the expected product. This lack of selectivity and the formation of polymers could be due to the poor preorganization of the tripodal precursor **11**. The cyclization was then performed in formic acid, which is frequently used for the synthesis of cryptophanes.[2e] Under these strong acidic conditions, hemicryptophane **3** was obtained in 30% yield. The tripodal unit may complex a proton via the triamide and amine functions, and hence a preorganized system and a template effect could account for the improvement of the reaction yield.[19] Surprisingly, the reduction of the triamide **3** was not straightforward. Reduction using $LiAlH_4$ gave only mixtures of inseparable products. The reduction of the amide functions and the deprotection of the methoxy groups of the CTV moieties occurred at the same rate. Lowering the temperature or decreasing the amount of $LiAlH_4$ also led to a mixture of partially reduced and deprotected compounds. The reduction of the amide functions was successfully performed with BH_3/THF and afforded the desired hemicryptophane **4** in 30% yield.

The ^1H NMR spectra of hemicryptophanes **3** and **4** indicate that both molecules are on average of C_3 symmetry (Figure 1). Both spectra display the usual features of the

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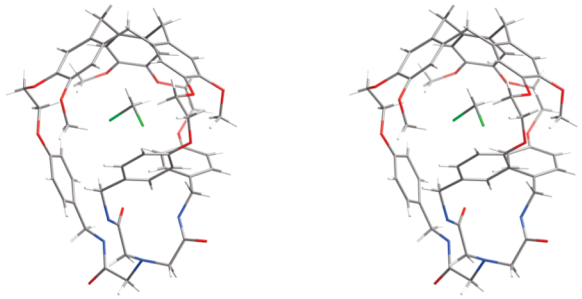

FIGURE 2. Stereoview of the X-ray molecular structure of **3**·CH_2Cl_2.

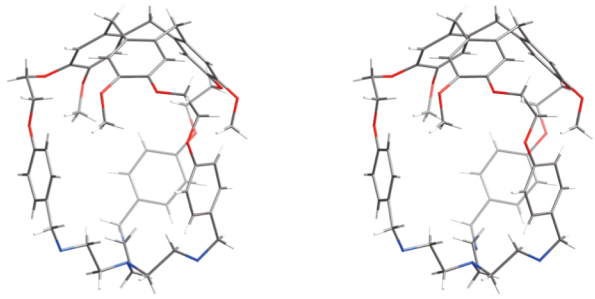

FIGURE 3. Stereoview of the X-ray molecular structure of **4**·C_5H_{12} (encapsulated pentane is omitted for clarity).

CTV unit, i.e., two singlets for the aromatic protons, one singlet for the OCH_3 groups, and the characteristic AB system for the $ArCH_2$ bridges. Two doublets for the H_3-H_4 aromatic protons of the linkers and the multiplets for the OCH_2 groups are also observed in the spectra. Changing the tripodal triamide unit by the tren structure induces modifications in the spectra with a particular effect on the NCH_2 protons in compound **4**, which appear as a complex pattern between 2.2 and 2.3 ppm (see Supporting Information).

Single crystals of **3** suitable for X-ray analysis were obtained by slow evaporation from a CH_2Cl_2 solution. A representation of the structure is shown in Figure 2. Hemicryptophane **3** exhibits an asymmetric structure with respect to the C_3 axis of the CTV cap, introduced by the inward orientation of one C=O amide bond stabilized by H-bonds with the adjacent NH groups. The two other C=O groups are oriented outward and participate in the crystalline cohesion through intermolecular H-bonding. One CH_2Cl_2 guest molecule is encapsulated in the host cavity and localized close to the CTV unit in the more lipophilic environment of the cavity. This is an interesting feature that anticipates the ditopic character of **3**.

Slow diffusion of pentane in a solution of **4** in CH_2Cl_2 gave crystals suitable for X-ray analysis (Figure 3). The most striking observations are on one hand the conservation of the C_3-symmetrical axis in the crystal structure and on the other hand the well-preorganized cavity defined by the cyclotriveratrylene and the tren moieties. Moreover, a molecule of *n*-pentane is imprisoned in this cavity, underlining the molecular receptor properties of **4**. It can be noticed that the host−guest complex is not detected by NMR spectroscopy since the guest is small enough to enter and depart the interior of the host so that mass-law driven exchange of guest with solvent occurs in solution at room temperature. The asymmetric crystal unit is constituted by one-third of the host molecule due to the $R-3$ space group, which leads to the presence of a C_3 axis colinear to that one of the CTV unit and aligned with the *c* parameter. As a consequence, the central carbon atom of the pentane guest lies on the C_3 axis, and the two CH_2CH_3 groups apart the central atom are delocalized on the three equivalent positions according to the C_3 repetition.

In summary, we have developed the synthesis of a new class of ditopic hosts, where a triamide or tren moiety faces a CTV unit to form a new class of hemicryptophanes. These chiral molecules could provide a suitable environment for the formation of metal complexes with catalytic properties. Furthermore, the CTV-triamide (**3**) and CTV-tren (**4**) platforms seem particularly well suited for the recognition of new cationic/anionic guests. Such studies will be reported in due course.

Experimental Section

Synthesis of Tris(*p*-methoxybenzylcarbamoylmethyl)-amine 9. To a solution of nitrilotriacetic acid (9.00 g, 47.1 mmol) in pyridine (80 mL) was added under vigorous stirring *p*-methoxybenzyl amine. (19 mL, 145.6 mmol). The solution was warmed to 50 °C, and triphenyl phosphite (49 mL, 187.2 mmol) was added. The mixture was heated at 110 °C for 1 day, and then the pyridine was removed under vacuum. The orange residue was dissolved in chloroform (400 mL) and was successively washed with 10% aq $NaHCO_3$ (2 × 200 mL) and distilled water (1 × 200 mL). The organic layers were dried with Na_2SO_4, and chloroform was removed under reduced pressure. The white solid obtained was dissolved in chloroform, precipitated, and washed with petroleum ether to give pure **9** as a white powder (18.1 g, 70%). ESI-MS *m*/*z* obsd 571.2548 ($[M + Na]^+$, calcd 571.2533 for $C_{30}H_{36}N_4O_6Na$). ^1H NMR ($CDCl_3$, 297 K, 497.80 MHz): δ 7.36 (t, 3H, ^3J = 5.83 Hz, NHC=O), 7.11 (d, 6H, ^3J = 8.66 Hz, ArH), 6.80 (d, 6H, ^3J = 8.66 Hz, ArH), 4.26 (d, 6H, ^3J = 5.83 Hz, $ArCH_2$), 3.76 (s, 9H, ArOMe), 3.26 (s, 6H, $N(CH_2)_3$). ^{13}C NMR ($CDCl_3$, 297 K, 125.17 MHz): δ 170.0 (NHC=O), 158.9 ($C_{Ar}O$), 130.0 (C_{Ar}), 129.0 (C_{Ar}), 114.0 (C_{Ar}), 60.3 (NCH_2C=O), 55.2 (OMe), 42.8 ($NHCH_2Ar$). Anal. Calcd for $C_{30}H_{36}N_4O_6$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.72; H, 6.54; N, 9.83.

Synthesis of Tris(*p*-hydroxybenzylcarbamoylmethyl)-amine 10. A 1 M boron tribromide solution in CH_2Cl_2 (200 mL, 200 mmol) was added dropwise at − 78 °C to a well-stirred solution of **9** (19.7 g, 35.9 mmol) in CH_2Cl_2 (450 mL). The mixture was allowed to warm to room temperature and stirred for 1 day. The solution was cooled to 0 °C, and 10% aqueous solution of $NaHCO_3$ (600 mL) was added slowly. After addition of methanol (10 mL) the organic layer was separated, and the aqueous phase was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were dried over Na_2SO_4, and the organic solvent was removed to give **10** as a white solid (15.8 g, 87%). ESI-MS *m*/*z* obsd 529.2075 ($[M + Na]^+$, calcd 529.2063 for $C_{27}H_{30}N_4O_6Na$). ^1H NMR (d_6-DMSO, 297 K, 497.80 MHz): δ 9.30 (s, 3H, ArOH), 8.53 (t, 3H, ^3J = 5.47 Hz, NHC=O), 7.025 (d, 6H, ^3J = 8.22 Hz, ArH), 6.68 (d, 6H, ^3J = 8.22 Hz, ArH), 4.165 (d, 6H, ^3J = 5.47 Hz, $ArCH_2$), 3.27 (s, 6H, $N(CH_2)_3$). ^{13}C NMR (d_6-DMSO, 297 K, 125.17 MHz): δ 169.8 (NHC=O), 156.2 ($C_{Ar}O$), 129.4 (C_{Ar}), 128.4 (C_{Ar}), 115.0 (C_{Ar}), 58.0 (NCH_2), 41.4 (NCH_2).

Synthesis of Hemicryptophane Precursor 11. Compounds **10** (6.63 g, 13.1 mmol) and **7** (14.87 g, 43.1 mmol) and Cs_2CO_3 (18.89 g, 57.9 mmol) were dissolved in DMF (60 mL). The solution was heated at 80 °C for 1 day. The mixture was cooled

to room temperature, and distilled water (250 mL) was added. The aqueous mixture was then extracted with ethyl acetate (4 × 150 mL). The combined organic layers were washed with distilled water (2 × 150 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was dissolved in CH_2Cl_2 and precipitated with diethyl ether to give pure **11** as a white powder (9.9 g, 58%). ESI-MS *m*/*z* obsd 1321.6171 ($[M + Na]^+$, calcd 1321.6148 for $C_{72}H_{90}N_4O_{18}Na$). ^1H NMR ($CDCl_3$, 297 K, 497.80 MHz): δ 7.41 (t, 3H, ^3J = 5.52 Hz, NHC═O), 7.10 (d, 6H, ^3J = 8.62 Hz, ArH), 6.86−6.90 (m, 9H, ArH), 6.83 (d, 6H, ^3J = 8.66 Hz, ArH), 4.70 (d, 3H, ^2J = 11.71 Hz, $ArCH_2O$), 4.66 (t, 3H, ^3J = 3.64 Hz, OTHP), 4.42 (d, 3H, ^2J = 11.71 Hz, $ArCH_2O$), 4.23−4.34 (m, 18H, $ArCH_2N$; $O(CH_2)_2O$), 3.91 (m, 3H, OTHP), 3.82 (s, 9H, ArOMe), 3.53 (m, 3H, OTHP), 3.25 (s, 6H, $N(CH_2)_3$) 1.47−1.89 (m, 18H, OTHP). ^{13}C NMR ($CDCl_3$, 297 K, 125.17 MHz): δ 170.1 (NHC═O), 158.0 ($C_{Ar}O$), 149.6 ($C_{Ar}O$), 147.5 ($C_{Ar}O$),131.8 (C_{Ar}), 130.4 (C_{Ar}), 129.0 (C_{Ar}), 120.5 (C_{Ar}), 114.8 (C_{Ar}), 114.0 (C_{Ar}), 112.0 (C_{Ar}), 97.6 (OCO), 68.7 (CH_2O), 67.8 (CH_2O), 66.5 (CH_2O), 62.3 (CH_2O), 60.2 (NCH_2), 55.9 (OMe), 42.8 (NCH_2), 30.6, 25.4, 19.5 (OTHP). Anal. Calcd for $C_{72}H_{90}N_4O_{18}\cdot CH_2Cl_2$: C, 63.33; H, 6.70; N, 4.05. Found: C, 63.65; H, 6.68; N, 4.21.

Synthesis of Triamide-hemicryptophane 3. Precursor **11** (2.50 g, 1.93 mmol) was dissolved in formic acid (2.5 L). The mixture was stirred for 1 day at room temperature, and then the formic acid was removed under vacuum. The brown residue was dissolved in chloroform (100 mL), and aqueous K_2CO_3 (10%, 50 mL) was added. The organic layer was separated, and the aqueous phase was extracted with chloroform (2 × 100 mL). The combined organic layers were dried with Na_2SO_4, and then the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel using a 15:3 mixture of chloroform and methanol as eluent to give **3** (575 mg, 30%) as a white powder. Crystallization from CH_2Cl_2 gave suitable material for X-ray crystallography analysis. ESI-MS *m*/*z* obsd 1015.4093 ($[M + Na]^+$, calcd 1015.4105 for $C_{57}H_{60}N_4O_{12}Na$). ^1H NMR ($CDCl_3$, 297 K, 497.80 MHz): δ 7.04 (s, 3H, ArH), 6.82 (s, 3H, ArH), 6.75 (l, 3H, NHC═O), 6.655 (d, 6H, ^3J = 8.56 Hz, ArH), 6.35 (d, 6H, ^3J = 8.56 Hz, ArH), 4.77 (d, 3H, ^2J = 13.69 Hz, Ha), 4.49−4.55 (m, 3H, $O(CH_2)_2O$), 4.31−4.37 (m, 3H, $O(CH_2)_2O$), 4.20−4.28 (m, 6H, $O(CH_2)_2O$; $ArCH_2N$), 4.13−4.19 (m, 3H, $O(CH_2)_2O$), 3.70 (dd, 3H, $ArCH_2N$), 3.64 (s, 9H, ArOMe), 3.55 (d, 3H, ^2J = 13.69 Hz, He), 3.18 (d, 3H, ^2J = 16.49 Hz, $N(CH_2)_3$), 3.12 (d, 3H, ^2J = *16.49 Hz*, $N(CH_2)_3$). ^{13}C NMR ($CDCl_3$, 297 K, 125.17 MHz): δ 169.5 (NHC═O), 157.7 ($C_{Ar}O$), 148.3 ($C_{Ar}O$), 146.3 ($C_{Ar}O$), 132.9 (C_{Ar}), 131.8 (C_{Ar}), 130.35 (C_{Ar}), 128.76 (C_{Ar}), 116.61 (C_{Ar}), 114.92 (C_{Ar}), 113.6 (C_{Ar}), 67.9 (OCH_2), 67.3 (OCH_2), 60.9 (NCH_2), 55.8 (OMe), 42.7 (NCH_2), 36.5 (ArCAr). Anal. Calcd for $C_{57}H_{60}N_4O_{12}\cdot 2CH_2Cl_2$: C, 60.93; H, 5.55; N, 4.82. Found: C, 60.63; H, 5.58; N, 5.01.

Synthesis of Tren-hemicryptophane 4. Compound **3** (310 mg) was dissolved under vigorous stirring in a 2 M solution of $H_3B\cdot SMe_2$ in THF (15 mL). The solution was stirred for 1 week at 65 °C. After the mixture cooled to room temperature, methanol (6 mL) and aqueous 1 M HCl (1 mL) were successively added dropwise. The solution was then heated at 40 °C for 1 day. The solvents were removed under vacuum, and the residue was dissolved in chloroform (10 mL). Methanol (7 mL) and aqueous 1 M HCl (1 mL) were then added, and the mixture was stirred for 2 days at 60 °C. The solvents were removed, and the residue was dissolved in chloroform (50 mL) and aqueous 1 M NaOH (50 mL). The organic layer was separated, and the aqueous phase was extracted with chloroform (3 × 40 mL).The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel using a 90:10:2 mixture of CH_2Cl_2, methanol, and triethylamine to give **4** as a white solid (89 mg, 30%). Crystals suitable for X-ray crystallography were obtained by allowing pentane to slowly diffuse in a concentrated solution of **4** in CH_2Cl_2 at 5 °C. ESI-MS *m*/*z* obsd 951.4916 ($[M + H]^+$, calcd 951.4908 for $C_{57}H_{67}N_4O_9$). ^1H NMR ($CDCl_3$, 297 K, 497.80 MHz): δ 7.01 (s, 3H, ArH), 6.91 (br, 6H, ArH), 6.82 (s, 3H, ArH), 6.48 (d, 6H, ^3J = 7.56 Hz, ArH), 4.75 (d, 3H, ^2J = 13.63 Hz, Ha), 4.14−4.42 (m, 12H, $O(CH_2)_2O$), 3.65 (s, 9H, OMe), 3.54 (d, 3H, ^2J = 13.63 Hz, He), 3.43−3.54 (br, 6H, $ArCH_2N$), 2.48−2.70 (br, 12H, $N(CH_2)_2N$). ^{13}C NMR ($CDCl_3$, 297 K, 125.17 MHz): δ 157.4 (NHC═O), 148.3 ($C_{Ar}O$), 146.4 ($C_{Ar}O$), 133.0 (C_{Ar}), 132.9 (C_{Ar}), 131.7 (C_{Ar}), 129.1 (C_{Ar}), 116.8 (C_{Ar}), 114.7 (C_{Ar}), 113.5 (C_{Ar}), 67.7 (OCH_2), 67.6 (OCH_2), 55.9 (OMe), 55.6 (NCH_2), 53.0 (NCH_2), 47.0 (NCH_2), 36.5 (ArCAr).

X-ray Crystallography. $\mathbf{3}\cdot CH_2Cl_2$: $C_{58}H_{62}Cl_2N_4O_{12}$, M_w 1078.05 monoclinic $P2_1/n$, a = 10.997(5) Å, b = 18.282(5) Å, c = 28.996(5) Å, β = 95.320(5)°, V = 5804(3) Å^3, D_c = 1.230 g cm^{-3}, Z = 4, μ = 0.17 mm^{-1}, R_1 = 0.136, wR_2 = 0.144 for 3218 reflections with $I > 2\sigma(I)$. **4**·Pentane: $C_{62}H_{78}N_4O_9$, M_w 1023.32 trigonal $R-3$, a = 16.61(2) Å, b = 16.61(8) Å, c = 37.24(1) Å, V = 8897(3) Å^3, D_c = 1.148 g cm^{-3}, Z = 2, μ = 0.08 mm^{-1}, R_1 = 0.139, wR_2 = 0.171 for 1469 reflections with $I > 2\sigma(I)$. Details on data collections and refinements are reported in Supporting Information.

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Supporting Information Available: General experimental methods for compounds **3**, **4**, and **9**−**11**; ^1H and ^{13}C NMR spectra for all new compounds; crystallographic information files in CIF format for $\mathbf{3}\cdot CH_2Cl_2$ (CCDC 758472) and **4**·pentane (CCDC 758471). This material is available free of charge via the Internet at http://pubs.acs.org.