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Supramolecular Ribbons from Amphiphilic Trisamides Self-Assembly

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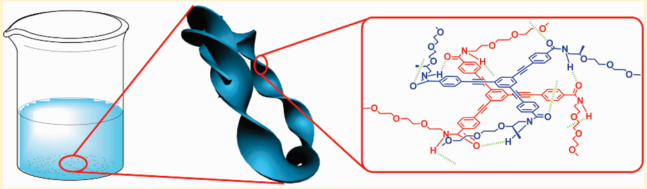
S Supporting Information



ABSTRACT: Two amphiphilic C_3-symmetric OPE-based trisamides have been synthesized and their self-assembling features investigated in solution and on surface. Variable-temperature UV—vis experiments demonstrate the cooperative supramolecular polymerization of these trisamides that self-assemble by the operation of triple C═O···H—N H-bonding arrays between the amide functional groups and $\pi-\pi$ stacking between the aromatic units. The helical organization of the aggregates has been demonstrated by circular dichroism at a concentration as low as 1×10^{-4} M in acetonitrile. In the reported trisamides, the large hydrophobic aromatic core acts as a solvophobic module impeding the interaction between the polar TEG chains and the amide H-bonds. This strategy makes unnecessary the separation of the amide functional groups to the polar tri(ethylene glycol) chains by paraffinic fragments. Achiral trisamide **1** self-assembles into flat ribbon-like structures that experience an amplification of chirality by the addition of a small amount of chiral **2** that generates twisted stripes.

INTRODUCTION

The delicate balance between hydrophobic and hydrophilic effects controls the organized self-assembly of molecules in water. A challenging goal in this topic is to emulate the formation of complex and functional structures by the assembly of biomolecules.[1] Drug delivery,[2] tissue engineering,[3] or hydrogels[4] exemplify the applicability of the supramolecular structures formed in aqueous media. In this regard, a combination of noncovalent forces like H-bonding, $\pi-\pi$ stacking, and ion-pairing is required to control the hydrophobic/hydrophilic balance.[5] However, highly directional H-bonds operate efficiently only in nonpolar environments,[6] and therefore, the H-bonding arrays in polar media need to be protected by the creation of a solvophobic pocket.[7]

A number of examples of artificial molecules utilize water-compatible ethylene oxide chains to achieve highly organized supramolecular structures in aqueous environments.[8] However, a drawback of ethylene oxide chains is the competence in the formation of H-bonds with polarizable N—H groups of amides or ureas that diminishes notably the corresponding binding constant. In these examples, only the separation between the intermolecular H-bonding donors and acceptors moieties to the polar ethylene oxide (EO) chains by paraffinic segments allows stabilizing the final supramolecular structures.[4c,9]

Our research group is actively working on the formation of supramolecular structures by utilizing radial oligo(phenylene ethynylene) (OPEs) platforms.[10,11] The different decoration and connectivity of the central OPE moiety with polar EO and/or paraffinic chains render a variety of ensembles of modulated morphology and dimensionality that also differ in the self-assembly mechanism.[12] While the attachment of the peripheral chains as alkoxy groups induces an isodesmic self-assembly,[10] the connection of these chains by means of amide functional groups results in a cooperative supramolecular polymerization.[11] Herein, we investigate the influence of the attachment of tri(ethelene glycol) (TEG) chains to C_3-symmetrical OPE trisamides on the self-assembly process in apolar and polar solvents. In the reported TEG-substituted achiral trisamide **1** and chiral trisamide **2**, the large aromatic skeleton acts as hydrophobic shielding factor that allows their supramolecular polymerization by the synergy of triple N—H···O═C amide H-bonding motifs and $\pi-\pi$ stacking.

RESULTS AND DISCUSSION

Synthesis. Polar trisamides **1** and **2** were readily synthesized by a multistep synthetic procedure starting from amines **3a**,**b** that were obtained by a slightly modified methodology to that previously reported (Scheme 1 and Supporting Information).[13] The condensation of these amines with 4-iodobenzoic acid and subsequent Sonogashira cross-coupling reaction of the resulting amides with 1,3,5-triethynylbenzene[14] yields the target OPEs **1** and **2** in 56 and 72% yield, respectively (Scheme 1).

The chemical structure of the new compounds has been confirmed by ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy and HRMS (ESI-FT) spectrometry. The C_3-symmetry of compounds **1** and **2** results in simple ^{1}H NMR spectra with two sets of resonances at δ ~7.8, and 7.6, ascribable to an AA′BB′ spin system typical of *para*-substituted aromatic compounds, and one singlet at δ ~7.7 corresponding to the central aromatic proton. The close proximity of the stereogenic center at the polar TEG chains to the amide proton at δ ~7.0 changes the multiplicity of this resonance. Thus, in achiral **1** the signal appears as a triplet but in chiral **2** a double doublet is clearly observed due to the

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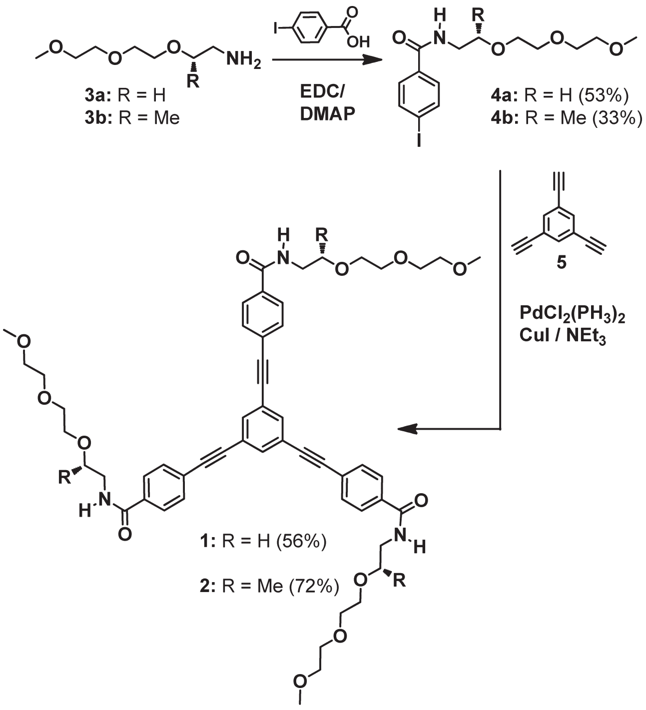
Scheme 1. Synthesis of Amphiphilic Trisamides 1 and 2



diastereotopic character of the methylene group adjacent to the amide and the stereogenic center.

Self-Assembly in Solution. We have previously shown that OPE-based trisamides exhibit a C_3 geometry with the OPE moiety almost planar and the amide groups twisted by 21.5°. This molecular geometry favors the operation of $\pi-\pi$ and H-bonding intermolecular interactions and induces the self-assembly of this class of molecules into helical columnar aggregates.[11a] The bands at ~3340, 1639, and 1546 cm^{-1} observed in the FTIR spectra of compounds **1** and **2** are ascribable to the amide A, amide I, and amide II bands and imply the formation of amide C=O···H−N H-bonds (Figure S1, Supporting Information).[11a,15] The stability of these C=O···H−N H-bonds and, therefore, the possible interaction between the TEG chains and the amide functionalities in amphiphile **1** have been investigated by concentration-dependent ^{1}H NMR experiments in deuterated solvents of different polarity (Figure S2−S4, Supporting Information). In all these experiments, the aromatic protons shield upon increasing concentration, thus suggesting the supramolecular interaction of **1** by π-stacking. However, the resonance diagnostic of the amide protons at δ ~7.0 is only visible in $CDCl_3$ and CD_3CN. In these solvents, the amide triplet shifts downfield with increasing concentration, which indicates the intermolecular interaction of **1** by the operation of H-bonding arrays between the amide groups. In CD_3OD, the amide triplet disappears as a consequence of the H/D exchange with the solvent. However, the protons of the TEG chains are unaffected in all these experiments, which could be diagnostic of a negligible interaction of these peripheral chains with the amide groups. Therefore, the large aromatic surface of the OPE moiety could act as solvophobic segment preventing the H-bonding of the TEG chains with the amide groups.

The significant role exerted by the aromatic skeleton has been demonstrated by ^{1}H NMR experiments in solvent mixtures (Figure 1 and Figure S5, Supporting Information). The amide resonance of amide **1** disappears and the upfield shift of the aromatic and TEG signals increases upon addition of CD_3OD into a solution of **1** in $CDCl_3$, a bad solvent for $\pi-\pi$ stacking, keeping the total concentration constant which implies an efficient aggregation (Figure S5, Supporting Information). Interestingly, the addition of small amounts of highly polar solvents like CD_3OD or even D_2O into a solution of **1** in CD_3CN does not break the intermolecular amide H-bonds (Figure 1). Under these conditions, the solvophobic effect of CD_3CN induces an efficient $\pi-\pi$ stacking of the hydrophobic aromatic units and impedes the approach of the more polar solvents (D_2O or CD_3OD) to the amide functional groups. Therefore, in these polar mixtures, the aggregation of amide **1** is driven by the triple intermolecular array of H-bonds between the three amide functionalities strongly reinforced by the $\pi-\pi$ stacking of the aromatic moieties.

To determine the self-assembly mechanism of trisamide **1** in solution, we have performed variable-temperature UV−vis experiments by using apolar methylcyclohexane (MCH) as solvent even though compound **1** is sparingly soluble in this solvent (Figure 2). In this experiment, the depletion of two well-defined waves at ~300 and ~314 nm, and the appearance of a shoulder at ~340 nm, is noticeable upon decreasing temperature (Figure 2).[11a] The nonsigmoidal shape of the melting curve is diagnostic of a nucleation−elongation or cooperative mechanism. A cooperative mechanism is defined by several parameters: ϕ_{SAT} is the quantity necessary to equate ϕ_n/ϕ_{SAT} to unity, h_e is the enthalpy released during elongation, T_e is the temperature at which the nucleation regime changes into elongation, and K_a indicates the degree of cooperativity. Fitting the experimental data to eqs 1 and 2, we can conclude that the supramolecular polymerization of **1** is exothermic (h_e = −52.15 $kJmol^{-1}$) and cooperative.

$$\phi_n = \phi_{SAT}\left(1 - exp\left[\frac{-h_e}{RT_e^{\,2}}(T - T_e)\right]\right) \tag{1}$$

$$\phi_n = K_a^{\,1/3} exp\left[\left(\frac{2}{3}K_a^{\,-1/3} - 1\right)\frac{h_e}{RT_e^{\,2}}(T - T_e)\right] \tag{2}$$

Considering that the lower the K_a value is the higher the cooperativity is, the calculated value for K_a of 6×10^{-5} indicates that the self-assembly process is highly cooperative.[16] This activation step is 3 orders of magnitude lower than that reported for previously reported OPE-based trisamides[11a] and suggests the difficulty of the molecules reported herein to form organized structures, most probably due to the coiling effect experienced by the polar TEG chains in an apolar media like MCH. Similar results have been obtained by using a mixture of MCH/1,2-dichloroethane 99/1 at 1×10^{-5} M. The slightly higher polarity of 1,2-dichloroethane increases the K_a value to 5×10^{-4} (Figure S6, Supporting Information). The cooperative mechanism followed by amphiphilic trisamide **1** contrasts with the isodesmic self-assembly experienced by referable triangular-shape OPE-based amphiphiles reported by our group[10a] and verifies the relevance of the directional H-bonding interactions to control the supramolecular polymerization mechanism.

The examples of helical supramolecular structures from amphiphilic chiral molecules involving H-bonds are still scarce, as the 1,3,5-benzenetrisamide is the most utilized structural motif to

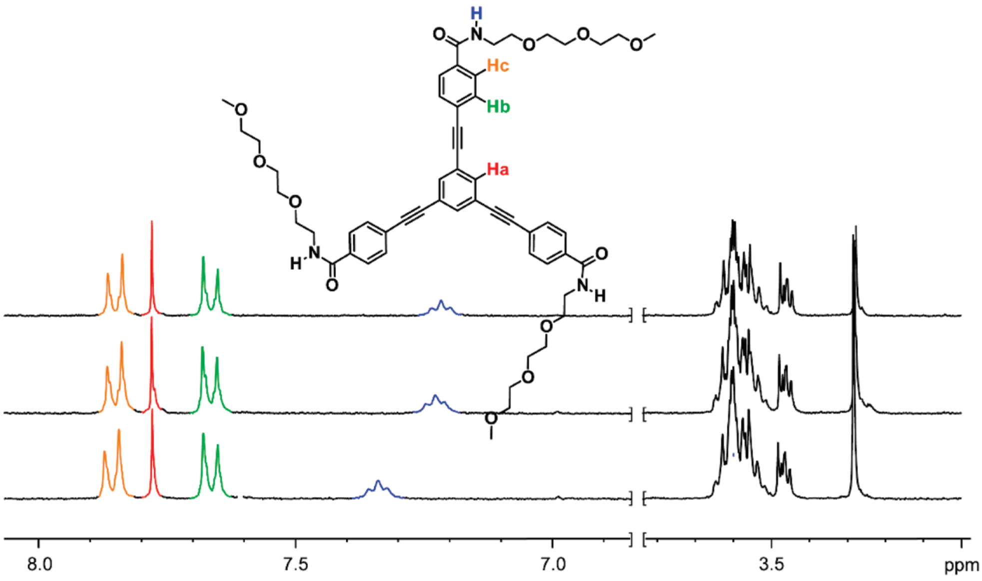


Figure 1. Partial concentration-dependent ^{1}H NMR (300 MHz, 298 K, 1 mM) spectra of **1** in CD_3CN (top), CD_3CN + 1% CD_3OD (middle), and CD_3CN + 1% D_2O (bottom) showing the aromatic, the amide, and the TEG protons.

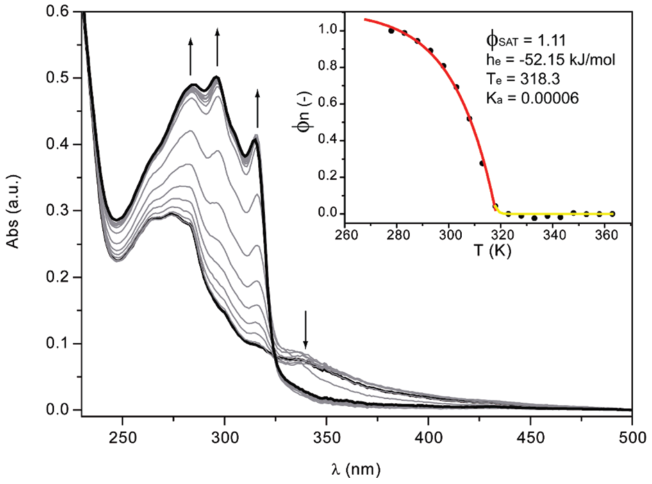


Figure 2. *T*-dependent UV−vis spectra of **1** (MCH, 5 × 10^{-6} M, from 363 to 283 K, at intervals of 5 K). Inset: plot of the molar fraction of aggregates versus temperature fitted within elongation (red line) and nucleation (yellow line) regimes. Arrows indicate the direction of change with increasing temperature.

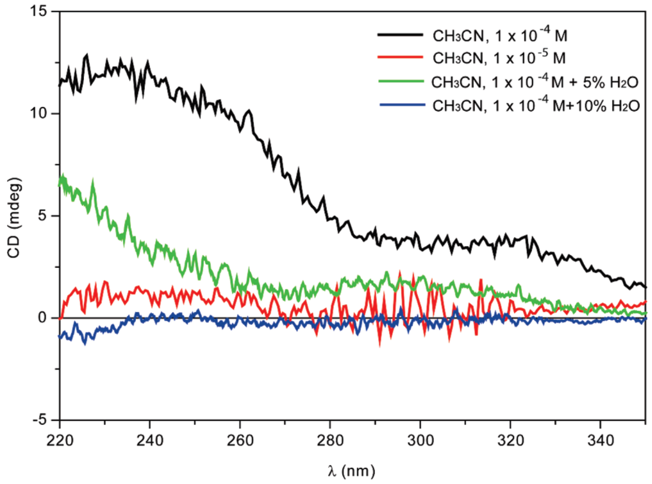


Figure 3. CD spectra (298 K) of chiral trisamide **2** in CH_3CN, 1 × 10^{-4} M (black), CH_3CN, 1 × 10^{-5} M (red), CH_3CN, 1 × 10^{-4} M + 5% H_2O (green), and CH_3CN, 1 × 10^{-4} M + 10% H_2O (blue).

achieve helicity.[17] In the case of amphiphilic trisamides **1** and **2**, the synergy of $\pi-\pi$ stacking between the aromatic units and the triple H-bonding array between the amide functionalities should favor their aggregation into helical columnar stacks.[11a] The helical arrangement of chiral trisamide **2** has been corroborated by circular dichroism (CD) at different experimental conditions (Figure 3 and Figure S7, Supporting Information). Compound **2** exhibits dichroic response in polar CH_3CN at 1 × 10^{-4} M, a concentration value more than 2 orders of magnitude lower than that described for amphiphilic 1,3,5-benzenetrisamides.[9a] The CD response of trisamide **2** is canceled by diluting the sample at 1 × 10^{-5} M. This concentration dependence implies the helical aggregation of **2**. As has been observed in ^{1}H NMR experiments, the addition of a small amount of water (5%) does not eliminate the H-bonds between the amide functionalities, and the CD response is also observed. However, the addition of a larger quantity of water (10%) definitively breaks the H-bonding arrays, and no CD signal is observed (Figure 3).

The helical organization of chiral trisamide **2** is also confirmed by utilizing a more apolar mixture of solvents. The low solubility of **2** in MCH results in a negligible CD response. However, the CD spectra of **2** in a 99/1 mixture of MCH and 1,2-dichloroethane exhibits a bisignated Cotton effect that disappears upon addition of a larger amount of 1,2-dichloroethane (Figure S7, Supporting Information).

Electron Microscopy Images of Supramolecular Structures. Finally, we have visualized the supramolecular aggregates formed by the directed self-assembly of amphiphilic trisamides

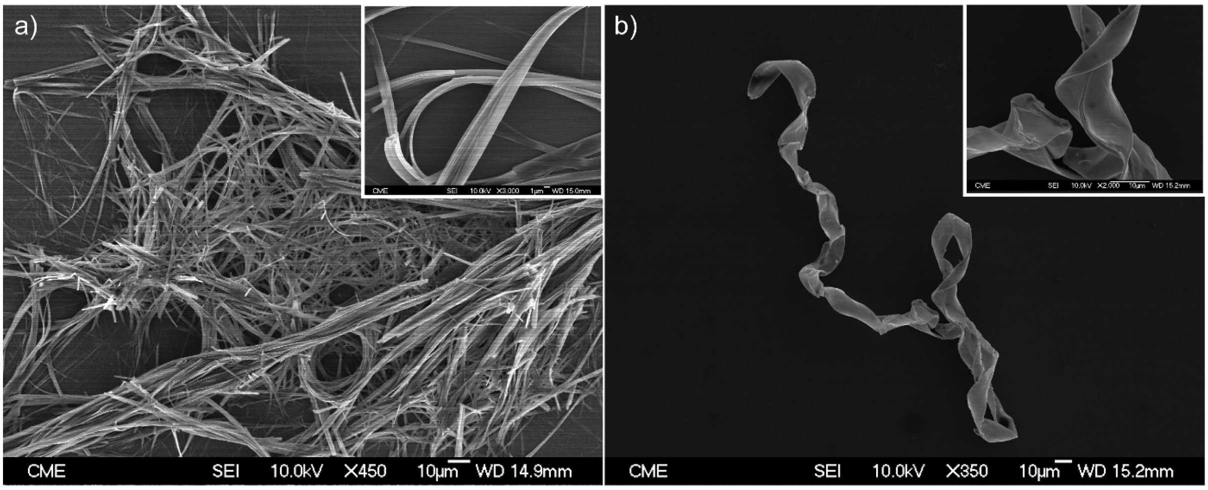


Figure 4. SEM images of the ribbon-like structures formed by the cooperative self-assembly of trisamides **1** (a) and the 9/1 mixture of **1** and **2** (b). The scale in the insets is 1 μm. The samples were prepared by slow diffusion of MCH vapor into dilute THF (1×10^{-4} M) solutions of the corresponding trisamides.

1 and **2** by scanning electron microscopy (SEM). The slow diffusion of MCH vapors into a 1×10^{-4} M solution of **1** in THF gives rise to a white suspension formed by strongly stacked fibrils organized into ribbon-like structures (Figure 4a and Figure S8, Supporting Information). Similarly to some other chiral molecules,[18] trisamide **2** is not able to self-assemble forming organized supramolecular structures as demonstrated by the corresponding SEM images (Figure S9, Supporting Information). Remarkably, the coassembly of chiral trisamide **2** and achiral **1** in a 1/9 ratio exerts a large influence on the morphology of the supramolecular structures, most probably due to a "sergeants and soldiers" effect.[19,20] The SEM images of the mixture of both amphiphiles **1** and **2** do not show a dense packing of ribbons, but only isolated twisted strips with highly uniform thickness of ∼1 μm are visualized (Figure 4b and Figure S10, Supporting Information). The stereogenic center present in the peripheral chains of **2** propagates the chiral information on the whole aggregate formed by the joint contribution of $\pi-\pi$ stacking between the aromatic units and the H-bonding interactions between the amide functionalities, provoking an amplification of chirality phenomenon.[21]

■ CONCLUSION

To summarize, we have synthesized two amphiphilic C_3-symmetrical OPE-based trisamides that experience a cooperative supramolecular polymerization with very low activation step (6×10^{-5}) in apolar MCH. The large hydrophobic aromatic surface impedes the interaction between the H-bonding amide groups and the polar TEG chains thus favoring a helical organization of the reported trisamides by the operation of triple intermolecular amide $C{=}O \cdots H{-}N$ H-bonds. The hierarchical self-assembly of achiral trisamide **1** forms fibrillar structures that bundle efficiently into flat ribbons. The addition of a small amount of chiral trisamide **2** (10%) to **1** transfers the chirality embedded in the steroegenic centers to the whole supramolecular structure which results in the apparition of twisted strips. Therefore, the utilization of large hydrophobic cores opens new avenues for the development of self-assembly in aqueous media.

■ EXPERIMENTAL SECTION

2-(2-(2-Methoxyethoxy)ethoxy)ethanamine (**3a**) and (*S*)-2-(2-(2-methoxyethoxy)ethoxy)propan-1-amine (**3b**) were prepared by a procedure slightly modified from that previously reported.[13] Compound **5** was prepared according to a previously reported synthetic procedure[22] and showed spectroscopic properties identical to those reported therein.

***N*-(2-(2-(2-Methoxyethoxy)ethoxy)ethyl)-4-iodobenzamide (4a).** To a stirred solution of 4-iodobenzoic acid (1.72 g, 6.92 mmol) in dry dichloromethane (30 mL) at 0 °C under argon atmosphere were slowly added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (1.46 g, 7.61 mmol) and 4,4-dimethylaminopyridine (DMAP) (0.93 g, 7.61 mmol). The reaction mixture was stirred for 15 min, and then 2-(2-(2-methoxyethoxy)ethoxy)ethanamine (1.24 g, 7.61 mmol) was added slowly. The reaction mixture was stirred overnight under room temperature. The reaction mixture was washed with solutions of HCl (1 N), NaOH (3 M), and water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, $CHCl_3/CH_3OH$ 40:1) to afford **4a** as a yellow oil (1.44 g, 53%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72 (2H, H_b, d, J = 8.6 Hz); 7.50 (2H, H_a, d, J = 8.6 Hz); 6.98 (1H, H_c, br); 3.63−3.47 (12H, $H_{d+e+f+g+h+i}$, m); 3.28 (3H, H_j, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 137.6, 134.0, 128.8, 98.3, 71.9, 70.5, 70.5, 70.2, 69.6, 60.0, 39.8. FTIR (neat): 618, 660, 753, 846, 938, 1007, 1031, 1106, 1196, 1304, 1353, 1478, 1540, 1588, 1645, 2875, 3064, 3337 cm^{-1}. HRMS-ESI: calcd for $C_{14}H_{20}INO_4$ $[M + H]^+$ 394.04371, found 394.04219.

***N*-((*S*)-2-(2-(2-Methoxyethoxy)ethoxy)propyl)-4-iodobenzamide (4b).** To a stirred solution of 4-iodobenzoic acid (1.63 g, 6.60 mmol) in dry dichloromethane (30 mL) at 0 °C under argon atmosphere were slowly added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (1.40 g, 7.25 mmol) and 4-4-dimethylaminopyridine (DMAP) (0.89 g, 7.25 mmol). The reaction mixture was stirred for 15 min, and then (*S*)-2-(2-(2-methoxyethoxy)ethoxy)propan-1-amine (**3b**) (0.94 g, 7.25 mmol) was added slowly. The reaction mixture was stirred overnight under room temperature. The reaction mixture was washed with solutions of HCl (1 N), NaOH (3 M), and water. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, $CHCl_3/CH_3OH$ 40:1) to afford **4b** as a colorless liquid

(0.88 g, 33%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.80 (2H, H_b, d, $J = 8.6$ Hz); 7.57 (2H, H_a, d, $J = 8.6$ Hz); 7.03 (1H, H_c, br); 3.80 (2H, $H_{d \text{ or } d'+e}$, m); 3.69−3.47 (8H, $H_{g+h+i+j}$, m); 3.29 (3H, H_k, s); 3.20 (1H, $H_{d \text{ or } d'}$, m); 1.22 (3H, H_f, d, $J = 6.2$ Hz). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 166.7, 137.6, 134.2, 128.9, 98.1, 74.8, 71.8, 70.7, 70.4, 67.9, 58.9, 44.9, 17.6. FTIR (neat): 651, 751, 844, 931, 1007, 1032, 1103, 1195, 1292, 1380, 1477, 1538, 1588, 1648, 2877, 2973, 3076, 3331 cm^{-1}. HRMS-ESI: calcd for $C_{15}H_{22}INO_4$ $[M + H]^+$ 408.05936, found 408.05843.

Compound 1. *N*-(2-(2-(2-Methoxyethoxy)ethoxy)ethyl)-4-iodobenzamide (**4a**) (1.44 g, 3.7 mmol), 1,3,5-triethynylbenzene (0.18 g, 1.2 mmol), copper(I) iodide (0.01 g, 0.07 mmol), and bis(triphenylphosphine)palladium(II) chloride (0.04 g, 0.06 mmol) were dissolved in dry triethylamine (40 mL) and dry THF (10 mL). The mixture was subjected to several vacuum/argon cycles and heated at 70 °C for 40 h. The solvent was evaporated under reduced pressure, and the residue was washed with HCl (1 N) and NH_4Cl and extracted with chloroform. After evaporation of the solvent, the residue was purified by column chromatography (silica gel, $CHCl_3/CH_3OH$ 50:1) to afford **1** as a yellow solid (0.65 g, 56%). ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.84 (6H, H_c, d, $J = 8.7$ Hz); 7.71 (3H, H_a, s); 7.61 (6H, H_b, d, $J = 8.7$ Hz); 6.87 (3H, H_d, br); 3.70−3.54 (36H, $H_{e+f+h+i+j}$, M); 3.35 (9H, H_k, s). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 166.7, 134.5, 131.7, 127.3, 125.8, 123.8, 90.0, 89.7, 71.9, 70.5, 70.5, 70.2, 69.8, 59.0, 39.9. FTIR (neat): 679, 765, 855, 936, 1024, 1105, 1196, 1304, 1353, 1456, 1500, 1546, 1607, 1644, 2875, 3066, 3338 cm^{-1}. HRMS-ESI: calcd for $C_{54}H_{64}N_3O_{12}$ $[M + H]^+$ 946.44845, found 946.44755.

Compound 2. *N*-((*S*)-2-(2-(2-Methoxyethoxy)ethoxy)propyl)-4-iodobenzamide (**4b**) (0.88 g, 2.16 mmol), 1,3,5-triethynylbenzene (0.10 g, 0.68 mmol), copper(I) iodide (0.008 g, 0.04 mmol), and bis(triphenylphosphine)palladium(II) chloride (0.008 g, 0.04 mmol) were dissolved in dry triethylamine (5 mL) and dry THF (10 mL). The mixture was heated at 70 °C for 36 h. The solvent was evaporated under reduced pressure, and the residue was washed with HCl (1 N) and NH_4Cl and extracted with chloroform. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, $CHCl_3/CH_3OH$ 50:1) to afford **2** as a brown oil (0.48 g, 72%). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.85 (6H, H_c, d, $J = 8.5$ Hz); 7.70 (3H, H_a, s); 7.60 (6H, H_b, d, $J = 8.5$ Hz); 7.03 (3H, H_d, dd, $J_1 = 6.4$ Hz, $J_2 = 6.6$ Hz); 3.70−3.33 (30H, $H_{e \text{ or } e'+f+h+i+j+k}$, m); 3.31 (9H, H_l, s); 3.26 (3H, $H_{e \text{ or } e'}$, m); 1.23 (9H, H_g, d, $J = 6.2$ Hz). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 166.7, 134.6, 134.4, 131.7, 127.3, 125.7, 123.9, 90.1, 89.6, 74.8, 71.9, 70.8, 70.4, 68.0, 58.9, 44.9, 17.7. FTIR (neat): 681, 767, 854, 933, 956, 1025, 1196, 1295, 1377, 1456, 1499, 1543, 1607, 1647, 2876, 2924, 2973, 3061 cm^{-1}. HRMS-ESI: calcd for $C_{57}H_{68}N_3O_{12}$ $[M - H]^+$ 986.48085, found 946.48452.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details and supplementary figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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