Syntheses of Ligands Containing Two and Three 2,2′-(Bisamino)diphenyl Ether Units Designed for Molecular Self-Assembly on Lithiation

Peter R. Ashton,[a] Bernd Hörner,[a] Oldrich Kocian,[a] Stephan Menzer,[b] Andrew J.P. White,[b] J. Fraser Stoddart,*[a] David J. Williams[b]
[a] School of Chemistry, University of Birmingham, Edgbaston, Birmingham B152TT, UK
[b] Department of Chemistry, Imperial College, South Kensington, London SW72AY, UK
Fax +44(121)4143531

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The syntheses of polyamines containing two or three 2,2′-(bisamino)diphenyl ether units linked together, designed for self-assembly following lithiation, are reported. The X-ray crystal structures of two of the bis[2,2′-(bisamido)diphenyl ethers] are described. The ligand, which is linked by an ethylene glycol spacer, exhibits a coiled conformation constrained by intramolecular hydrogen bonds and supplemented by [CH-π] interactions. The ligand, which is linked by a more rigid bridge, containing a paraphenylene unit, displays a stretched conformation stabilised by intramolecular hydrogen bonds and intramolecular T-type aromatic-aromatic edge-to-face interactions.

It is well established that lithium amides generally exist as complex superstructures[1] held together by noncovalent bonds, i.e. they are supramolecular species. This complexity arises from the high propensity of amidolithium compounds to self-associate and form higher aggregates – a phenomenon that depends markedly upon the choice of the solvent and the precise reaction conditions. The dilithiation of the acyclic aromatic diamines, 2,2′-bis(2-methoxyethylamino)diphenyl ether (**1**) and 2,2′-bis(*N*,*N*-dimethylethylenediamino)diphenyl ether (**2**), which can be considered as acyclic polyethers, resulted in the formation of the dimeric lithium amides **3** and **4**[2-4] (Scheme 1).

1 : Y = OMe
2 : Y = NMe$_2$

3 : Y = OMe
4 : Y = NMe$_2$

Scheme 1

The X-ray crystal structure analyses of the lithium amides **3** and **4** reveal an adamantanoid metal-containing core (Figure 1) as a consequence of the self-recognition and self-assembly involving the two metallated subunits.

The dimeric and geometric characteristics of the solid-state structures, together with the evidence of the retention of the solid-state structure in solution, suggest that, by using this structural motif, a new family of molecular assemblies and supramolecular arrays can be constructed around suitably chosen cyclic and acyclic ligands.

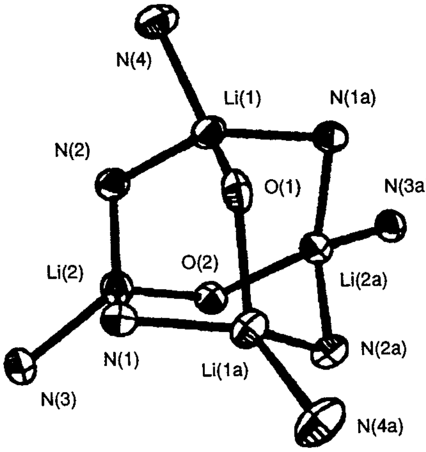
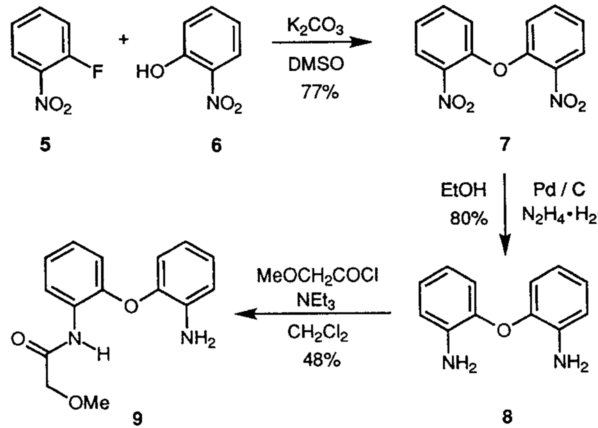


Figure 1. The adamantanoid $Li_4O_2N_8$ central core of the lithium amides **3** and **4**

This paper describes the synthesis of extended ligands, i.e. polyamines[5] containing two or three 2,2′-(bisamino)diphenyl ether units linked together and capable of self-assembly following lithiation.

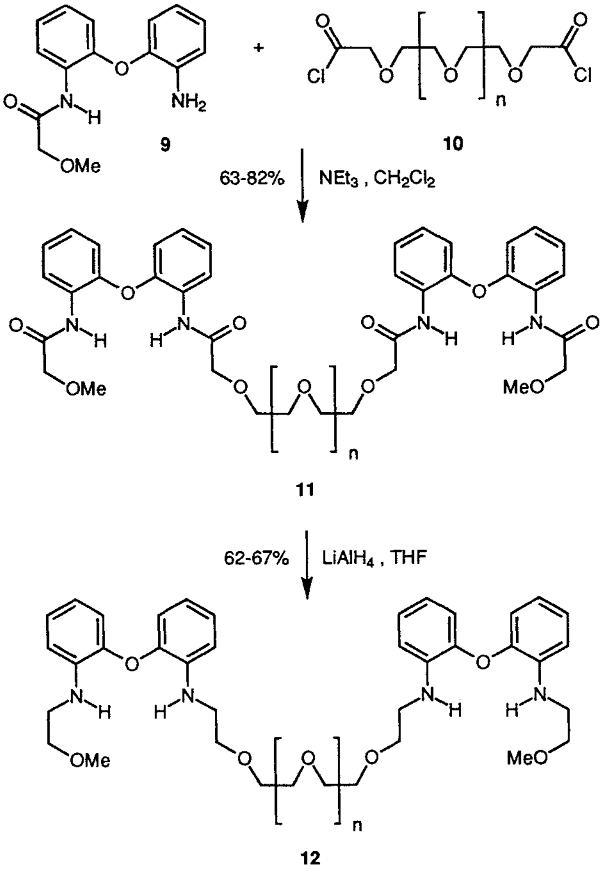
The synthesis of the monofunctionalised key component (Scheme 2) starts from bis(2-nitrophenyl) ether (**7**) which is easily available in 77 % yield by reaction of 1-fluoro-2-nitrobenzene (**5**) with 2-nitrophenol (**6**) and potassium carbonate in DMSO.[6] Bis(2-nitrophenyl) ether (**7**) was then reduced with hydrazine hydrate in the presence of 10 % palladium on charcoal in ethanol[7] to give bis(2-aminophenyl) ether (**8**) in 80 % yield. The diamine **8** was reacted with commercially available methoxyacetyl chloride in dichloromethane using triethylamine as the base.



Scheme 2

The reaction, which was carried out with **8** at high dilution, involves addition of methoxyacetyl chloride very slowly to prevent attack at the second amino group. Purification and separation from the byproduct bis(2-methoxyacetamido)diphenyl ether were performed by column chromatography, producing 2-amino-2′-(2-methoxyacetamido)diphenyl ether (**9**) in 48 % yield.

The nature of the linker between these 2,2′-(bisamino)diphenyl ether units is crucial for the onset of self-assembly following lithiation. It is imperative that the linker is sufficiently large and that it displays the required balance between flexibility in some of its parts and rigidity in other parts. Ethylene glycol dicarbonyl compounds,[8] which have been used widely in azacrown ether syntheses[5] appeared to be appropriate linkers. Acylation of the 2-amino-2′-(2-methoxyacetamido)diphenyl ether (**9**) with the dicarbonyl dichlorides **10** in dichloromethane, using triethylamine as the base, gave the ethylene glycol linked bis[2,2′-(bisamido)diphenyl ether] compounds **11** in 63–82 % yields. Reductions of **11** with lithium aluminium hydride in THF, and their subsequent purifications by column chromatography, afforded the ethylene glycol linked bis[2,2′-(bisamino)diphenyl ethers] **12** in 62–67 % yields (Scheme 3).



Scheme 3

10,11,12	a	b	c
n	0	1	2

Single crystals of **11a**, suitable for X-ray crystallographic structure determination, were grown by vapour diffusion of hexane into a solution of **11a** in ethyl acetate and yielded the solid-state structure shown in Figure 2.[9] Compound **11a** crystallises as a coiled chain with C_2 symmetry about an axis passing through the central CH_2CH_2 linkage. The conformation is constrained by intramolecular hydrogen bonds between the amide protons and the ether oxygen atoms, supplemented by an additional four [CH-π] interactions involving one of the hydrogen atoms on each of the four methylene groups bonded to the amide functions and all four aromatic rings. The [H···ring centroid] distances are 2.55 and 2.60 Å and the [H···ring centroid] vectors are inclined by 85° to their respective ring planes.

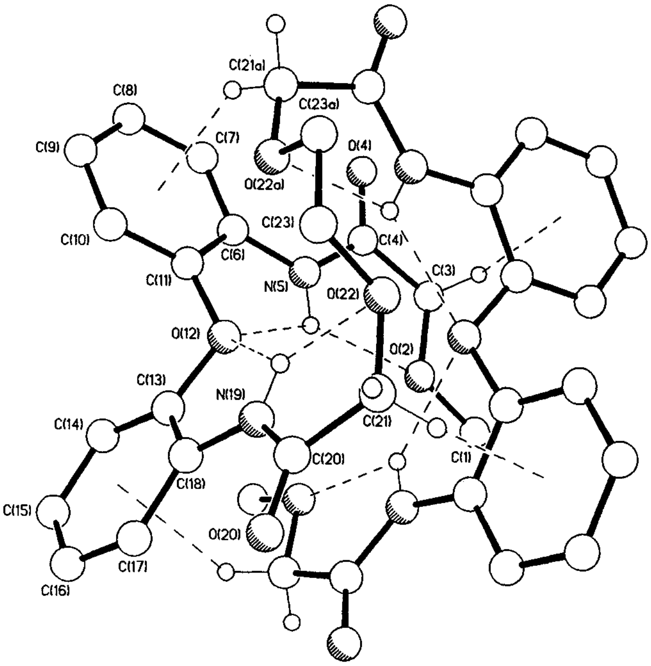


Figure 2. Ball-and-stick representation of the X-ray crystal structure of the bis[2,2′-(bisamido)diphenyl ether] **11a**

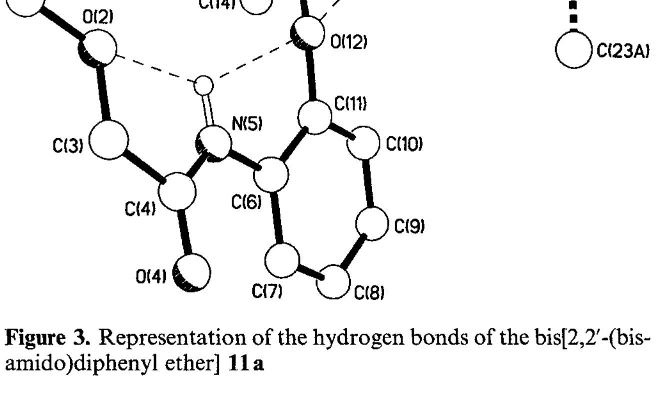


Figure 3. Representation of the hydrogen bonds of the bis[2,2′-(bisamido)diphenyl ether] **11a**

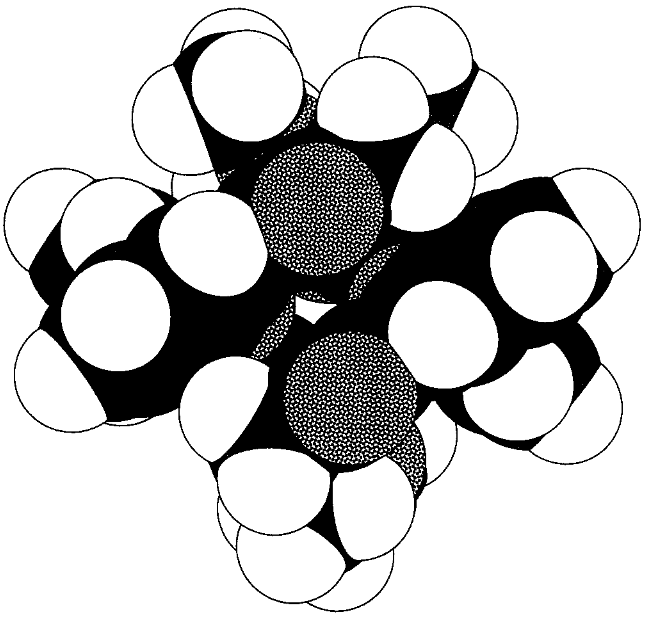


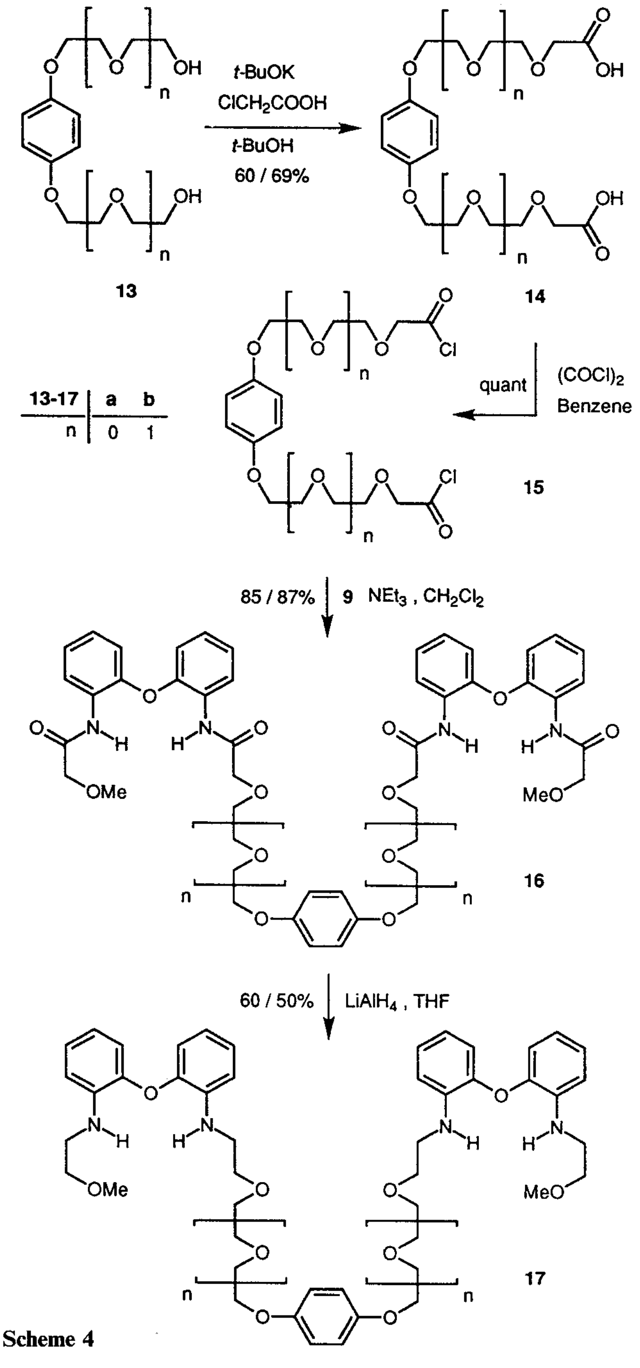
Figure 4. Space-filling representation of the X-ray structure of **11a**, illustrating the tightly coiled conformation

All amide groups are oriented essentially coplanar with respect to their associated phenyl ethers. All carbonyl oxygen atoms are directed away from the centre of the molecule. The diphenyl ether units adopt a skewed conformation with twists of 41° and 42° about the two C-O-bonds.[10,11] The length of the hydrogen bond between the amide hydrogen atom and the methoxy oxygen atom is 2.24 Å, whilst the length between the amide hydrogen atom and the polyether oxygen atom is 2.26 Å. The separations between the amide hydrogen atoms and the diphenyl ether oxygen atoms are 2.23 Å and 2.30 Å (Figure 3).

The effect of these combined intramolecular interactions is to produce the tightly coiled conformation portrayed in Figure 2 – a feature which is emphasised by the space filling representation of the molecule illustrated in Figure 4.

The X-ray crystal structure analysis of the bis[2,2'-(bisamido)diphenyl ether] **11a** shows that, because of the flexibility of the linker, the extended chain structure is disfavoured and that, on account of intramolecular hydrogen bonds of amide hydrogen atoms with ether oxygen atoms, a coiled structure is formed. Although hydrogen bonds between amine hydrogen atoms and ether oxygen atoms in the bis[2,2'-(bisamino)diphenyl ethers] **12** are weaker, it is likely that **12** also tend to form coiled conformations, which would be unfavourable for sustaining molecular self-assemblies on lithiation. To prevent such a coiling, it was decided next to introduce a rigid para-phenylene bridge into the linker. The greater rigidity of this linker should force the ligand to adopt a stretched conformation. The general scheme for the synthesis of these ligands is shown (Scheme 4).

1,4-Bis(2-hydroxyethoxy)benzene (**13a**) and 1,4-bis[2-(2-hydroxyethoxy)ethoxy]benzene (**13b**) were deprotonated separately with potassium *tert*-butoxide in *tert*-butanol and reacted with chloroacetic acid to produce the expected diacids **14** in 60 and 69% yields, respectively. Conversions of the diacids **14** into their dicarbonyl dichlorides **15** were achieved quantitatively by reactions with oxalyl chloride and DMF in benzene. Acylation of the 2-amino-2'-(2-methoxyacetamido)diphenyl ether (**9**) with dicarbonyl dichlorides **15** in dichloromethane, using triethylamine as the base, gave the bis[2,2'-(bisamido)diphenyl ether] compounds **16** in 85 and 87% yields, respectively. These compounds **16** were finally reduced by lithium aluminium hydride in THF to produce the desired bis[2,2'-(bisamino)diphenyl ether] compounds **17** in 60 and 50% yields, respectively.



Scheme 4

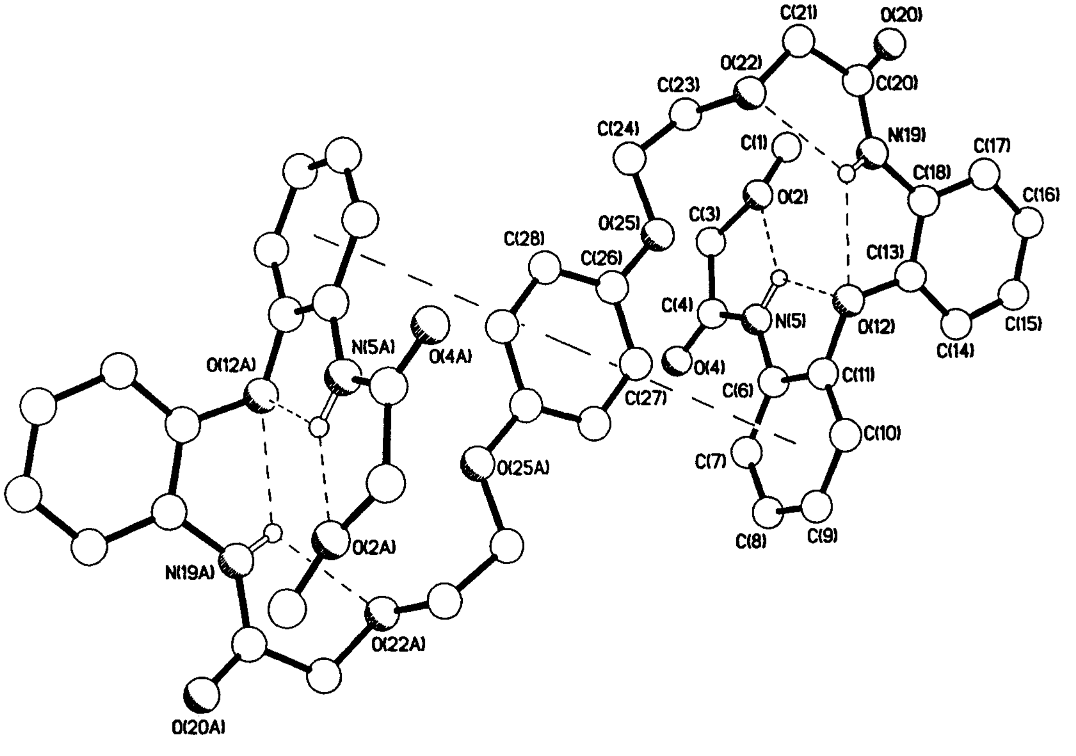
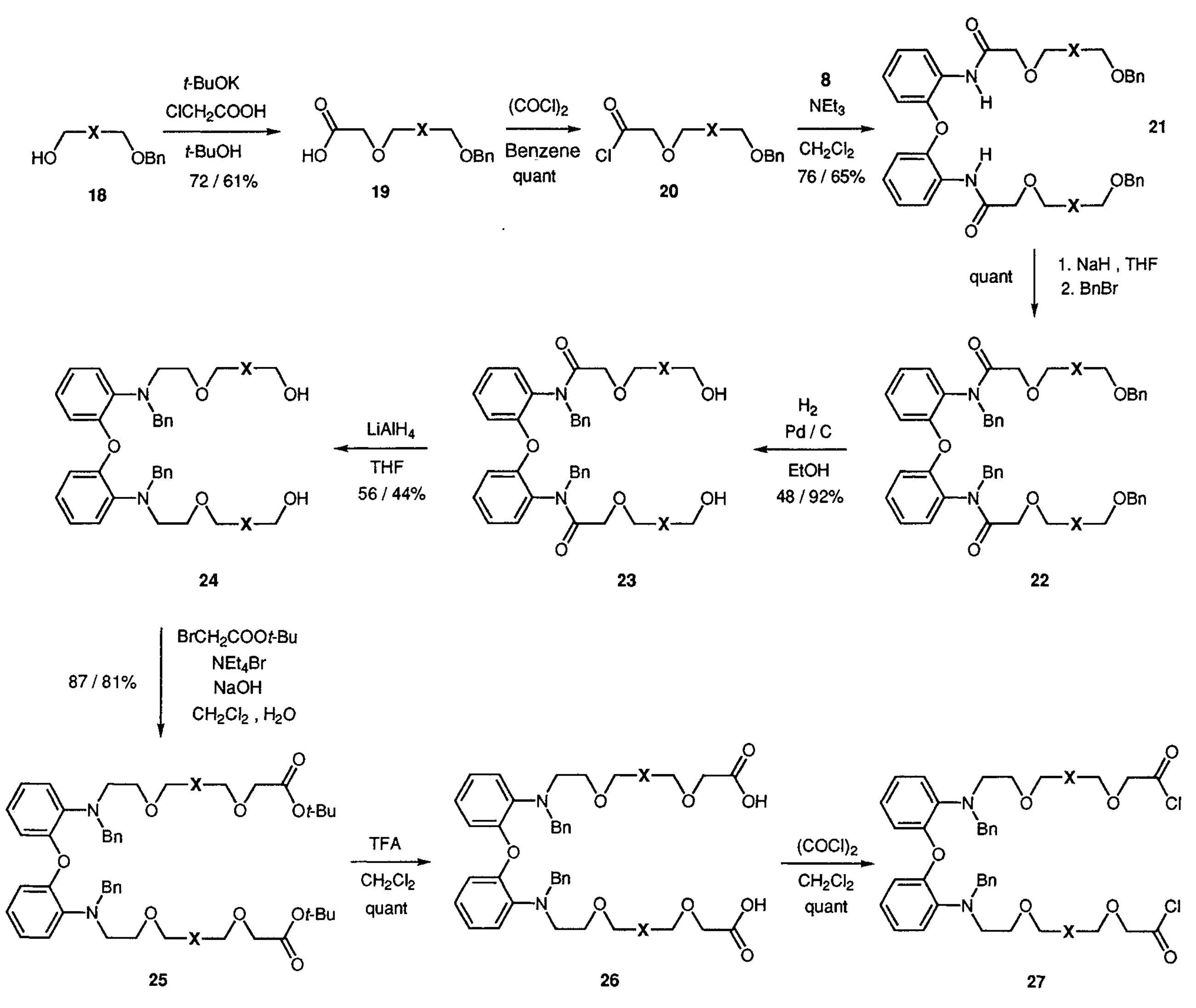
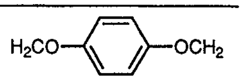


Figure 5. Ball-and-stick representation of the X-ray crystal structure of the bis[2,2'-(bisamide)diphenyl ether] **16a**, revealing the stretched conformation

In order to prove that the introduction of a rigid para-phenylene bridge forces the bis[2,2'-(bisamido)diphenyl ether] compounds **16** to adopt a stretched conformation, an X-ray structural analysis was carried out.[12] Single crystals were grown by vapour diffusion of hexane into a solution of **16a** in chloroform. In the solid state, **16a** has the desired extended conformation (Figure 5) with crystallographic C_i symmetry. Once again, it is stabilised by a combination of [NH···O] hydrogen bonds and intramolecular T-type aromatic-aromatic edge-to-face interactions. The length of the hydrogen bond between the amide hydrogen atom and the methoxy oxygen atom is 2.09 Å, whilst the length between the amide hydrogen atom and the polyether oxygen atom is 2.26 Å.The separations between the amide hydrogen atoms and the diphenyl ether oxygen atoms are 2.25 Å and 2.31 Å, respectively. The aromatic-aromatic edge-to-face interactions are fairly weak with the [ring centroid···ring centroid] separation being 5.31 Å. The associated [H···ring centroid] distance is 3.02 Å and the [CH···ring centroid] angle is 167°. As observed in the solid-state structure of **11a**, in **16a** there is a retention of coplanarity between the amide groups and their associated phenyl rings. The molecules are loosely linked in the crystal by weak [CH···O] hydrogen bonds between one of the *ortho* diphenyl ether hydrogen atoms in one molecule and the C 20 carbonyl oxygen atom of another and vice versa. The [C···O], [H···O] distances are 3.31, 2.36 Å, and the associated [CH···O] angle is 171°.

The synthesis of ligands containing three [2,2'-(bisamino)diphenyl ether] units linked together were performed by multistep sequences (Schemes 5,6), starting either from 2-benzyloxyethanol (**18a**) or from 1-(2-hydroxyethoxy)-4-(2-benzyloxyethoxy)benzene (**18b**). Deprotonations of **18** with potassium *tert*-butoxide in *tert*-butanol, and their subsequent reaction with chloroacetic acid, afforded the expected acids **19** in 72 and 61 % yields, respectively. The acids **19** were converted quantitatively into their carbonyl chlorides **20** by reactions with oxalyl chloride and DMF in benzene. Bis(2-aminophenyl) ether (**8**) was then acylated with **20** in dichloromethane, using triethylamine as the base, to yield (76 and 65 %) the bisamides **21**. In order to prevent, in following steps, the deprotonation of the primary amides in **21**, they were protected as *N*-benzyl derivatives. Thus, the bisamides **21** were deprotonated with sodium hydride in THF, and reacted with benzyl bromide to give the tetrabenzyl compounds **22** in quantitative yields. Selective *O*-debenzylation of the tetrabenzyl compounds **22** could then be performed by hydrogenolysis in the presence of 10 % palladium on charcoal as the catalyst, and yielded 48 and 92 % of *N*-benzylated bisamides **23**. In order to avoid intramolecular nucleophilic attack of the intermediate alkoxides, which have to be generated in the next step, at the amide carbonyl functions, and could cause the cleavage of the amides, the *N*-benzylated bisamides **23** were reduced with lithium aluminium hydride in THF to afford the *N*-benzylated bisamines **24** in 56 and 44 % yields. Introduction of the carbonyl groups were then achieved by mild phase-transfer reactions, using *tert*-butyl bromoacetate in dichloromethane with aqueous sodium hydroxide as the base, producing the bis-*tert*-butyl esters **25** in 87 and 81 % yields. Saponifications of the *tert*-butyl esters **25** with trifluoroacetic acid in dichloromethane yielded quantitatively the bisacids **26**, which were then converted



18 - 27	a	b
X	—	

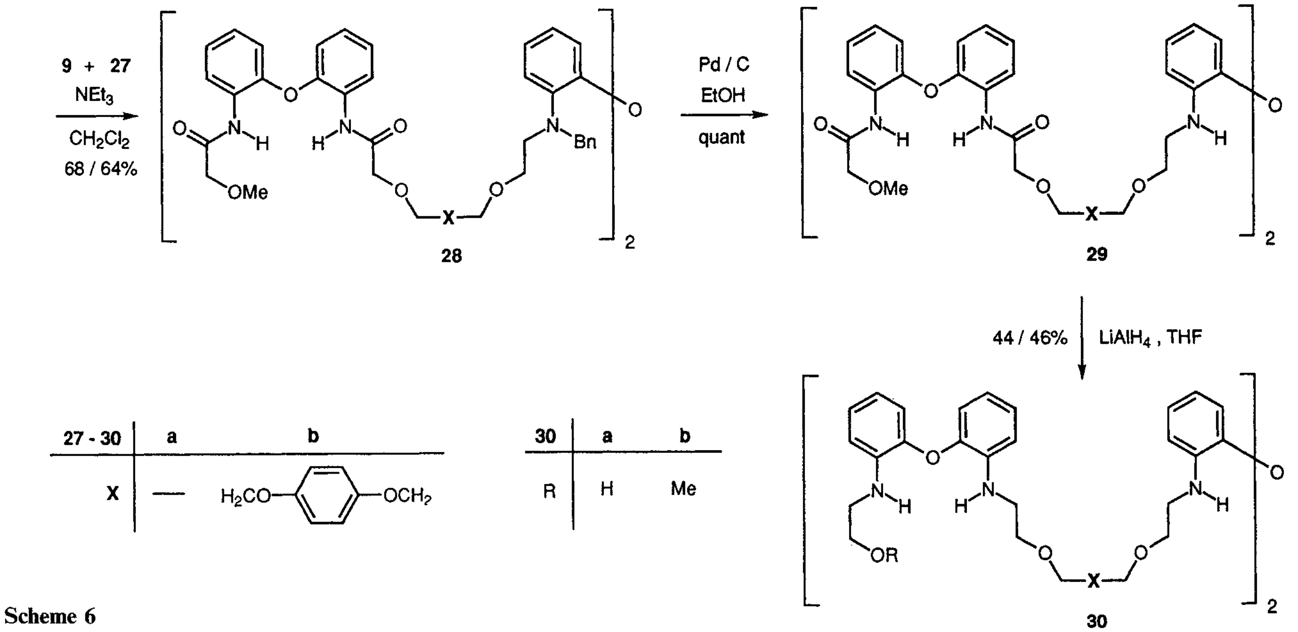
Scheme 5

in quantitative yields into the biscarbonyl chlorides **27** with oxalyl chloride and DMF in dichloromethane (Scheme 5).

Acylation of the 2-amino-2′-(2-methoxyacetamido)diphenyl ether (**9**) with the biscarbonyl chlorides **27** in dichloromethane and triethylamine gave, in 68 and 64% yields, the first derivatives **28** containing three diphenyl ether units. *N*-Debenzylations of **28** by hydrogenolysis in the presence of 10% palladium on charcoal as the catalyst afforded quantitatively the unprotected **29**. The final step, leading to the desired compounds were the reductions of the four carbamoyl groups in **29** with lithium aluminium hydride in THF to produce the tris[2,2′-(bisamino)diphenyl ether] compounds **30**. While **30 b** was isolated as the expected bismethoxy compound in 46% yield, during the reduction of **29 a** an unexpected cleavage of the methoxy groups[13] occurred under the reaction conditions and the main product was the bishydroxy derivative **30 a** in 44% yield (Scheme 6).

In conclusion, we have reported the syntheses of polyamines containing two or three 2,2′-(bisamino)diphenyl ether units linked together. We have demonstrated the influence of the nature of the linker between two 2,2′-(bisamido)diphenyl ether units on the conformation of these molecules and have described the intramolecular interactions which force these molecules to adopt a particular conformation. Studies of molecular self-assemblies obtained on lithiation of the ligands described in this paper will be described elsewhere.

Solvents were purified and dried using literature methods where necessary or they were used directly as obtained from the suppliers. Reagents were employed as purchased from Aldrich. Thin layer chromatography (TLC) was carried out using aluminium sheets precoated with silica gel 60F (Merck 5554). The plates were inspected by UV-light prior to development with iodine vapour or by treatment with ceric ammonium molybdate reagent and subsequent heating. Column chromatography was performed using silica gel 60 (Merck 7734, 0.063–0.200 mm). Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. Elemen-



Scheme 6

tal analyses were performed in the University of Sheffield and the University of Birmingham Microanalytical Laboratories. Mass spectra (EI and CI) were recorded on either Kratos Profile or VG Prospec mass spectrometers. Fast Atom Bombardment mass spectra (FABMS) were obtained from a Kratos MS80RF instrument equipped with a saddle-field source (Ion Tech Limited) operating at 8 keV using a krypton primary atom beam. Liquid Secondary Ion mass spectra (LSIMS) were recorded on a VG Zabspec spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC 300 (300 MHz) or a Bruker AMX 400 (400 MHz). ^{13}C NMR spectra were recorded on a Bruker AC 300 (75.5 MHz) using the JMOD pulse sequence. All chemical shifts are quoted in ppm on the δ scale using TMS or the solvent as an internal standard. Coupling constants are expressed in Hz.

Bis(2-nitrophenyl) Ether (7):

A suspension of 2-nitrophenol (**6**) (41.7 g, 0.30 mol), 1-fluoro-2-nitrobenzene (**5**) (31.6 mL, 0.30 mol) and K_2CO_3 (91.2 g, 0.66 mol) in DMSO (600 mL) was stirred at 95 °C. After 16 h, the mixture was cooled and poured into ice/water (1.5 L). The precipitated solid was filtered off and washed thoroughly with H_2O. Recrystallisation of the residual solid from EtOH afforded 60.1 g (77 %) of **7** as yellow crystals, mp 116 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.06 (dd, J = 7.3 and 1.3 Hz, 2 H, ArH), 7.32 (ddd, J = 7.0, 7.0 and 1.2 Hz, 1 H, ArH), 7.59 (ddd, J = 7.0, 7.0 and 1.4 Hz, 1 H, ArH), 8.04 (dd, J = 7.2 and 1.4 Hz, 2 H, ArH).

MS (70 eV, EI): m/z (%): 260 (50) [M$^+$], 122 (100).

Bis(2-aminophenyl) Ether (8):

$NH_2NH_2 \cdot H_2O$ (58.2 mL, 1.2 mol) was added dropwise to a suspension of **7** (52.0 g, 020 mol) and catalyst (8 g, 10 % Pd/C) in EtOH (1400 mL). The mixture was heated under reflux for 1 h, cooled down to r.t., and filtered through a pad of Celite. The solvent was evaporated, the residue dissolved in $CHCl_3$, washed with brine, dried (Na_2SO_4), and concentrated. The product crystallised upon standing, yielded 32.0 g (80 %) of **8** as a white solid, mp 61–63 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.89 (br s, 4 H, NH_2), 6.67–6.74 (m, 2 H, ArH), 6.78–6.84 (m, 4 H, ArH), 6.92–6.99 (m, 2 H, ArH).

MS (70 eV, EI): m/z (%): 200 (92) [M$^+$], 93 (100).

$C_{12}H_{12}N_2O$ (200.2): calcd C 71.98, H 6.04, N 13.99; found C 71.73, H 5.82, N 14.16.

2-Amino-2′-(2-methoxyacetamido)diphenyl Ether (9):

A solution of methoxyacetyl chloride (5.43 g, 50 mmol) in CH_2Cl_2 (600 mL) was added dropwise during 12 h to a solution of **8** (10.0 g, 50 mmol) and Et_3N (7.59 g, 75 mmol) in CH_2Cl_2 (600 mL). After additional stirring for 16 h at r.t., the solvent was partially evaporated and treated with dilute HCl (100 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent afforded a residue, which was subjected to column chromatography [silica gel, EtOAc/hexane 1 : 1] to yield 6.54 g (48 %) of **9** as a white solid, mp 148 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.43 (s, 3 H, CH_3), 3.86 (br s, 2 H, NH_2), 4.02 (s, 2 H, CH_2), 6.69–6.85 (m, 4 H, ArH), 6.97–7.04 (m, 3 H, ArH), 8.38–8.41 (m, 1 H, ArH), 8.89 (br s, 1 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 59.4 (CH_3), 72.4 (OCH_2), 115.9, 116.6, 118.8, 120.0, 121.2, 123.4, 124.6, 125.4, 127.9, 138.6, 142.4, 146.4 (ArC), 167.8 (C=O).

MS (70 eV, EI): m/z (%): 272 (95) [M$^+$], 183 (100).

$C_{15}H_{16}N_2O_3$ (272.3): calcd C 66.16, H 5.92, N 10.29; found C 66.19, H 5.93, N 10.43.

Synthesis of Bis[2,2′-(bisamido)diphenyl Ethers] (11); General Procedure:

A solution of the ethylene glycol dicarbonyl dichloride **10** (5.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of **9** (2.72 g, 10 mmol) and Et_3N (1.52 g, 15 mmol) in CH_2Cl_2 (100 mL). After additional stirring for 16 h at r.t., the solution was treated with dilute HCl (100 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was evaporated and the remaining oil dissolved in EtOAc (30 mL), from which the product crystallised upon standing to afford **11**.

11 a:

Colourless crystals, 2.61 g (76 %), mp 147 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.27 (s, 6 H, CH_3), 3.52 (s, 4 H, CH_2), 3.84, 3.88 (s, 4 H, $CH_2C{=}O$), 6.78–6.82 (m, 4 H, ArH), 6.98–7.06 (m, 4 H, ArH), 7.11–7.17 (m, 4 H, ArH), 8.33–8.37 (m, 4 H, ArH), 8.73, 8.85 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 59.2 (CH_3), 70.9, 70.9, 72.1 (OCH_2), 117.6, 118.0, 121.5, 121.9, 124.6, 124.8, 124.9, 128.7, 145.5, 145.5 (10 of 12 ArC), 167.7, 167.8 (C=O).

MS (70 eV, EI): m/z (%): 686 (90) [M$^+$], 641 (100).

$C_{36}H_{38}N_4O_{10}$ (686.7): calcd C 62.96, H 5.58, N 8.16; found C 63.04, H 5.53, N 7.95.

11b:

Colourless crystals, 3.00 g (82 %), mp 120 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.33$ (s, 6 H, CH_3), 3.37–3.41, 3.43–3.47 (m, 4 H, CH_2), 3.96, 3.99 (s, 4 H, $CH_2C{=}O$), 6.81–6.85, 7.01–7.08, 7.11–7.18, 8.32–8.42 (m, 4 H, ArH), 8.80, 8.87 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 59.3$ (CH_3), 70.4, 70.9, 71.1, 72.2 (OCH_2), 117.5, 118.0, 121.7, 121.9, 124.6, 124.7, 125.0, 128.7, 128.9, 145.2, 145.7 (11 of 12 ArC), 167.8, 168.0 (C=O).

MS (70 eV, EI): *m/z* (%): 730 (22) [M + H$^+$], 239 (100).

$C_{38}H_{42}N_4O_{11}$ (730.8): calcd C 62.45, H 5.79, N 7.67; found C 62.25, H 5.81, N 7.56.

11c:

The solvent was evaporated and the remaining oil subjected to column chromatography [silica gel, 6 % $MeOH/CH_2Cl_2$] to yield 2.44 g (63 %) of a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.34$ (s, 6 H, CH_3), 3.37 (s, 4 H, OCH_2CH_2O), 3.42–3.46, 3.56–3.60 (m, 4 H, CH_2), 3.97, 4.10 (s, 4 H, $CH_2C{=}O$), 6.81–6.86, 7.01–7.08, 7.12–7.18, 8.32–8.44 (m, 4 H, ArH), 8.83, 8.91 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 59.3$ (CH_3), 70.3, 70.5, 71.0, 71.1, 72.2 (OCH_2), 117.5, 118.0, 121.6, 122.0, 124.6, 124.7, 125.0, 128.6, 128.9, 145.2, 145.8 (11 of 12 ArC), 167.9, 168.2 (C=O).

MS (FAB): *m/z* (%): 775 (99) [M + H$^+$], 357 (100).

$C_{40}H_{46}N_4O_{12}$ (774.8): calcd C 62.00, H 5.98, N 7.23; found C 60.97, H 6.05, N 7.04.

Reduction of 11 to the Corresponding Bis[2,2′-(bisamino)diphenyl Ethers] (12); General Procedure:

A solution of the bis[2,2′-(bisamido)diphenyl ether] **11** (5 mmol) in anhyd THF (80 mL) was added dropwise to a refluxing slurry of $LiAlH_4$ (1.90 g, 50 mmol) in anhyd THF (120 mL). The mixture was heated under reflux for an additional 16 h. It was then cooled to 0 °C and excess $LiAlH_4$ was destroyed by addition of H_2O/THF (1 : 1). The precipitate was removed by filtration and washed with THF (2 × 80 mL) and EtOAc (2 × 80 mL). The combined filtrates were evaporated and the remaining oil was purified by column chromatography [silica gel, EtOAc/hexane 10 : 2].

12a:

Yellow oil, 2.11 g (67 %).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.28$–3.36 (m, 8 H, CH_2), 3.33 (s, 6 H, CH_3), 3.54 (s, 4 H, OCH_2CH_2O), 3.56–3.59 (m, 4 H, CH_2), 3.62–3.66 (m, 4 H, CH_2), 4.60 (br s, 4 H, NH), 6.55–6.62 (m, 4 H, ArH), 6.68–6.75 (m, 8 H, ArH), 6.94–7.01 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 43.4$, 43.4 (NCH_2), 58.8 (CH_3), 69.8, 70.5, 71.1 (OCH_2), 111.4, 111.5, 116.9, 116.9, 117.5, 117.9, 124.2, 124.4, 139.9, 140.0, 143.9, 144.2 (ArC).

MS (70 eV, EI): *m/z* (%): 630 (11) [M$^+$], 346 (100).

$C_{36}H_{46}N_4O_6$ (630.8): calcd C 68.55, H 7.35, N 8.88; found C 68.34, H 7.28, N 8.76.

12b:

Yellow oil, 2.09 g (62 %).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.31$–3.35 (m, 8 H, CH_2), 3.33 (s, 6 H, CH_3), 3.55 (s, 8 H, OCH_2CH_2O), 3.56–3.60, 3.62–3.66 (m, 4 H, CH_2), 4.57 (br s, 4 H, NH), 6.55–6.62 (m, 4 H, ArH), 6.70–6.75 (m, 8 H, ArH), 6.94–7.01 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 43.3$, 43.4 (NCH_2), 58.8 (CH_3), 69.7, 70.5, 70.6, 71.1 (OCH_2), 111.3, 111.4, 116.9, 116.9, 117.6, 117.7, 124.2, 124.3, 139.9, 139.9, 144.0, 144.1 (ArC).

MS (70 eV, EI): *m/z* (%): 674 (20) [M + H$^+$], 390 (100).

$C_{38}H_{50}N_4O_7$ (674.8): calcd C 67.63, H 7.47, N 8.30; found C 66.83, H 7.42, N 7.29.

12c:

Yellow oil, 2.26 g (63 %).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.32$–3.37 (m, 8 H, CH_2), 3.34 (s, 6 H, CH_3), 3.54–3.61 (m, 16 H, CH_2), 3.65–3.69 (m, 4 H, CH_2), 4.56 (br s, 4 H, NH), 6.56–6.62 (m, 4 H, ArH), 6.70–6.74 (m, 8 H, ArH), 6.95–7.02 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 43.3$ (1 of 2 NCH_2), 58.8 (CH_3), 69.7, 70.4, 70.5, 70.6, 71.1 (OCH_2), 111.3, 111.3, 116.9, 117.5, 117.7, 124.2, 124.2, 139.9, 143.9, 144.1 (10 of 12 ArC).

MS (FAB): *m/z* (%): 719 (100 [M + H$^+$].

$C_{40}H_{54}H_4O_8$ (718.9): calcd C 66.83, H 7.57, N 7.80; found C 66.43, H 7.73, N 7.68.

1,4-Bis[2-(2-carboxyethoxy)ethoxy]benzene (14a):

Compound **13a** (7.93 g, 40 mmol) was added to a solution of *t*-BuOK (20.2 g, 180 mmol) in *t*-BuOH (200 mL). After stirring for 10 min at r.t., the solution was heated under reflux for 1 h. A solution of $ClCH_2CO_2H$ (7.75 g, 82 mmol) in *t*-BuOH (60 mL) was added and refluxing continued for 36 h. After cooling, the solvent was evaporated, the residue dissolved in H_2O, and washed with Et_2O (2 × 80 mL). The aqueous phase was acidified with 6 M HCl and extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4) and evaporated to obtain 7.54 g (60 %) of **14a** as a white powder, mp 114 °C (EtOAc).

^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): $\delta = 3.88$–3.91 (m, 4 H, CH_2), 4.00–4.03 (m, 4 H, CH_2), 4.19 (s, 4 H, $CH_2C{=}O$), 6.59 (s, 4 H, ArH).

^{13}C NMR (75.5 MHz, CD_3COCD_3, 25 °C): $\delta = 68.6$, 68.7, 70.5 (OCH_2), 116.2, 154.0 (ArC), 171.5 (C=O).

MS (70 eV, EI): *m/z* (%): 314 (50) [M$^+$], 45 (100).

$C_{14}H_{18}O_8$ (314.3): calcd C 53.50, H 5.77; found C 53.40, H 5.66.

1,4-Bis{2-[2-(2-carboxyethoxy)ethoxy]ethoxy}benzene (14b):

13b (5.73 g, 20 mmol) was added to a solution of *t*-BuOK (10.1 g, 90 mmol) in *t*-BuOH (100 mL). After stirring for 10 min at r.t., the solution was heated under reflux for 1 h. A solution of $ClCH_2CO_2H$ (3.87, 41 mmol) in *t*-BuOH (30 mL) was added and refluxing continued for 48 h. After cooling, the solvent was evaporated, the residue dissolved in H_2O, and washed with Et_2O (2 × 80 mL). The aqueous phase was acidified with 6 M HCl and extracted with EtOAc. The organic layers were washed with brine, dried (Na_2SO_4), and evaporated to obtained 5.55 g (69 %) of **14b** as a white powder, mp 78 °C (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 3.88$ (s, 8 H, CH_2), 3.85–3.88 (m, 4 H, CH_2), 4.08–4.12 (m, 4 H, CH_2), 4.19 (s, 4 H, $CH_2C{=}O$), 6.87 (s, 4 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 68.0$, 68.6, 70.1, 70.6, 71.3 (OCH_2), 115.9, 153.1 (ArC), 173.3 (C=O).

MS (70 eV, EI): *m/z* (%): 402 (100) [M$^+$].

$C_{18}H_{26}O_{10}$ (402.4): calcd C 53.72, H 6.51; found C 53.69, H 6.68.

1,4-Bis[2-(2-chlorocarbonylethoxy)ethoxy]benzene (15a) and 1,4-Bis{2-[2-(2-chlorocarbonylethoxy)ethoxy]ethoxy}benzene (15b):

A solution of the diacid **14** (15 mmol), $(COCl)_2$ (9.52 g, 75 mmol), and 5 drops of DMF in benzene (50 mL) was stirred for 16 h at r.t. The solvent and excess $(COCl)_2$ were removed under reduced pressure. Benzene (20 mL) was added, again removed under reduced pressure, and the product dried in vacuo. The dicarbonyl dichloride was usually obtained in quantitative yield and used without further purification.

Bis[2,2′-(bisamido)diphenyl Ethers] (16):

A solution of the dicarbonyl dichloride **15** (6 mmol) in CH_2Cl_2 (50 mL) was addded dropwise to a solution of **9** (2.72 g, 10 mmol) and Et_3N (1.52 g, 15 mmol) in CH_2Cl_2 (100 mL). After additional stirring for 16 h at r.t., the solution was treated with dilute HCl (100 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated.

16a:

Colourless crystals, 3.50 g (85 %), mp 168 °C (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.30$ (s, 6 H, CH_3), 3.79–3.82 (m, 4 H, CH_2), 3.89 (s, 4 H, $CH_2C{=}O$), 3.93–3.96 (m, 4 H, CH_2), 4.20 (s, 4 H, $CH_2C{=}O$), 6.63 (s, 4 H, hydroquinone-

ArH), 6.78–6.85 (m, 4 H, ArH), 6.99–7.19 (m, 8 H, ArH), 8.35–8.41 (m, 4 H, ArH), 8.78, 8.91 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 59.2 (CH$_3$), 67.9, 70.4, 71.1, 72.2 (OCH$_2$), 115.6, 117.7, 117.8, 121.5, 122.0, 124.7, 124.7, 125.0, 128.6, 128.8, 145.2, 145.6, 152.9 (13 of 14 ArC), 167.8, 168.0 (C=O).

MS (FAB): *m/z* (%): 823 (100) [M + H$^+$].

$C_{44}H_{46}N_4O_{12}$ (822.9): calcd. C 64.22, H 5.64, N 6.81; found C 64.28 H 5.80, N 6.71.

16b:

The remaining oil was subjected to column chromatography [silica gel, 5 % MeOH/CH$_2$Cl$_2$] to yield 3.96 g (87 %) of a colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.34 (s, 6 H, CH$_3$), 3.60–3.63 (m, 4 H, CH$_2$), 3.65–3.70 (m, 8 H, CH$_2$), 3.87–3.91 (m, 4 H, CH$_2$), 3.97, 4.13 (s, 4 H, CH$_2$C=O), 6.71 (s, 4 H, hydroquinone-ArH), 6.81–6.85 (m, 4 H, ArH), 7.01–7.18 (m, 8 H, ArH), 8.32–8.45 (m, 4 H, ArH), 8.85, 8.95 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 59.3 (CH$_3$), 67.9, 70.0, 70.5, 71.0, 71.2, 72.2 (OCH$_2$), 115.6, 117.6, 117.9, 121.6, 122.0, 124.6, 124.7, 124.7, 125.0, 128.7, 128.8, 145.3, 145.7, 153.0 (ArC), 167.9, 168.2 (C=O).

MS (FAB): *m/z* (%): 911 (100) [M + H$^+$].

$C_{48}H_{54}N_4O_{14}$ (910.9): calcd C 63.28, H 5.98, N 6.15; found C 61.99 H 6.06, N 5.99.

Bis[2,2′-(bisamino)diphenyl Ethers] 17:

A solution of **16** (3.5 mmol) in anhyd THF (60 mL) was added dropwise to a refluxing slurry of LiAlH$_4$ (1.33 g, 35 mmol) in anhyd THF (100 mL). The mixture was heated under reflux for an additional 16 h. It was then cooled down to 0 °C and excess LiAlH$_4$ was destroyed by addition of H$_2$O/THF (1 : 1). The precipitate was removed by filtration and washed with THF(2 × 80 mL) and EtOAc (2 × 80 mL). The combined filtrates were evaporated and the remaining oil was subjected to column chromatography.

17a:

[Silica gel, EtOAc/hexane 1 : 1]. 1.61 g (60 %) was obtained as a yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.32 (s, 6 H, CH$_3$), 3.30–3.34, 3.37–3.41, 3.55–3.59 (m, 4 H, CH$_2$), 3.73–3.77 (m, 8 H, CH$_2$), 3.97–4.00 (m, 4 H, CH$_2$), 4.58 (br s, 4 H, NH), 6.55–6.64 (m, 4 H, ArH), 6.70–6.74 (m, 8 H, ArH), 6.76 (s, 4 H, hydroquinone-ArH), 6.95–7.03 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 43.3, 43.4 (NCH$_2$), 58.8 (CH$_3$), 68.0, 69.6, 69.9, 71.1 (OCH$_2$), 111.3, 111.4, 115.6, 116.9, 116.9, 117.4, 117.9, 124.1, 124.3, 139.8, 139.9, 143.9, 144.1, 153.1 (ArC).

MS (FAB): *m/z* (%): 767 (100) [M + H$^+$].

$C_{44}H_{54}N_4O_8$ (766.9): calcd C 68.90, H 7.10, N 7.31; found C 68.49, H 7.15, N 7.16.

17b:

[Silica gel, EtOAc/hexane 2 : 1]. 1.50 g (50 %) was obtained as a colourless oil.

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.31–3.38 (m, 8 H, CH$_2$), 3.33 (s, 6 H, CH$_3$), 3.56–3.72 (m, 16 H, CH$_2$), 3.75–3.79 (m, 4 H, CH$_2$), 3.97–4.00 (m, 4 H, CH$_2$), 4.58 (br s, 4 H, NH), 6.56–6.63 (m, 4 H, ArH), 6.70–6.75 (m, 8 H, ArH), 6.77 (s, 4 H, hydroquinone-ArH), 6.95–7.01 (m, 4 H, ArH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 43.4 (1 of 2 NCH$_2$), 58.8 (CH$_3$), 68.1, 69.7, 70.0, 70.5, 70.8, 71.1 (OCH$_2$), 111.3, 111.4, 115.6, 116.9, 117.5, 117.8, 118.0, 124.2, 124.3, 139.8, 139.9, 143.9, 144.1, 153.1 (ArC).

MS (FAB): *m/z* (%): 855 (100) [M$^+$].

$C_{48}H_{62}N_4O_{10}$ (855.0): calcd C 67.42, H 7.31, N 6.55; found C 66.98, H 7.31, N 6.56.

2-(2-Benzyloxyethoxy)acetic Acid (19a):

Compound **18a** (7.61 g, 50 mmol) was added to a solution of *t*-BuOK (11.8 g, 105 mmol) in *t*-BuOH (150 mL). After stirring for 30 min the solution was brought to reflux temperature and a solution of ClCH$_2$CO$_2$H (5.20 g, 55 mmol) in *t*-BuOH (50 mL) was added dropwise. The mixture was heated under reflux for 24 h, the solvent evaporated, and the residue dissolved in H$_2$O (150 mL).The aqueous phase was washed with Et$_2$O (2 × 80 mL), acidified with 6 M HCl, and the product was extracted with EtOAc. The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and the solvent evaporated. The product was distilled under reduced pressure to yield 7.57 g (72 %) of **19a** as a pale yellow oil, bp 142–147 °C (0.05 mm).

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.64–3.68, 3.75–3.79 (m, 2 H, CH$_2$), 4.19 (s, 2 H, CH$_2$C=O), 4.60 (s, 2 H, ArCH$_2$), 7.30–7.38 (m, 5 H, ArH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 68.4, 69.1, 71.2, 73.4 (OCH$_2$), 127.9, 128.5, 137.6 (3 of 4 ArC), 174.3 (C=O).

MS (CI): *m/z* (%): 228 (60 [M + NH$_4^+$], 211 (62) [M + H$^+$], 91 (100).

$C_{11}H_{14}O_4$ (210.2); calcd C 62.84, H 6.71; found C 62.09, H 6.70.

1-(2-Benzyloxyethoxy)-4-[2-(2-carboxyethoxy)ethoxy]benzene (19b):

Compound **18b** (14.4 g, 50 mmol) was added to a solution of *t*-BuOK (11.8 g, 105 mmol) in *t*-BuOH (500 mL). After stirring for 30 min the solution was brought to reflux temperature and a solution of ClCH$_2$CO$_2$H (5.20 g, 55 mmol) in *t*-BuOH (100 mL) was added dropwise. The mixture was heated under reflux for 24 h, the solvent evaporated, and the residue dissolved in H$_2$O (150 mL). The aqueous phase was washed with Et$_2$O (2 × 80 mL), acidified with 6 M HCl, and the product was extracted with EtOAc. The combined extracts were washed with brine, dried (Na$_2$SO$_4$), and the solvent evaporated to yield 10.6 g (61 %) of **19b** as a yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.79–3.82, 3.92–3.95 (m, 2 H, CH$_2$), 4.08–4.13 (m, 4 H, CH$_2$), 4.25 (s, 2 H, CH$_2$C=O), 4.63 (s, 2 H, ArCH$_2$), 6.82–6.88 (m, 4 H, hydroquinone-ArH), 7.27–7.38 (m, 5 H, benzyl-ArH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 68.0, 68.1, 68.4, 68.6, 70.6, 73.4 (OCH$_2$), 115.6, 115.7, 127.8, 127.8, 128.4, 138.0, 152.7, 153.4 (ArC), 174.3 (C=O).

MS (70 eV, EI): *m/z* (%): 346 (84) [M$^+$], 91 (100).

$C_{19}H_{22}O_6$ (346.4): calcd C 65.88, H 6.40; found C 66.22, H 6.60.

2-(2-Benzyloxyethoxy)acetyl Chloride (20a) and 1-(2-Benzyloxyethoxy)-4-[2-(2-Chlorocarbonylethoxy)ethoxy]benzene (20b):

A solution of the carboxylic acid **19** (50 mmol), (COCl)$_2$ (15.9 g, 125 mmol), and 5 drops of DMF in benzene (100 mL) was stirred for 16 h at r. t. The solvent and excess (COCl)$_2$ were removed under reduced pressure. Benzene (20 mL) was added, again removed under reduced pressure, and the product dried in vacuo. The carbonyl chloride was usually obtained in quantitative yield and used without further purification.

Bis[2-(2-benzyloxyethoxy)acetamidophenyl] Ether (21a) and Bis{2-[2-(2-benzyloxyethoxy)phenoxy]ethoxyacetamidophenyl} Ether (21b):

A solution of the carbonyl chloride **20** (25 mmol) in CH$_2$Cl$_2$ (30 mL) was added dropwise to a solution of **8** (2.00 g, 10 mmol) and Et$_3$N (3.04 g, 30 mmol) in CH$_2$Cl$_2$ (100 mL). After additional stirring for 1 h, the solution was brought to reflux temperature for 2 h. The solution was cooled and treated with dilute HCl (100 mL). The organic layer was separated, washed with brine, dried (Na$_2$SO$_4$), and the solvent was evaporated.

21a:

The remaining oil was purified by column chromatography [silica gel, 2 % MeOH/CH$_2$Cl$_2$] to afford 4.44 g (76 %) of a yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$, 25 °C, TMS): δ = 3.46–3.50, 3.60–3.64 (m, 4 H, CH$_2$), 4.08 (s, 4 H, CH$_2$C=O), 4.40 (s, 4 H, ArCH$_2$), 6.79 (dd, *J* = 7.2 and 1.4 Hz, 2 H, ArH), 7.02 (ddd, *J* = 7.2, 7.2 and 1.4 Hz, 2 H, ArH), 7.13 (ddd, *J* = 7.2, 7.2 and 1.4 Hz, 2 H, ArH), 7.19–7.30 (m, 10 H, benzyl-ArH), 8.36 (dd, *J* = 7.2 and 1.4 Hz, 2 H, ArH), 8.98 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 69.2, 71.0, 71.2, 73.3

(OCH_2), 117.7, 121.9, 124.6, 124.9, 127.7, 127.7, 128.4, 128.8, 137.9, 145.6 (ArC), 169.2 (C=O).

MS (70 eV, EI): *m*/*z* (%): 584 (9) [M^+], 91 (100).

$C_{34}H_{36}N_2O_7$ (584.7): calcd C 69.84, H 6.21, N 4.79; found C 69.04, H 6.14, N 4.78.

21b:

The remaining oil was purified by column chromatography [silica gel, EtOAc/hexane 1:1] to afford 5.57 g (65%) of a yellow oil, which, upon standing, crystallised, mp 97 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.69$–3.72, 3.77–3.81, 3.90–3.94, 4.05–4.08 (m, 4 H, CH_2), 4.07 (s, 4 H, $CH_2C=O$), 4.62 (s, 4 H, $ArCH_2$), 6.67–6.80 (m, 10 H, ArH), 6.98–7.15 (m, 4 H, ArH), 7.25–7.39 (m, 10 H, ArH), 8.32–8.35 (m, 2 H, ArH), 8.88 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 67.9$, 68.1, 68.7, 70.4, 71.1, 73.4 (OCH_2), 115.6, 115.7, 117.7, 121.9, 124.6, 124.9, 127.7, 127.8, 128.4, 128.7, 138.1, 145.5, 152.7, 153.4 (ArC), 167.9 (C=O).

MS (FAB): *m*/*z* (%): 857 (57) [$M + H^+$], 613 (100).

$C_{50}H_{52}N_2O_{11}$ (856.9): calcd C 70.08, H 6.12, N 3.27; found C 69.36, H 5.99, N 3.17.

Bis[2-(*N*-benzyl-2-benzyloxyethoxy)acetamidophenyl] Ether (22a) and Bis{2-[2-(*N*-benzyl-2-benzyloxyethoxy)phenoxy]ethoxyacetamidophenyl) Ether (22b):

A solution of the bisamide **21** (10 mmol) in THF (50 mL) was added to a suspension of NaH (0.53 g, 22 mmol) in THF (50 mL). The suspension was stirred for 30 min and heated under reflux for 2 h. After cooling, a solution of BnBr (4.11 g, 24 mmol) in THF (40 mL) was added dropwise. After additional stirring for 16 h, H_2O (100 mL) and EtOAc (100 mL) were added and the solution acidified with 6 M HCl. The organic layer was separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvents were evaporated.

22a:

Yellow oil, 7.65 g (quant).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.54$–3.69 (m, 6 H, CH_2), 3.74–3.86 (m, 4 H, CH_2), 4.04–4.10, 4.26–4.40, 4.50–4.52, 5.32–5.37 (m, 2 H, CH_2), 6.53–6.65 (m, 2 H, ArH), 6.86–7.00 (m, 6 H, ArH), 7.12–7.30 (m, 20 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 52.0$, 52.2 (NCH_2), 69.4, 69.6, 69.6, 69.7, 70.9, 71.02, 73.2 (OCH_2), 118.5, 118.7, 124.4, 127.5, 127.6, 127.7, 128.3, 128.4, 128.4, 129.2, 129.3, 129.7, 131.1, 131.2, 136.9, 138.4, 151.8, 152.0 (ArC), 169.5, 169.6 (C=O).

MS (FAB): *m*/*z* (%): 787 [$M + Na^+$] (15), 765 (100) [$M + H^+$].

$C_{48}H_{48}N_2O_7$ (764.9): calcd C 75.37, H 6.33, N 3.66; found C 74.85, H 6.18, N 3.56.

22b:

Yellow oil, 10.4 g (quant).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.75$–3.83 (m, 6 H, CH_2), 3.89–4.13 (m, 14 H, CH_2), 4.28–4.50, 5.27–5.40 (m, 2 H, CH_2), 6.52–7.02 (m, 12 H, ArH), 7.12–7.40 (m, 24 H), ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 52.1$, 52.3 (NCH_2), 68.1, 68.2, 68.7, 69.5, 69.7, 70.2, 70.3, 73.4 (OCH_2), 115.6, 118.5, 118.8, 124.4, 124.5, 127.6, 127.7, 127.8, 128.4, 128.8, 129.0, 129.2, 129.3, 129.8, 131.0, 131.2, 136.8, 138.2, 151.8, 152.0, 153.1 (ArC), 169.4, 169.5 (C=O).

MS (FAB): *m*/*z* (%): 1059 [$M + Na^+$] (13), 1037 (16) [$M + H^+$], 793 (100).

$C_{64}H_{64}N_2O_{11}$ (1037.2): calcd C 74.11, H 6.22, N 2.70; found C 73.38, H 6.47, N 2.69.

Bis[2-(*N*-benzyl-2-hydroxyethoxy)acetamidophenyl] Ether (23a) and Bis{2-[2-(*N*-benzyl-2-hydroxyethoxy)phenoxy]ethoxyacetamidophenyl} Ether (23b):

A solution of the tetrabenzyl compound **22** (5 mmol) in EtOH (60 mL) was subjected to hydrogenolysis at r.t. in the presence of 10% Pd/C (500 mg) for 16 h. The mixture was filtered through a pad of Celite and the solvent was evaporated.

23a:

The remaining oil was purified by column chromatography [silica gel, EtOAc/EtOH 4 : 1] to give 1.40 g (48%) of a colourless oil.

^{1}H NMR (300 MHz, CD_3COCD_3, 25 °C): $\delta = 3.51$–3.67 (m, 8 H, CH_2), 3.90–4.14 (m, 4 H, CH_2), 4.48–5.40 (m, 4 H, CH_2), 6.55–6.59 (m, 1 H, ArH), 6.92–6.96 (m, 1 H, ArH), 7.10–7.48 (m, 16 H, ArH).

^{13}C NMR (75.5 MHz, CD_3COCD_3, 25 °C): $\delta = 52.5$, 52.9 (NCH_2), 61.8, 61.9, 69.4, 69.8, 74.4, 74.5 (OCH_2), 119.4, 119.9, 125.2, 125.3, 128.1, 128.2, 129.1, 129.7, 129.8, 130.7, 131.4, 131.8, 132.0, 138.1, 152.5, 153.0 (ArC), 171.1, 171.2 (C=O).

MS (FAB): *m*/*z* (%): 607 [$M + Na^+$] (70), 585 (100) [$M + H^+$].

$C_{34}H_{36}N_2O_7$ (584.7): calcd C 69.84, H 6.21, N 4.79; found C 69.06, H 6.11, N 4.51.

23b:

Colourless oil, 3.94 g (92%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.60$ (br s, 2 H, OH), 3.80–4.48 (m, 23 H, CH_2), 5.17–5.38 (m, 1 H, CH_2), 6.48–6.84 (m, 12 H, ArH), 6.90–7.04 (m, 4 H, ArH), 7.13–7.18 (m, 10 H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 52.1$, 52.3 (NCH_2), 68.2, 68.3, 69.6, 69.9, 70.2 (OCH_2), 115.5, 115.6, 115.7, 118.4, 118.4, 124.5, 124.6, 127.6, 127.7, 128.4, 128.5, 129.2, 129.3, 129.9, 130.9, 131.2, 136.7, 136.8, 151.8, 151.9, 152.9, 153.2 (ArC), 171.1, 171.2 (C=O).

MS (FAB): *m*/*z* (%): 879 [$M + Na^+$] (19), 857 (100) [$M + H^+$].

$C_{50}H_{52}N_2O_{11}$ (856.9): calcd C 70.08, H 6.22, N 3.27; found C 69.50, H 6.19, N 3.08.

Bis[2-(*N*-benzyl-2-hydroxyethoxy)ethylaminophenyl] Ether (23a) and Bis{2-[2-(*N*-benzyl-2-hydroxyethoxy)phenoxy]ethoxyethylaminophenyl} Ether (23b):

A solution of the *N*-benzylated bisamide **23** (5 mmol) in anhyd THF (60 mL) was added dropwise to a refluxing slurry of $LiAlH_4$ (1.42 g, 37.5 mmol) in anhyd THF (100 mL). The mixture was heated under reflux for an additional 16 h. It was then cooled to 0 °C and excess $LiAlH_4$ was destroyed by addition of H_2O/THF (1 : 1). The precipitate was removed by filtration and washed with THF (2 × 80 mL) and EtOAc (2 × 80 mL). The combined filtrates were evaporated and the remaining oil was subjected to column chromatography.

24a:

[Silica gel, $CHCl_3/CH_3COCH_3$ 5 : 2]. 1.56 g (56%) of a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.30$ (br s, 2 H, OH), 3.36–3.43 (m, 8 H, CH_2), 3.53–3.59 (m, 8 H, CH_2), 4.40 (s, 4 H, $ArCH_2$), 6.75–6.78, 6.87–6.93 (m, 2 H, ArH), 6.97–7.08 (m, 4 H, ArH), 7.17–7.24 (m, 10 H, benzyl-ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 50.9$, 57.5 (NCH_2), 61.8, 69.1, 72.1 (OCH_2), 119.6, 121.9, 122.7, 123.4, 126.9, 128.2, 128.4, 138.4, 142.0, 150.4 (ArC).

MS (FAB): *m*/*z* (%): 557 [$M + H^+$] (100).

$C_{34}H_{40}N_2O_5$ (556.7): calcd C 73.35, H 7.24, N 5.03; found C 71.84, H 7.28, N 5.00.

24b:

[Silica gel, EtOAc/hexane 3 : 1]. 1.82 g (44%) of a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 2.19$ (br s, 2 H, OH), 3.37–3.41 (m, 4 H, CH_2), 3.54–3.60, 3.88–3.93 (m, 8 H, CH_2), 3.98–4.02 (m, 4 H, CH_2), 4.41 (s, 4 H, $ArCH_2$), 6.72–6.89 (m, 12 H, ArH), 6.94–6.99 (m, 2 H, ArH), 7.06–7.10 (m, 2 H, ArH), 7.13–7.22 (m, 10 H, benzyl-ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): $\delta = 50.8$, 57.7 (NCH_2), 61.6, 68.1, 69.4, 69.7, 69.9 (OCH_2), 115.6, 115.7, 119.5, 122.0, 122.5, 123.4, 126.8, 128.1, 128.4, 139.2, 141.9, 150.4, 152.9, 153.4 (ArC).

MS (FAB): *m*/*z* (%): 829 [$M + H^+$] (100).

$C_{50}H_{56}N_2O_9$ (829.0): calcd C 72.44, H 6.81, N 3.38; found C 71.81, H 7.08, N 3.32.

Bis{2-[N-benzyl-2-(tert-butoxycarbonyl)ethoxy]ethylaminophenyl} Ether (25a) and Bis(2-{2-[N-benzyl-2-(tert-butoxycarbonyl)ethoxy]phenoxy}ethoxyethylaminophenyl) Ether (25b):

The *N*-benzylated bisamine **24** (10 mmol), Et_4NBr (2.31 g, 11 mmol) and $BrCH_2CO_2$-*t*-Bu (15.4 g, 80 mmol) were dissolved in CH_2Cl_2 (150 mL). A solution of NaOH (70 g, 1.75 mol) in H_2O (150 mL) was added and the mixture was stirred rapidly. After 3 days, H_2O (200 mL) and CH_2Cl_2 (100 mL) were added and the organic layer was separated. The organic phase was washed with brine, dried (Na_2SO_4), and the solvent evaporated.

25a:

The remaining oil was subjected to column chromatography [silica gel, EtOAc/hexane 1 : 3] to yield 6.83 g (87%) of a yellow oil.

^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.46 (s, 18 H, CH_3), 3.34–3.38 (m, 4 H, CH_2) 3.43–3.52 (m, 8 H, CH_2), 3.56–3.59 (m, 4 H, CH_2), 3.96 (s, 4 H, $CH_2C{=}O$), 4.40 (s, 4 H, $ArCH_2$), 6.73 (dd, J = 7.2 and 1.4 Hz, 2 H, ArH), 6.87 (ddd, J = 7.2, 7.2 and 1.4 Hz, 2 H, ArH), 6.99 (ddd, J = 7.2, 7.2 and 1.4 Hz, 2 H, ArH), 7.09 (dd, J = 7.2 and 1.4 Hz, 2 H, ArH), 7.14–7.22 (m, 10 H, benzyl-ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 28.1 (CH_3), 50.6, 57.7 (NCH_2), 69.1, 69.5, 70.3, 70.7 (OCH_2), 81.5 (C_{tert}), 119.5, 122.0, 122.4, 123.4, 126.7, 128.1, 128.4, 139.3, 141.9, 150.4 (ArC), 169.7 (C=O).

MS (FAB): *m/z* (%): 785 [M + H$^+$] (100).

$C_{46}H_{60}N_2O_9$ (785.0): calcd C 70.38, H 7.71, N 3.57; found C 69.71, H 7.78, N 3.42.

25b:

The remaining oil was subjected to column chromatography [silica gel, EtOAc/hexane 1 : 2] to yield 8.56 g (81%) of a colourless oil.

^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.48 (s, 18 H, CH_3), 3.37–3.42 (m, 4 H, CH_2), 3.54–3.60, 3.87–3.92 (m, 8 H, CH_2), 4.07–4.12 (m, 4 H, CH_2), 4.08 (s, 4 H, $CH_2C{=}O$), 4.41 (s, 4 H, $ArCH_2$), 6.71–6.89 (m, 12 H, ArH), 6.94–7.00, 7.07–7.11 (m, 2 H, ArH), 7.14–7.23 (m, 10 H, benzyl-ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 28.2 (CH_3), 50.7, 57.7 (NCH_2), 68.0, 68.2, 69.2, 69.4, 69.7, 70.0 (OCH_2), 81.7 (C_{tert}), 115.6, 119.5, 122.0, 122.5, 123.4, 126.8, 128.1, 128.4, 139.3, 141.9, 150.3, 153.0, 153.2, (13 of 14 ArC), 169.6 (C=O).

MS (FAB): *m/z* (%): 1057 [M + H$^+$] (100).

$C_{62}H_{76}N_2O_{13}$ (1057.3): calcd C 70.43, H 7.25, N 2.65; found C 70.25, H 7.57, N 2.65.

Bis[2-(N-benzyl-2-carboxyethoxy)ethylaminophenyl] Ether (26a) and Bis{2-[2-(N-benzyl-2-carboxyethoxy)phenoxy]ethylaminophenyl} Ether (26b):

CF_3CO_2H (6.84 g, 60 mmol) was added to a solution of the bis-*tert*-butyl ester **25** (5 mmol) in CH_2Cl_2 (100 mL). After stirring for 3 days, the solvent and excess CF_3CO_2H were evaporated and the product dried in vacuo.

26a:

Yellow oil, 3.36 g (quant).

^1H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 3.51–3.55, 3.57–3.61 (m, 4 H, CH_2), 3.70 (s, 8 H, CH_2), 4.06 (s, 4 H, $CH_2C{=}O$), 4.74 (s, 4 H, $ArCH_2$), 6.62–6.68 (m, 2 H, ArH), 7.14–7.19 (m, 4 H, ArH), 7.24–7.33 (m, 10 H, ArH), 7.50–7.54 (m, 2 H, ArH), 9.53 (br s, 2 H, OH).

^{13}C NMR (75.5 MHz, CD_3COCD_3, 25 °C): δ = 55.1, 60.4 (NCH_2), 68.5, 69.2, 70.9, 71.2 (OCH_2), 120.4, 124.6, 125.5, 128.4, 129.2, 129.3, 131.0, 134.6, 135.1, 150.2 (ArC), 171.9 (C=O).

MS (FAB): *m/z* (%): 673 [M + H$^+$] (90), 196 (100).

26b:

Yellow oil, 4.73 g (quant).

^1H NMR (300 MHz, CD_3COCD_3, 25 °C): δ = 3.58–3.71 (m, 12 H, CH_2), 3.87–3.96 (m, 8 H, CH_2), 4.08–4.11 (m, 4 H, CH_2), 4.19 (s, 4 H, $CH_2C{=}O$), 4.63 (s, 4 H, $ArCH_2$), 6.67–6.70 (m, 2 H, ArH), 6.78–6.88 (m, 8 H, ArH), 6.98–7.11 (m, 4 H, ArH), 7.20–7.39 (m, 12 H, ArH).

MS (FAB): *m/z* (%): 945 [M + H$^+$] (100).

Bis{2-[N-benzyl.-2-(chlorocarbonyl)ethoxy]ethylaminophenyl} Ether (27a) and Bis(-2-{2-[N-benzyl-2-(chlorocarbonyl)ethoxy]phenoxy} ethylaminophenyl) Ether (27b):

A solution of the bisacid **26** (5 mmol), $(COCl)_2$ (3.17 g, 25 mmol), and 5 drops of DMF in CH_2Cl_2 (50 mL) was stirred for 16 h at r.t. The solvent and excess of $(COCl)_2$ were removed under reduced pressure, and the product dried in vacuo. The biscarbonyl chloride obtained was used without further purification.

N-Benzyl-Protected Tris[2,2′-(bisamido)diphenyl Ethers] 28:

A solution of the biscarbonyl chloride **27** (5.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a solution of **9** (2.72 g, 10 mmol) and Et_3N (3.04 g, 30 mmol) in CH_2Cl_2 (100 mL). After additional stirring for 1 h, the solution was brought to reflux temperature for 2 h. The solution was cooled and treated with dilute HCl (100 mL). The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was evaporated and the remaining oil subjected to column chromatography.

28a:

[Silica gel, EtOAc/hexane 3 : 1]. 4.02 g (68%) of a yellow oil.

^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.20–3.25 (m, 4 H, CH_2), 3.28 (s, 6 H, CH_3), 3.28–3.31, 3.35–3.39, 3.45–3.50 (m, 4 H, CH_2), 3.92, 4.03 (s, 4 H, $CH_2C{=}O$), 4.29 (s, 4 H, $ArCH_2$), 6.67–7.17 (m, 30 H, ArH), 8.30–8.41 (m, 2 H, ArH), 8.80, 8.87 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 50.5, 57.7 (NCH_2), 59.3 (CH_3), 69.4, 69.9, 71.0, 71.1, 72.2 (OCH_2), 117.5, 118.0, 119.5, 121.6, 121.9, 122.0, 122.5, 123.4, 124.5, 124.7, 124.8, 125.0, 126.8, 128.1, 128.3, 128.5, 128.9, 139.1, 141.8, 145.1, 145.8, 150.3 (ArC), 167.9, 168.2 (C=O).

MS (FAB): *m/z* (%): 1181 (100) [M + H$^+$].

$C_{68}H_{72}N_6O_{13}$ (1181.3): calcd C 69.13, H 6.14, N 7.12; found C 68.93, H 6.07, N 7.09.

28b:

[Silica gel, EtOAc/hexane 5 : 1]. 4.65 g (64%) of a colourless oil.

^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.29 (s, 6 H, CH_3), 3.37–3.42 (m, 4 H, CH_2), 3.55–3.60 (m, 8 H, CH_2), 3.77–3.81, 3.87–3.91, 3.93–3.96 (m, 4 H, CH_2), 3.88, 4.19 (s, 4 H, $CH_2C{=}O$), 4.42 (s, 4 H, $ArCH_2$), 6.65–6.89 (m, 16 H, ArH), 6.95–7.22 (m, 22 H, ArH), 8.34–8.42 (m, 4 H, ArH), 8.77, 8.90 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 50.7, 57.7 (NCH_2), 59.2 (CH_3), 68.0, 69.4, 69.7, 70.5, 71.2, 72.2 (6 of 7 OCH_2), 115.6, 117.7, 117.8, 119.5, 121.6, 122.0, 122.5, 123.4, 124.6, 124.7, 125.0, 126.8, 128.1, 128.4, 128.6, 128.8, 139.3, 141.9, 145.2, 145.6, 150.4, 152.6, 153.4 (23 of 26 ArC), 167.8, 168.0 (C=O).

MS (FAB): *m/z* (%): 1454 (100) [M + H$^+$].

$C_{84}H_{88}N_6O_{17}$ (1453.6): calcd C 69.40, H 6.10, N 5.78; found C 67.61, H 6.22, N 5.63.

Tris[2,2′-(bisamido)diphenyl Ethers] 29:

A solution of **28** (1 mmol) in EtOH (60 mL) was subjected to hydrogenolysis at r.t. in the presence of 10% Pd/C (200 mg) for 16 h. The mixture was filtered through a pad of Celite and the solvent was evaporated.

29a:

Yellow oil, 1.00 g (quant).

^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 3.15–3.20 (m, 4 H, CH_2), 3.30 (s, 6 H, CH_3), 3.43–3.55 (m, 12 H, CH_2), 3.94, 4.04 (s, 4 H, $CH_2C{=}O$), 4.62 (br s, 2 H, NH), 6.53–6.68 (m, 6 H, ArH), 6.79–6.83 (m, 4 H, ArH), 6.92–7.16 (m, 10 H, ArH), 8.33–8.43 (m, 4 H, ArH), 8.83, 8.89 (br s, 2 H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 43.2 (NCH_2), 59.3 (CH_3), 69.7, 70.0, 71.0, 71.2, 72.2 (OCH_2), 111.5, 117.1, 117.5, 117.7, 121.6, 121.8, 124.2, 124.6, 124.7, 124.7, 124.9, 128.8, 139.5, 143.9, 145.3, 145.5, (16 of 18 ArC), 167.9, 168.1 (C=O).

MS (FAB): *m/z* (%): 1001 (27) [M + H$^+$], 518 (100).

$C_{54}H_{60}N_6O_{13}$ (1001.1): calcd C 64.78, H 6.04, N 8.40; found C 63.97, H 6.15, N 8.31.

29b:

Yellow oil, 1.27 g (quant).

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.30 (s, 6H, CH_3), 3.35–3.40 (m, 4H, CH_2), 3.70–3.80 (m, 12H, CH_2), 3.84 (s, 4H, $CH_2C{=}O$), 3.93–4.00 (m, 8H, CH_2), 4.19 (s, 4H, $CH_2C{=}O$), 6.57–6.86 (m, 18H, ArH), 6.96–7.20 (m, 10H, ArH), 8.34–8.41 (m, 4H, ArH), 8.78, 8.90 (br s, 2H, NH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 43.4 (NCH_2), 59.3 (CH_3), 66.9, 68.0, 69.6, 69.8, 70.4, 71.1, 72.1 (7 of 8 OCH_2), 111.6, 115.5, 115.6, 117.1, 117.7, 117.8, 118.0, 121.5, 121.9, 124.2, 124.6, 124.7, 125.0, 128.6, 128.8, 145.2, 145.6, 147.0, 152.7, 153.1 (20 of 22 ArC), 168.0 (C=O).

MS (FAB): *m/z* (%): 1273 (100) [M + H$^+$].

$C_{70}H_{76}N_6O_{17}$ (1273.4): calcd C 66.02, H 6.02, N 6.60; found C 65.12, H 6.22, N 6.47.

Tris[2,2′-(bisamino)diphenyl Ethers] 30:

A solution of **29** (1 mmol) in anhyd THF (30 mL) was added dropwise to a refluxing slurry of $LiAlH_4$ (0.38 g, 10 mmol) in anhyd THF (30 mL). The mixture was heated under reflux for an additional 16 h. It was then cooled to 0°C and excess $LiAlH_4$ was destroyed by addition of H_2O/THF (1 : 1). The precipitate was removed by filtration and washed with THF (2 × 40 mL) and EtOAc (2 × 40 mL). The combined filtrates were evaporated and the remaining oil was subjected to column chromatography.

30a:

[Silica gel, EtOAc/hexane 10 : 1]. 0.42 g (44%) of a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 2.77 (br s, 2H, OH), 3.21–3.33 (m, 12H, CH_2), 3.53 (s, 8H, CH_2), 3.61–3.73 (m, 12H, CH_2), 4.63 (br s, 6H, NH), 6.56–6.80 (m, 18H, ArH), 6.94–7.02 (m, 6H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 43.2, 45.8 (2 of 3 NCH_2), 60.9, 69.5, 69.6, 70.2, 70.3 (OCH_2), 111.4, 111.5, 111.7, 116.9, 117.0, 117.4, 117.5, 117.6, 124.2, 124.2, 124.2, 139.6, 139.7, 143.8, 143.9, (15 of 18 ArC).

MS (FAB): *m/z* (%): 917 (100 [M + H$^+$].

$C_{52}H_{64}N_6O_9$ (917.1): calcd C 68.10, H 7.03, N 9.17; found C 67.29, H 7.09, N 8.94.

30b:

[Silica gel, EtOAc/hexane 2 : 1]. 0.56 g (46%) of a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 3.30–3.40 (m, 12H, CH_2), 3.32 (s, 6H, CH_3), 3.54–3.58 (m, 4H, CH_2), 3.70–3.76 (m, 16H, CH_2), 3.94–3.99 (m, 8H, CH_2), 4.61 (br s, 6H, NH), 6.55–6.64 (m, 6H, ArH), 6.69–6.76 (m, 20H, ArH), 6.94–7.02 (m, 6H, ArH).

^{13}C NMR (75.5 MHz, $CDCl_3$, 25°C): δ = 43.4 (1 of 3 NCH_2), 58.8 (CH_3), 68.0, 69.6, 69.8, 69.9, 71.1 (OCH_2), 111.4, 111.5, 111.5, 115.7, 116.9, 117.0, 117.0, 117.5, 117.7, 117.9, 124.2, 124.3, 124.4, 139.9, 139.9, 143.9, 144.0, 144.1, 153.1 (19 of 24 ArC).

MS (FAB): *m/z* (%): 1218 (100) [M + H$^+$].

$C_{70}H_{84}N_6O_{13}$ (1217.43): calcd C 69.06, H 6.96, N 6.91; found C 65.59, H 6.81, N 6.49.

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(9) Crystal data for **11a**: $C_{36}H_{38}N_4O_{10}$, M = 686.7, orthorhombic, a = 11.656(2), b = 18.029(3), c = 16.120(2) Å, V = 3387(1) Å^3, space group *Pbcn*, Z = 4 (the molecule has crystallographic C_2 symmetry), D_c = 1.347 cm^{-3}, μ(Mo-K$_\alpha$) = 0.099 mm^{-1}, λ = 0.71073 Å, F(000) = 1448. Data for a crystal of dimensions 0.87 × 0.70 × 0.43 mm were collected on a Siemens P4 diffractometer with Mo-K$_\alpha$ radiation (graphite monochromator) using ω-scans. Of the 2919 independent reflections measured ($2\theta < 45°$), 2227 had $|F_o| > 4\sigma(|F_o|)$ and were considered to be observed. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically to give R = 0.040, R_w = 0.045. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).

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