ARTICLE

OBC
www.rsc.org/obc

The chirality of dendrimer-based supramolecular complexes

Maarten A. C. Broeren, Bas F. M. de Waal, Joost L. J. van Dongen, Marcel H. P. van Genderen and E. W. Meijer*

Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600, MB Eindhoven, The Netherlands

Received 8th September 2004, Accepted 1st November 2004
First published as an Advance Article on the web 9th December 2004

Boc-protected L-phenylalanine has been connected to a spacer-armed ureido–acetic acid derivative, which can form multiple supramolecular complexes with urea–adamantyl modified poly(propylene imine) dendrimers in chloroform. Complexes of this guest with several generations of urea–adamantyl dendrimers were prepared. The dendrimer–guest complexes were characterized in detail by ^{1}H-NMR, ^{1}H–^{1}H-NOESY spectroscopy and mass spectrometry to prove their formation. Optical rotation experiments performed on different generations of dendrimer–guest complexes showed a constant positive value. These observations indicate that, though guest molecules decrease the flexibility at the periphery of the dendrimer upon binding, the amino acid at the terminus of the guest molecule retains its high local conformational freedom. This is in agreement with values found for covalently modified spacer-armed dendrimers.

Introduction

The chirality of dendritic macromolecules has been a topic of interest since the first report by Denkewalter *et al*. in 1981.[1] Chiral units can be built in dendrimers at different positions, *e.g.* the core, the branching points or the periphery, resulting in different architectures that have been the subject of numerous studies.[2–5] In our group, we modified the periphery of a fifth generation poly(propylene imine) dendrimer with *N*-*tert*-Boc-L-phenylalanine, resulting in the so-called "dendritic box". It was found that the periphery forms a dense shell and that small molecules can be encapsulated inside the dendrimer.[6] This dense-shell behaviour was reflected in the chiroptical properties of the dendritic box. The specific optical rotation of DAB–*dendr*–(NH-*tert*-Boc-L-Phe)$_x$, **2a–2e** (Fig. 1), vanishes to zero on going from the first generation with 4 end groups ($[\alpha]_D^{20} = -11$, $c = 1$, $CHCl_3$)[7] to the fifth generation with 64 end groups ($[\alpha]_D^{20} = -0.1$, $c = 1$, $CHCl_3$).[4]

For other bulky Boc-protected amino acids, a similar effect was observed. Though never completely understood, the vanishing optical rotation was explained by the rigid character of the shell which does not enable all end groups to adopt their most favourable conformation. Since this particular end group possesses a strongly conformation-dependent optical rotation, the presence of many different conformations in the shell results in averaging of the optical rotation. In addition, dendrimers with amide–acetal end groups, which do not possess a conformation-dependent optical rotation, exhibited the same optical rotation for all generations.[4] This issue was further investigated by introduction of a C-12 alkyl spacer between the *N*-*tert*-Boc-L-phenylalanine unit and the dendrimer surface.[4] The alkyl spacer played a crucial role in the specific optical rotation obtained for dendrimers **3a** and **3e** (Fig. 1), revealing a constant value of approximately $[\alpha]_D^{20} = +4$. This is in sharp contrast to the values found for the dendritic box analogues and supports the idea that the conformational freedom of the *N*-*tert*-Boc-L-phenylalanine unit is reflected in the optical rotation.

More recently, new dendritic architectures have been obtained by a supramolecular approach in which modification of the dendrimer periphery is based on non-covalent interactions such as electrostatic interactions, hydrogen bonding or hydrophobic interactions.[8–12]

In our group, we designed a methodology in which poly(propylene imine) dendrimers are modified with urea–adamantyl end groups covalently attached to the dendrimer (host) which can be used as a scaffold to reversibly bind ureido–acetic acid building blocks (guests, Scheme 1) due to electrostatic and hydrogen-bonding interactions.[13–18] We are now interested in investigating the conformational freedom of end groups that are non-covalently attached to dendrimers more thoroughly. T_1-Relaxation measurements already gave some indication that the local mobility of the dangling end of guest molecules remains unperturbed.[13] On the other hand, T_1-relaxation measurements also showed that at the dendrimer periphery the mobility decreases. In this article *N*-*tert*-Boc-L-phenylalanine has been used as a chiral probe to investigate the conformational freedom of the dangling ends of guest molecules. Therefore, an *N*-*tert*-Boc-L-phenylalanine containing guest molecule has been synthesized. Complexes of this guest with several generations of urea–adamantyl dendrimers have been prepared. ^{1}H-NMR measurements, ^{1}H–^{1}H-NOESY experiments and mass spectrometry have been performed to prove that the guest molecules are bound to the dendrimer. The chiroptical properties of the host–guest complex of different dendrimer generations have been studied in chloroform and have been compared to the chiroptical properties of both the dendritic box and spacer armed dendrimers **3a** and **3e**.

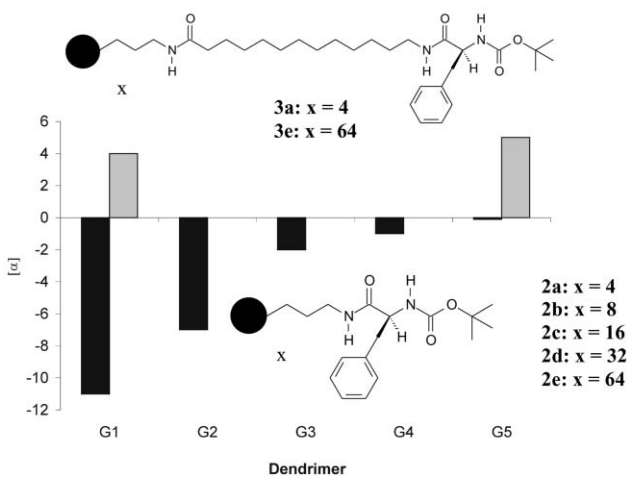
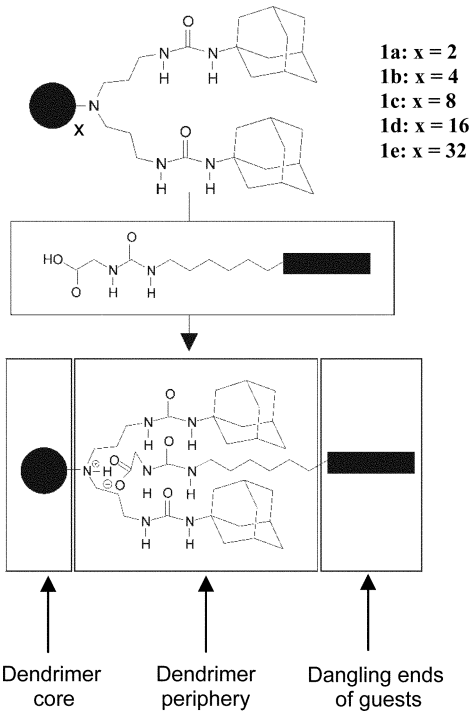


Fig. 1 Optical rotation values of spacer armed dendrimers **3a** and **3e** in comparison to the values for the dendritic box (**2a–2e**).

DOI: 10.1039/b413724h

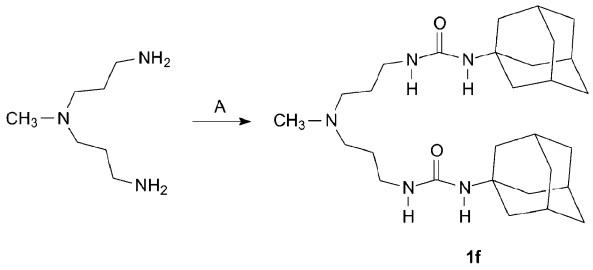


Scheme 1 Schematic representation of the dendritic host–guest system.

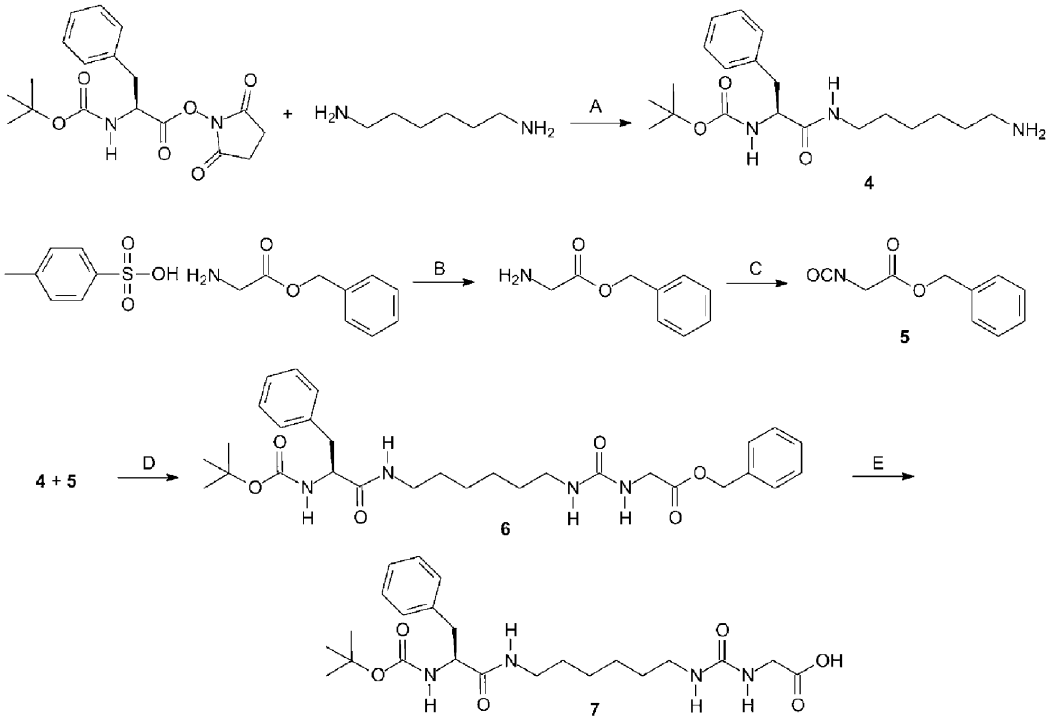
Results and discussion

Guest **7** (Scheme 2) was synthesized starting from *N-tert*-Boc-L-phenylalanine-*N*-hydroxysuccinimide ester and 1,6-hexanediamine. By using a large excess of 1,6-hexanediamine, the mono-functionalized amine is formed as the main product. The purified amine **4** was converted to ester **6** *via* isocyanate **5**. This isocyanate is formed in a two-step procedure starting from *p*-toluenesulfonyl glycine benzyl ester. First the salt was washed with a NaOH solution to liberate the free amine and subsequently the amine was converted *in situ* to isocyanate **5** using di-*tert*-butyl-tricarbonate.[19]

By addition of amine **4** to isocyanate **5**, pure ester **6** could be obtained after column chromatography. Catalytic hydrogenation using Pd/C as a catalyst resulted in acid **7**. All compounds could be obtained in good yields and were characterized by ^{1}H-NMR, ^{13}C-NMR, ATR-IR spectroscopy and MALDI-TOF mass spectrometry. The dendrimers were prepared according to previously published work.[13] Pincer molecule **1f** is obtained when bis(propylamine)methylamine is reacted with two equivalents of 1-adamantyl isocyanate and can be used as a model compound for dendritic hosts **1a–1e** (Scheme 3). Guest molecule **7** is barely soluble in chloroform. However, upon addition of 4, 8 and 32 equivalents of guest **7** to second, third and fifth-generation dendrimer respectively, a clear solution is obtained. The resulting complexes are stable and can be characterised with mass spectrometry and ^{1}H-NMR. Using electrospray ionisation mass spectrometry, it is possible to transfer the complexes from solution to the gas phase,[14] and this has been done for dendrimer **1c** with approximately six equivalents of **7**. As can be seen in Fig. 2, apart from dendrimer **1c** other peaks are visible that have a mass difference equal to the mass of **7**. These peaks are the dendrimer with one to eight guest molecules bound to it. Most likely, the distribution is different in solution as some guest molecules will dissociate upon transfer to the gas phase. The electrospray measurements do show, however, that the complex is formed and that individual complexes can be observed.



Scheme 3 Synthesis of pincer molecule **1f**. A) 1-adamantyl isocyanate, CH_2Cl_2, 2 h.



Scheme 2 A) CH_2Cl_2, 12 h; B) 2.4 M NaOH (aq.), CH_2Cl_2; C) CH_2Cl_2, di-*t*-butyltricarbonate, 0.5 h; D) CH_2Cl_2, 2 h; E) Pd/C catalyst (10%), *tert*-butanol : H_2O 1 : 1 (v/v), 4 h.

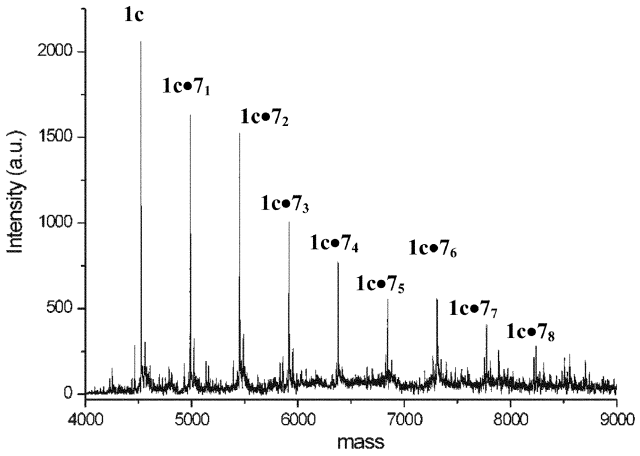


Fig. 2 The mass-spectrum of dendrimer **1c** with six equivalents of **7**. Apart from the "naked" dendrimer, several peaks at higher mass are present that correspond to the dendrimer with one to eight guest molecules bound to it.

^{1}H-NMR measurements of the complexes revealed a downfield shift of both the urea protons of the dendrimer (signals **a** and **b**) and the methylene protons adjacent to the tertiary amine of the outermost shell (signal **f**) in all cases, as depicted for the **1e**·7_{32} complex in Fig. 3.

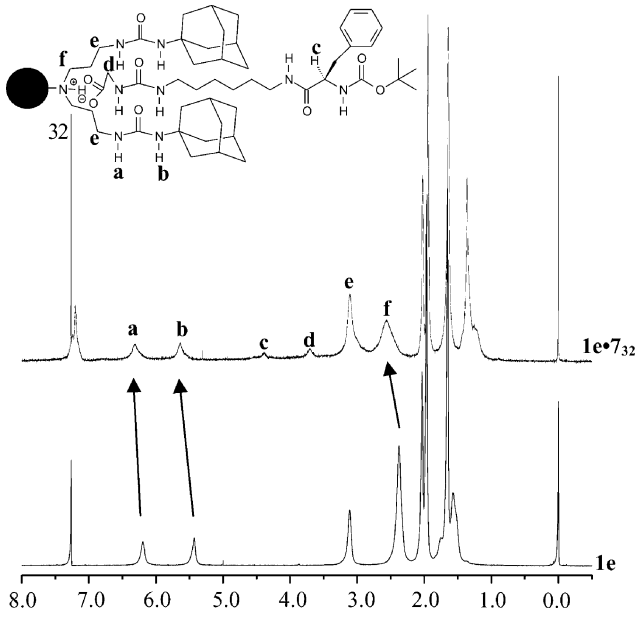


Fig. 3 ^{1}H-NMR spectra of dendrimer **1e** and the complex **1e**·7_{32}. The changes upon complexation are indicated with arrows.

This is indicative of hydrogen bonding between the urea groups of guest and host and protonation of the tertiary amines of the dendrimer. Due to the poor solubility of guest **7** in chloroform, it was dissolved in deuterated 1,1,2,2-tetrachloroethane and a ^{1}H-NMR spectrum was obtained at a high temperature (120 °C). This spectrum was used to assign signals **c** and **d** of the **1e**·7_{32} complex. ^{1}H–^{1}H-NOESY measurements of the **1e**·7_{32} complex have been performed in $CDCl_3$ to investigate the location of the guest molecules.[20] The spectrum depicted in Fig. 4 shows NOE interactions between the ureido–acetic acid part of **7** and the methylene protons next to the tertirary amines of dendrimer **1e**.

As a reference experiment, a ^{1}H–^{1}H-NOESY spectrum was obtained of **1e** and 32 equivalents of **6** in $CDCl_3$. In this case no NOE interactions were found between these compounds. All other cross-peaks in the spectrum can be assigned to intramolecular NOE-effects of the dendrimer or guest.

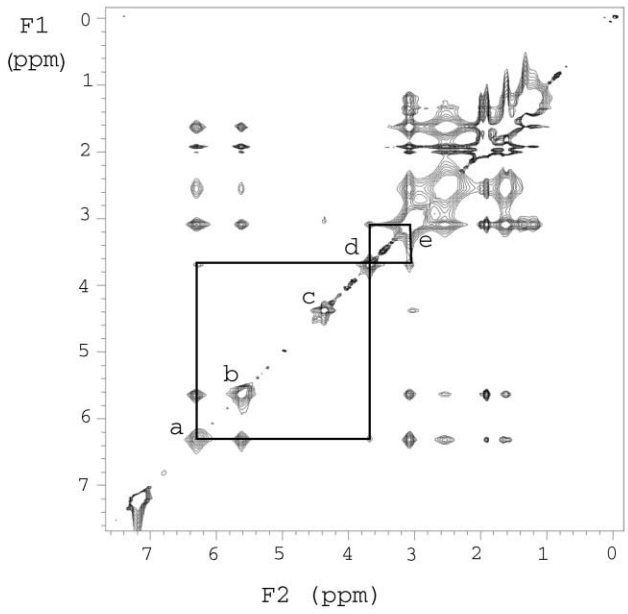


Fig. 4 ^{1}H–^{1}H-NOESY spectrum of **1e**·7_{32} in $CDCl_3$ recorded at 25 ± 0.5 °C. The NOE effects between the methylene protons of the guest (**d**) and the periphery of the fifth generation urea adamantyl dendrimer (**a**, **e**) are indicated.

T_1-Relaxation measurements in chloroform for methylene protons **f** give values of 0.84 s for pure **1e** and 1.05 s for **1e**·7_{32}, which is in agreement with earlier measurements.[13] This is an indication that the periphery of the dendrimer becomes more rigid upon complexation of the guest. Of course, we would like to compare T_1 values of the dangling ends of the guest upon binding to **1e**. Unfortunately, for chiral proton **c** this proved to be very difficult due to the low intensity. The signal of the Boc-group overlaps with the dendrimer, making it unsuitable for reliable T_1-measurements. However, the optical rotation can be monitored easily and gives information about the mobility of the dangling end. It can be compared to values found for the covalently modified dendrimers, as well as with free guest **6**.

Optical rotation measurements were performed in chloroform to investigate the chiroptical properties of the complexes formed. In all cases the concentration of **7** was kept constant at 10 mg mL^{-1} ($c = 1$), so that the number of chiral groups was constant in all samples. The different generations of dendrimer or pincer were added in such an amount that a stoichiometry of one guest per two end groups was present. This means that theoretically all the guest molecules can bind to the peripheral tertiary amines of the host. The results are depicted in Fig. 5. Compound **6** was taken as a reference (chosen because of the poor solubility of **7** in chloroform) and gives a value of $[\alpha]_D^{20} = 5 \pm 1$. This value is also found for all of the different host–guest complexes. This is comparable to spacer-armed dendrimers **3a** and **3e** and

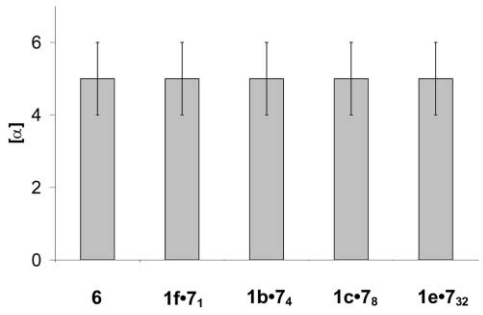


Fig. 5 Optical rotation measurements show a constant value for the complexes of different generations of the urea–adamantyl dendrimer with guest **7**, which can be compared to the results obtained for the spacer-armed dendrimers described in Fig. 1.

can be explained, as the amount of chiral groups present is approximately equal in all cases.[21]

The results show a different behaviour than measurements performed on the dendritic box, in which the optical rotation decreased from $[a]_D^{20} = -11$ to -0.1 in going from the first to the fifth generation dendrimer (Fig. 1), but are in agreement with the spacer-armed dendrimers **3a** and **3e**. These results indicate that the local conformational freedom of the *N*-*tert*-Boc-L-phenylalanine part of the guest molecules remains constant upon complexation and is comparable to the molecular motion of molecules covalently attached to dendrimers *via* a spacer.

Conclusions

In conclusion, we have been able to synthesize an *N*-*tert*-Boc-L-phenylalanine containing guest molecule. ^{1}H-NMR has revealed that this molecule is able to form a complex in chloroform with poly(propylene imine) dendrimers functionalized with urea adamantyl end groups. ^{1}H–^{1}H-NOESY spectroscopy and mass spectrometry further confirmed the existence of the supramolecular structures. T_1-Measurements have shown that the dendrimer periphery becomes more rigid when guest molecules bind to the dendrimer due to complexation, but optical rotation measurements on the complexes of different generations revealed a constant value. These results indicate that while the dendrimer periphery rigidifies upon complexation with guest molecules, the conformational freedom at the dangling ends of guest molecules non-covalently attached to dendrimers does not change significantly upon complexation. We have to take into account that the supramolecular complex is a dynamic system. This means that guest molecules constantly associate and dissociate from the dendrimer. Ureido–acetic acid guest molecules that have a good solubility in chloroform have an association constant of around 10^2–10^3 M^{-1}.[22] However, we expect the association constant for **7** to be higher, as the solubility of this guest in chloroform is limited and the dendrimer actually helps to keep the guest solubilized. This most likely gives rise to a higher association constant. Nevertheless, the dynamics can influence the conformational freedom of the dangling end groups. In addition to this, the chiral centre is connected to the ureido–acetic acid binding site of the guest *via* a C-6 spacer, which also allows for more possibilities of reorganisation. However, no change at all is observed in the specific optical rotation, which is in sharp contrast with the dendritic box dendrimers. This indicates that the mobility must be significantly different from the covalently modified dendritic box analogues.

Experimental

General experimental

All solvents used were provided by Biosolve and of p.a. quality. *N*-*tert*-Boc-L-phenylalanine-*N*-hydroxysuccinimide ester (Sigma), *p*-toluenesulfonyl glycine benzyl ester (Fluka) and 1,6-hexanediamine (Janssen Chimica) were used as received. Standard ^{1}H-NMR, ^{13}C-NMR and ^{1}H–^{1}H-NOESY spectra were recorded at 25 °C on a Varian Gemini 300 or Varian Mercury 400 MHz spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (0 ppm). IR spectra were obtained using a Perkin Elmer Spectrum One ATR-FT-IR machine. MALDI-TOF MS spectra were measured on a Perspective DE Voyager spectrometer utilising an α-cyano-4-hydroxycinnamic acid matrix. The ESI mass spectrum of the dendrimer complex was recorded with a Q-Tof Ultima GLOBAL mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray source. The sample (10 μL) was injected in the Flow Injection Analysis (FIA) mode. The HPLC-grade chloroform was pumped with a Shimadzu LC-10ADvp at a flow rate of 30 μL min^{-1}. Electrospray ionization was achieved in the positive ion mode by application of 5 kV on the needle. The source block temperature was maintained at 60 °C and the desolvation gas was heated to 60 °C. The complex analysed with mass spectrometry was prepared by adding four equivalents of guest **7** to third generation urea–adamantyl dendrimer in a concentration of approximately 1 mg mL^{-1} of total complex in chloroform. To 400 μL of this solution was added 100 μL of a solution of 1% acetic acid in chloroform. This mixture was immediately injected into the mass spectrometer.

Optical rotation experiments were performed on a Pleuger Optical Activity polarimeter and a Jasco DIP-370 digital polarimeter and are expressed as 10^{-1} deg cm^2 g^{-1}. All samples had a concentration of 10 mg mL^{-1} of guest molecule. The NMR relaxation time experiments and the 2D NMR ^{1}H–^{1}H-NOESY experiments were carried out on a Varian Unity Inova 500 spectrometer operating at 500.618 MHz and equipped with a 5 mm 500 SW/PFG probe from Varian. Spectra were referenced to TMS and were obtained at 25 °C. Prior to fourier-transformation, the f1 and f2 data points were processed with a squared shifted sinebell weighing function (for f1: sb = −0.13 and sbs = −0.13; for f2, sb1 = −0.065 and sbs1 = −0.065). A mixing time of 0.1 s was used. Spin–lattice relaxation time (T_1) measurements were conducted using a standard ^{1}H inversion recovery experiment supplied by Varian.

***N′*(6-Aminohexyl)-*N*-*tert*-Boc-L-phenylalaninamide (4).** To a solution of 60 g (51 mmol) of 1,6-hexanediamine in 120 mL of dichloromethane was added dropwise a solution of 3.62 g (10 mmol) *N*-*tert*-Boc-L-phenylalanine-*N*-hydroxy-succinimide ester in 200 mL of dichloromethane over 2 hours. Upon addition of the ester a white precipitate started to form. After stirring overnight the reaction mixture was transferred to a separatory funnel and washed with water (6 × 300 mL) and a saturated NaCl solution (1 × 100 mL). During this procedure the formed precipitate disappeared. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. Column chromatography (50 g SiO_2) starting with $CHCl_3$: MeOH, 95 : 5 (v/v) as an eluent was used to remove the doubly functionalized species from the residue, and subsequently the eluent was changed to $CHCl_3$: MeOH : $N(Et)_3$, 90 : 5 : 5 v/v to remove the mono-functionalized species from the column. Evaporation of the solvent *in vacuo* gave pure amine **4** as a yellow oil (2.5 g, 69%). ATR-IR: ν (cm^{-1}) = 3301.0, 2977.8, 2931.0, 2857.7, 1651.5, 1525.9, 1497.1, 1455.3, 1391.4, 1365.9, 1247.2, 1166.0, 1047.0, 1021.4, 748.7, 698.4. ^{1}H-NMR (DMSO-d6): δ = 1.05–1.4 (m, 17 H, $(CH_3)_3C$ (9H) + $CH_2(CH_2)_4CH_2$ (8H)), 2.55 (t, 2H, J = 7, H_2NCH_2), 2.7 (dd, 1H, $J_{H'-H\alpha}$ = 9.9, $J_{H'-H''}$ = 13.6, PhCH'H″C*), 2.85 (dd, 1H, $J_{H'-H''}$ = 13.6, $J_{H''-H\alpha}$ = 5.1, PhCH′H''C*), 3.0 (m, 2H, CH_2NHC(O)), 4.05 (pseudo dt, 1H, $J_{H\alpha-NH}$ = 8.8, $J_{H\alpha-H'}$ = 9.9, $J_{H\alpha-H''}$ = 5.1, C*H), 6.8 (d, 1H, $J_{H\alpha-NH}$ = 8.8, C*HNHC(O)), 7.2 (m, 5H, PhH), 7.8 (br t, 1H, J_{NH-CH_2} = 5.5, CH_2NHC(O)). ^{13}C-NMR ($CDCl_3$): δ = 26.42, 26.56 ($H_2NCH_2CH_2(CH_2)_2$), 28.29 ($C(CH_3)_3$), 29.27, 33.48 ($H_2NCH_2CH_2(CH_2)_2CH_2CH_2$), 38.84 ($CH_2$NHC(O)), 39.33 (ArC$CH_2$), 42.03 ($H_2NCH_2$), 56.06 (C*), 80.0 ($C(CH_3)_3$), 126.87, 128.61, 129.34 (PhCH), 136.95 (PhC_{ipso}), 155.70 (NHC(O)OC$(CH_3)_3$), 171.03 (NHC(O)C*). MALDI-TOF MS: M_r calc. for $[M + H]^+$: 364.25, found 364.17; M_r calc. for $[M + Na]^+$: 386.24 found 386.16.

***N′*(6(Benzyloxycarbonylmethyl-1,3-ureido)hexyl)-*N*-*tert*-Boc-L-phenylalaninamide (6).** A solution of 1.44 g (14.8 mmol) of *p*-toluenesulfonyl glycine benzyl ester in 150 mL of dichloromethane was washed with 75 mL of a NaOH solution (2.4 M) and water (2 × 75 mL). Drying of the organic layer with Na_2SO_4 and evaporation of the solvent gave glycine benzyl ester as a slightly yellow oil (0.6 g, 85%). ^{1}H-NMR ($CDCl_3$): δ = 7.35 (s, 5H, PhH), 5.16 (s, 2H, PhCH_2), 3.46 (s, 2H, CH_2NH_2), 1.42 (br, s, 2H, NH_2). Of this amine 0.446 g (2.7 mmol) in 2 mL of distilled dichloromethane was added to a solution of 0.708 g (2.7 mmol) di-*t*-butyl-tricarbonate in 3 mL

of distilled dichloromethane. IR spectroscopy showed a large peak at 2252.3 cm^{-1}, indicating that the amine was converted to isocyanate **5**. After stirring for half an hour a solution of 1.0 g (2.8 mmol) of amine **4** in 3 mL of distilled dichloromethane was added. IR spectroscopy revealed a complete disappearance of the isocyanate peak after two hours. The reaction mixture was subjected to column chromatography (SiO_2, $CHCl_3$: MeOH, 95 : 5 v/v) and precipitation in hexane to obtain pure **6** as a white solid (1.27 g, 85%). Mp: 107–109 °C. $[\alpha]_D^{20} = 5$ ($c = 1$ in $CHCl_3$). Calc. for $C_{30}H_{42}N_4O_6$: C, 64.96; H, 7.63; N, 10.10%, found C, 64.82; H, 7.55; N, 10.14%. ATR-IR: ν (cm^{-1}) = 3317.3, 2931.1, 2858.3, 1732.7, 1687.1, 1645.9, 1562.5, 1521. 9, 1455.4, 1439.0, 1390.9, 1365.3, 1290.7, 1232.2, 1200.8, 1168.0, 1024.7, 734.2, 697.0. ^{1}H-NMR (DMSO-d6): δ = 1.18–1.45 (br m, 8H, $CH_2(CH_2)_4CH_2$), 1.38 (s, 9H, $(CH_3)_3C$), 2.7 (dd, 1H, $J_{H'-H''} = 13.6$, $J_{H'-H\alpha} = 9.9$, PhC*H*′H″C*), 2.9 (dd, 1H, $J_{H''-H\alpha} = 5.0$, $J_{H'-H''} = 13.6$, PhCH′*H*″C*), 2.95–3.1 (m, 4H, $(CH_2(CH_2)_4CH_2)$), 3.8 (d, 2H, $J_{CH2-NH} = 6.2$, NHCH_2C(O)), 4.1 (pseudo dt, 1H, $J_{H\alpha-NH} = 8.5$, $J_{H\alpha-H''} = 5.0$, $J_{H\alpha-H'} = 9.9$, C*H), 5.1 (s, 2H, PhCH_2O), 6.15 (m, 2H, N*H*CON*H*), 6.8 (d, 1H, $J_{H\alpha-NH} = 8.5$, N*H*C*), 7.18–7.38 (m, 10H, PhH), 7.8 (br t, 1H, C*C(O)NH). ^{13}C NMR ($CDCl_3$): δ = 25.86, 25.91 ($CH_2CH_2(CH_2)_2CH_2CH_2$), 28.06 ($CH_3)_3C$), 28.84, 29.75 ($CH_2CH_2(CH_2)_2CH_2CH_2$), 38.84 ($CH_2(CH_2)_4CH_2$), 39.54 (Ph*C*H$_2$C*), 41.93 (*C*H$_2$C(O)O), 55.85 (*C**), 66.48 (*C*H$_2$-benzyl), 79.40 (*C*(CH$_3$)$_3$), 126.42, 127.93, 128.08, 128.12, 128.30, 129.10 (Ar*C*H), 135.21, 136.86 (PhC_{ipso}-benzyl + PhC_{ipso}CH$_2$C*), 155.56 (NH*C*(O)O), 158.72 (NH*C*(O)NH), 171.40 (*C*(O)O), 171.93 (NH*C*(O)). MALDI-TOF MS: M_r. calc. for $[M + Na]^+$ 577.30, found 577.07.

***N*′(6(Carboxymethyl-1,3-ureido)hexyl)-*N*-*tert*-Boc-L-phenylalaninamide (7).** To a 1 : 1 v/v mixture of *t*-butanol and water (50 mL) was added 1.00 g (0.15 mmol) of ester **2** and 40 mg of Pd/C catalyst (load: 10%). Subsequently, N_2 gas was bubbled through the solution for 15 minutes. The flask was put in a Parr-apparatus, and was shaken for 3 hours under a H_2 atmosphere (pressure: 50 Psi). Subsequently the suspension was filtered to remove the catalyst and the solvent was evaporated *in vacuo*, to give acid **7** as a white sticky foam (0.75 g, 89%). Mp: 71–73 °C. Calc. for $C_{23}H_{36}N_4O_6$: C, 59.47; H, 7.81; N, 12.06%, found C, 59.73; H, 7.94; N, 11.68%. ATR-IR: ν (cm^{-1}) = 3312.3, 2978.7, 2932.9, 2859.8, 1646.6, 1563.3, 1498.3, 1455.3, 1440.3, 1392.6, 1366.7, 1264.9, 1248.0, 1165.4, 699.6. ^{1}H NMR (DMSO-d6): δ = 1.18–1.40 (br, 8H, $CH_2(CH_2)_4CH_2$), 1.29 (s, 9H, $(CH_3)_3C$), 2.7 (dd, 1H, $J_{H'-H\alpha} = 9.0$, $J_{H'-H''} = 13.6$, PhC*H*′H″C*), 2.9 (dd, 1H, $J_{H'-H''} = 13.6$, $J_{H''-H\alpha} = 5.0$, PhCH′*H*″C*), 2.95–3.1 (m, 4H, $(CH_2(CH_2)_4CH_2)$), 3.63 (d, 2H, $J_{CH2-NH} = 5.9$, NHCH_2C(O)), 4.1 (pseudo dt, 1H, $J_{H\alpha-NH} = 8.8$, $J_{H\alpha-H'} = 9.0$, $J_{H\alpha-H''} = 5.0$, C*H), 6.0, 6.1 (t, 2H, $J_{NH-CH2} = 5.8$, N*H*CON*H*), 6.8 (d, 1H, $J_{H\alpha-NH} = 8.8$, N*H*C*), 7.23 (m, 5H, Ph*H*), 7.84 (t, 1H, C*HN*H*C(O)). ^{13}C-NMR (DMSO-d_6): δ = 26.34 ($CH_2CH_2(CH_2)_2CH_2CH_2$), 28.36 (C(CH_3)$_3$, 29.22, 30.22 (NHC(O)NHCH$_2$*C*H$_2$ + *C*H$_2$CH$_2$NHC(O)C*), 38.01 (*C*H$_2$NHC(O)C*), 42.96 (*C*H$_2$C(O)OH), 56.01 (*C**H), 78.15 (*C*(CH$_3$)$_3$), 126.37, 128.20, 129.40 (Ph*C*H), 138.37 (PhC_{ipso}), 155.36 (NH*C*(O)O(CH$_3$)$_3$), 158.23 (NH*C*(O)NH), 171.51 (*C*(O)OH), 173.39 (NH*C*(O)C*). MALDI-TOF MS: M_r calc. for $[M + Na]^+$ 487.25, found 487.09.

References

1 R. G. Denkewalter, J. Kolc and W. J. Lukasavage, *US Pat.*, 4, 289, 872, Sept. 15, 1981.
2 D. Seebach, J. M. Lapierre, K. Skobridis and G. Greiveldinger, *Angew. Chem., Int. Ed. Engl.*, 1994, **106**, 457–458.
3 D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz and H. Sellner, *Top. Curr. Chem.*, 1998, **197**, 125–164.
4 H. W. I. Peerlings and E. W. Meijer, *Chem. Eur. J.*, 1997, **3**, 1563–1570. In this publication the values for DAB(PA-LPhe)$_x$ should be negative instead of positive.
5 J. R. McElhanon and D. V. McGrath, *J. Am. Chem. Soc.*, 1998, **120**, 1647–1656.
6 J. F. G. A. Jansen, E. M. M. de Brabander van den Berg and E. W. Meijer, *Science*, 1994, **266**, 1226–1229.
7 The specific optical rotation was originally defined as $[\alpha]_D^{20} = 100.\alpha/(c.l)$, in which α is the observed optical rotation in degrees, c the concentration in grams per 100 milliliter solution and l the length of the tube in decimeters. The notation $[\alpha]_D^{20}$ is used to indicate the temperature (20 °C) and the wavelength of the light (D line of a sodium lamp: $\lambda = 599.6$ nm). Nowadays the following equation is used in textbooks, which is slightly different: $[\alpha]_D^{20} = \alpha/(c.l)$. In this case the concentration is given in grams per milliliter solution, resulting in the same value for the specific optical rotation. Throughout this article the old convention is used, so $c = 1$ refers to a concentration in grams per 100 milliliters.
8 W. T. S. Huck, L. J. Prins, R. H. Fokkens, N. M. M. Nibbering, F. C. J. M. van Veggel and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1998, **120**, 6240–6246.
9 S. Uppuluri, D. R. Swanson, L. T. Piehler, J. Li, G. L. Hagnauer and D. A. Tomalia, *Adv. Mater.*, 2000, **12**, 796–800.
10 R. M. Crooks, M. Zhao, L. Sun, V. Chechik and L. K. Yeung, *Acc. Chem. Res.*, 2001, **34**, 181–190.
11 M. Blanzat, C.-O. Turrin, E. Perez, I. Rico-Lattes, A.-M. Caminade and J.-P. Majoral, *Chem. Commun.*, 2002, 1864–1865.
12 N. Higashi, T. Koga and M. Niwa, *ChemBioChem*, 2002, **3**, 448–454.
13 M. W. P. L. Baars, A. J. Karlsson, V. Sorokin, B. F. W. de Waal and E. W. Meijer, *Angew. Chem. Int. Ed.*, 2000, **39**, 4262–4265.
14 M. A. C. Broeren, J. L. J. van Dongen, M. Pittelkow, J. B. Christensen, M. H. P. van Genderen and E. W. Meijer, *Angew. Chem. Int. Ed.*, 2004, **43**, 3557–3562.
15 D. de Groot, B. F. M. de Waal, J. N. H. Reek, A. P. H. J. Schenning, P. C. J. Kamer, E. W. Meijer and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2001, **123**, 8453–8458.
16 U. Boas, A. J. Karlsson, B. F. M. de Waal and E. W. Meijer, *J. Org. Chem.*, 2001, **66**, 2136–2145.
17 U. Boas, S. H. M. Söntjens, K. J. Jensen, J. B. Christensen and E. W. Meijer, *ChemBioChem*, 2002, **3**, 433–439.
18 M. Pittelkow, J. B. Christensen and E. W. Meijer, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 3792–3799.
19 H. W. I. Peerlings and E. W. Meijer, *Tetrahedron Lett.*, 1999, **40**, 1021–1024.
20 D. Banerjee, M. A. C. Broeren, M. H. P. van Genderen, E. W. Meijer and P. L. Rinaldi, *Macromolecules*, 2004, **37**, 8313–8318.
21 10 mg of **6** results in 0.01/554.69 = 1.80 × 10^{-5} moles of L-phenylalanine units. 10 mg of **3a** results in (0.01/2038.88) × 4 = 1.96 × 10^{-5} moles of L-phenylalanine units. 10 mg of **3e** results in (0.01/34725.58) × 64 = 1.84 × 10^{-5} moles of L-phenylalanine units. The amount of chiral units that determine the optical rotation are approximately the same.
22 These results will be published elsewhere.