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ORIGINAL ARTICLE

Molecular recognition: minimizing the acid–base interaction of a tunable host–guest system changes the selectivity of binding

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Abstract Two new receptors incorporating a 4-*n*-butyl aniline moiety has been designed, synthesized and evaluated for their binding properties towards a series of ureidoglycine derivatives. The host design is based on an urea adamantyl host motif known from large generations of poly(propylene imine) dendrimers functionalized with urea adamantyl moieties on the periphery. The design of the host molecules was directed towards a study of the effects of basicity of an amine function versus the effect of molecular recognition on the binding strength as seen from comparing the results obtained in the present work with previously guest–host studies. The guest–host interaction features an electrostatic interaction and multiple hydrogen binding interactions, where the main difference between the hosts described here and previously described is a substitution from an amine to aniline. Anilines are weaker bases than aliphatic amines and they generally give lower binding constants when treated with acidic guest molecules. The association constants have been measured using NMR titrations and the nature of the guest–host system is discussed based on these results. A general decrease in binding affinities is observed upon changing from the trialkyl amine hosts to the dialkyl aniline based hosts. One exception was observed where the weaker base host had stronger affinity to one of the guests. Thus, when the basicity of the host is decreased other factors influence the binding such as a better geometric fit. A crystal structure of one of the receptors has been solved and it shows no intramolecular hydrogen bonding.

Keywords Anilines · Hydrogen bonding · NMR · Supramolecular chemistry · X-ray crystallography

Introduction

Detection of small molecules, development of supramolecular polymers, understanding biological systems and the design of larger structures held together by supramolecular interactions are merely some of the subjects that rely on the understanding of non-covalent interactions [1]. Many guest–host systems utilize a combination of non-covalent interactions that allows the introduction of both high association constants and controllable spatial arrangement [2]. When a combination of non-covalent interactions is utilized in a guest–host system the factors governing the strength of the formed complex becomes increasingly complicated to quantify due to the combination of molecular recognition motifs [3]. Systematic studies of the sophisticated guest–host systems require careful molecular design in order to separate the different recognition motifs which in turn requires significant synthetic efforts and reliable physical measurements [4].

Recently a series of new guest–host motifs for exocomplexation of poly(propylene imine) dendrimers was introduced by Meijer and coworkers [5, 6]. This guest–host binding motif is outlined in Fig. 1. The guest molecules are functionalized with a carboxylic acid, a phosphonic acid or a sulfonic acid ($X = CO_2^-$, $PO(OH)O^-$, SO_3^-) [7]. The adamantyl urea functionalized poly(propylene imine) dendrimer (with the third generation shown in Fig. 1)

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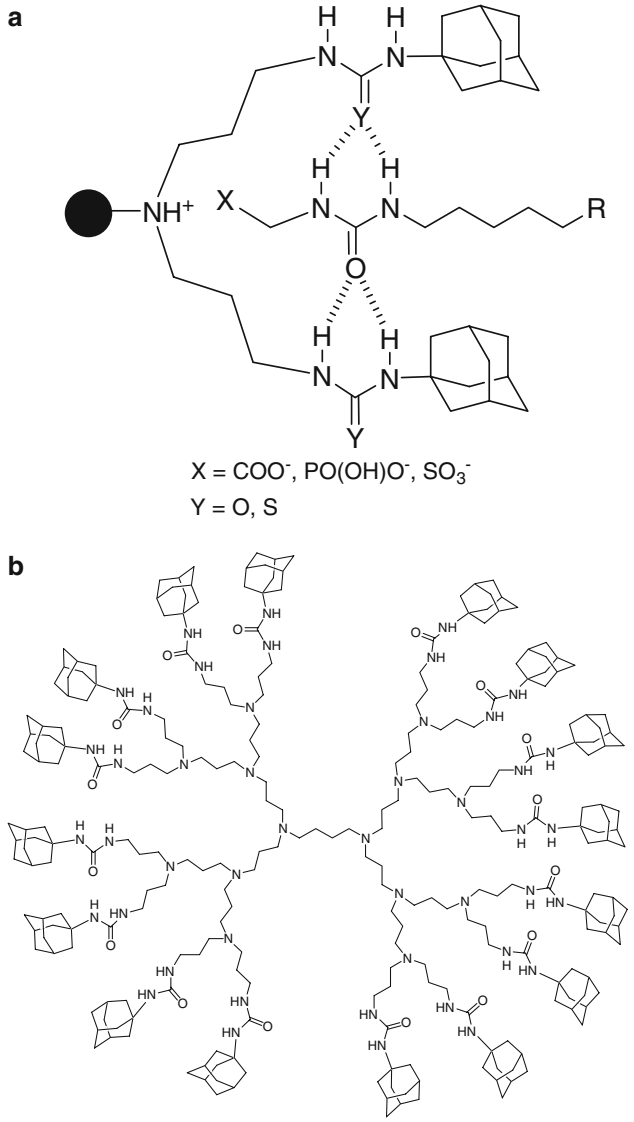


Fig. 1 (**a**) Schematic representation of the guest–host systems previously studied (**b**) third generation adamantyl urea terminated poly(propylene imine) dendrimer that are capable of binding 8 guest molecules

serves as a multivalent host for the guest molecules enabling the isolation of well-defined complexes with one guest per host motif at the periphery of the dendrimer [8]. The complexation is due to a combination of effects: multivalent hydrogen bonding between the urea moieties of the guests and the host and an electrostatic interaction between the acidic part of the guest and the tertiary amine in the host moiety. In the large generations of dendrimers many different conformations and protonation states are possible for the dendrimer. This opens for the possibility of different binding options for the acidic guest molecules; however, this does not significantly alter the stoichiometry of dendrimer-guest binding in the system introduced by Meijer [9–11]. It has been shown that the binding affinity of the guest–host system is tuneable by rational design of the guest molecules, as studied in solution by NMR and fluorescence spectroscopy [9–11]. Stability studies have been carried out in the gas-phase employing electrospray mass spectrometry [12]. Fréchet and co-workers have used the guest–host system to construct dendritic 'bow-ties' by complexing two different dendrons (wedges) fitted with the guest and the host motif, respectively [13, 14].

In the present work anilines have been incorporated into the known adamantyl urea host where the amine functionality is placed as a substituent on a benzene derivative. This enables a direct comparison of the dialkyl aniline based hosts with the trialkyl amine based hosts. Association constants have been measured using NMR titrations and are used to discuss the nature of the guest–host system supported with a single crystal X-ray structure of one of the host molecules.

Experimental section

General comments

Unless otherwise stated, all starting materials were obtained from commercial suppliers and used as received. Solvents were HPLC grade and were used as received. Thin-layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F (Merck 5554). Dry column vacuum chromatography was carried out using silica gel 60 (Merck 9385, 0.015–0.040 mm). Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian instrument. Samples were prepared using deuterated solvents ($CDCl_3$, DMSO-d_6, CD_2Cl_2) purchased from Cambridge Isotope Labs. Fast atom bombardment (FAB) spectra were obtained on a Jeol JMS-HX 110 Tandem Mass Spectrometer in the positive ion mode using 3-nitrobenzyl alcohol (NBA) as matrix. EI-MS spectra were recorded on a ZAB-EQ (VG-Analytical) instrument. Microanalyses were performed by Mrs Birgitta Kegel at the Microanalytical Laboratory at the Department of Chemistry, University of Copenhagen. MALDI-TOF mass spectra were recorded on a Bruker instrument. ESI (electrospray ionization) mass spectra were recorded on a Micromass Q-TOF apparatus. Compounds **3** [9–11], **4** [9–11], **5** [9–11], **8** [15], **10** [15], **11** [16] and **13** [17] were prepared according to literature procedures.

X-ray crystallographic data: Intensity data were collected at 122 K on a Bruker–Nonius KappaCCD diffractometer equipped with an Oxford Cryostream and graphite monochromized MoK_α radiation. The compound crystallizes in

the monoclinic space group $P2_1/c$. Data were reduced with EvalCCD [18], the structures solved by direct methods and refined by least-squares against F^2 with SHELX97 [19, 20] as incorporated in the maXus program [21].

1-(2-{(4-Butyl-phenyl)-[2-(3-adamantyl-ureido)-propyl]-amino}-propyl)-3-adamantyl urea (1_i)

Dinitrile **7** (5.0 g, 20 mmol) was dissolved in 96% EtOH (100 mL) and 2 M NaOH (100 mL) was added. Raney-Ni alloy (15 g) was added in small portions to the stirred mixture. The reaction mixture was stirred over night, filtered and the metal residue was washed with CH_2Cl_2. The combined phases were extracted with CH_2Cl_2, which was dried over K_2CO_3, filtered through paper and concentrated in vacuo to give the crude triamine product (3.7 g, 72%), which was used without further purification in the next step. 85% pure according to GC–MS: 263 (M^+). A portion of the crude triamine (**9**) (0.99 g, 3.76 mmol) was dissolved in CH_2Cl_2 (20 mL) and a solution of 1-adamantyl isocyanate (1.47 g, 8.27 mmol) in CH_2Cl_2 (20 mL) was added. The reaction mixture was stirred at room temperature over night. The crude product was filtered off and crystallized from EtOH to give the title compound as a white crystalline material. Yield: 0.96 g, 38% (2 steps). ^{1}H-NMR showed the presence of EtOH and the elemental analysis corresponds to **1 EtOH**. Mp: I: 63.8. II: 175.8 (DSC). ^{1}H-NMR (300 MHz; $CDCl_3$) δ 7.00 (d, $J = 8.2$ Hz, 2H); 6.67 (d, $J = 8.5$ Hz, 2H); 4.72 (br s, 2H); 4.41 (s, 2H); 3.22 (m, 8H); 2.50 (t, $J = 7.3$ Hz, 2H); 2.06 (s, 6H); 1.96 (m, 12H); 1.57 (m, 16H); 0.90 (t, $J = 7.3$ Hz, 3H). ^{13}C-NMR. MS: (FAB$^+$): *m/z* 618 [M^+]. Anal. Calcd. For $C_{40}H_{65}N_5O_3$ (**1 EtOH**): C, 72.36%; H, 9.87%; N, 10.55%. Found: C, 72.31%; H, 9.76%; N, 10.79%. Crystal of X-ray quality was obtained by slow evaporation from a saturated solution of the compound in ethanol.

1-(2-{(4-Butyl-phenyl)-[2-(3-adamantyl-ureido)-ethyl]-amino}-ethyl)-3-adamantyl urea ($\mathbf{2_i}$)

Ditosylate (**14**) (1.0 g, 1.83 mmol) and NaN_3 (0.30 g, 4.58 mmol) were mixed in dry DMF (15 mL) and heated to 80 °C for 3 h. The reaction mixture was cooled to room temperature and water (50 mL) was added. The reaction mixture was extracted with ether (2 × 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered through paper and evaporated to dryness in vacuo resulting in the crude di-azide (**15**). The residue was redissolved in 96% EtOH (25 mL) and hydrogenated over night at 1 atmosphere H_2 using Pd/C (50 mg, 10%) as the catalyst. The reaction mixture was filtered through paper and evaporated to dryness. Water (50 mL) was added and the solution was acidified to pH 1–2 with concentrated HCl and extracted with CH_2Cl_2 (50 mL). The aqueous phase was made strongly basic with 12 M NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered through paper and evaporated to dryness in vacuo resulting in the crude triamine (**16**). The colorless oil was then re-dissolved in dry CH_2Cl_2 (20 mL) and adamantyl isocyanate (0.81 g, 4.56 mmol) was added at room temperature under N_2. After the reaction mixture had stirred over night at room temperature it was evaporated to dryness in vacuo and purified by dry column vacuum chromatography (heptane to EtOAc with 10% increments, then EtOAc to 1:1 EtOAc/MeOH with 10% increments) to give the title compound as a white solid material. Yield 0.79 g, 73% (from **14**). Mp. 141–143°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, 2H), 6.70 (d, 2H), 5.26 (br s, 2H), 4.69 (br s, 2H), 3.30–3.38 (m, 8H), 2.49 (t, 2H), 2.02–2.04 (m, 6H), 1.92–1.94 (m, 12H), 1.63–1.65 (m, 12H), 1.55 (quint, 2H), 1.25–1.36 (m, 2H), 0.91 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 129.1, 113.7, 110.7, 90.1, 54.5, 50.6, 42.4, 38.7, 36.4, 34.5, 33.9, 29.5, 22.3, 13.9. MS (FAB$^+$): *m/z* 590.5 [$M + H^+$]. Anal. Calcd. for $C_{36}H_{55}N_5O_2$: C, 73.30; H, 9.40; N, 11.87. Found: C, 72.92; H, 9.51; N, 11.70.

1,1′-(3,3′-(Phenylazanediyl)bis(propane-3,1-diyl))bis(3-adamantyl urea) (**6**)

Triamine [11] (**10**) (1.11 g, 5.53 mmol) and 1-adamantyl isocyanate (2.09 g, 11.78 mmol) were suspended in anhydrous CH_2Cl_2 (25 mL) and stirred over night at room temperature. The resulting white precipitate was filtered off, washed with additional CH_2Cl_2 (25 mL) and dried in vacuo. The crude was recrystallized from abs. ethanol to yield the title compound as a white solid material. Yield: 2.40 g, 80%. Mp. 222–223°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ. ^{13}C NMR (100 MHz, $CDCl_3$) δ. MS (FAB$^+$): *m/z* [$M + H^+$]. Anal. Calcd. for $C_{34}H_{51}N_5O_2$: C, 72.69; H, 9.15; N, 12.47. Found: C, 72.49; H, 9.37; N, 12.18.

3,3′-(4-Butylphenylazanediyl)dipropanenitrile (**7**)

A mixture of 4-*n*-butyl aniline (14.9 g, 0.10 mol), CuCl (1.0 g, 0.01 mol), AcOH (10 mL) and acrylonitrile (20 mL) was heated to 120 °C under N_2 for 24 h. After cooling to room temperature the reaction mixture was diluted with ether (200 mL) and filtered. The organic phase was washed with 2 M NaOH (2 × 75 mL), dried ($MgSO_4$), filtered and concentrated in vacuo leaving 23 g of dark tea-colored oil. The crude was purified by column chromatography (Silica gel 60) with EtOAc. The resulting crude product was crystallized twice from EtOH (treatment

with activated carbon the first time) gave pure **7**. Yield: 8.0 g, 31%. ^{1}H NMR: (250 MHz, $CDCl_3$) δ 7.12 (d, $J = 8.7$ Hz, 2H), 6.67 (d, $J = 8.7$ Hz, 2H), 3.72 (t, $J = 6.7$ Hz, 4H), 2.60 (m, 6H), 1.57 (m, 2H), 1.34 (m, 2H), 0.93 (t, $J = 7.3$ Hz, 3 H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 142.6, 134.2, 129.7, 118.1, 114.2, 48.3, 34.4, 33.6, 22.2, 16.3, 13.8. MS (FAB$^+$) *m/z* 255 [M$^+$]. Mp. I: 65.80, II: 188.40 (DSC). Anal. Calcd. for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 74.73; H, 8.45; N, 16.49.

N-(3-Amino-propyl)-N-phenyl-propane-1,3-diamine (**10**)

Dinitrile (**8**) (5.0 g, 25.1 mmol) was dissolved in ethanol (96%, 100 mL) and aqueous NaOH (2 M, 100 mL). Raney nickel alloy (15 g) was added and the reaction mixture was stirred over night. CH_2Cl_2 (200 mL) was added and the mixture was filtered, the phases were separated and the aqueous phase extracted with additional CH_2Cl_2 (2 × 100 mL). The combined organic extracts were extracted with aqueous HCl (3 × 100 mL) and the combined aqueous phases were made strongly alkaline by addition of 12 M NaOH and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered through paper and concentrated in vacuo to give a pale yellow oil. Yield: 5.15 g, 94%. ^{1}H NMR ($CDCl_3$) δ 7.13 (t, $J = 7.7$ Hz, 2H), 6.63 (d, $J = 7.7$ Hz, 2H), 6.57 (t, $J = 7.7$ Hz, 1H), 3.28 (t, $J = 6.8$ Hz, 4H), 2.69 (t, $J = 6.8$ Hz, 4H), 1.66 (p, $J = 6.8$ Hz, 4H), 1.25 (br s, 4H). ^{13}C NMR ($CDCl_3$) δ 129.2, 115.7, 112.4, 112.3, 48.7, 40.0, 31.5. MS (FAB$^+$) *m/z* 208.2 [M + H$^+$].

2,2′-(4-Butylphenylazanediyl)diethanenitrile (**11**)

A mixture of 4-*n*-butyl aniline (9.0 g, 60 mmol), KCN (11.8 g, 0.18 mol) and $(CH_2O)_n$ (5.4 g, 0.18 mol) was cooled on ice. Acetic acid (100 mL) containing four drops of concentrated H_2SO_4 were added carefully to the stirring solution. The mixture was stirred in the ice bath for 20 min, and then heated to 50 °C overnight. The mixture was cooled to room temperature and water (250 mL) was added and the mixture was stirred over night. The crude product was filtered off, washed with water and crystallized from MeOH (50 mL, cooling to −20 °C) to yield the title compound. Yield: 6.3 g, 46%. ^{1}H-NMR: (250 MHz; $CDCl_3$): δ 7.19 (d, $J = 8.6$ Hz, 2H); 6.92 (d, $J = 8.6$ Hz, 2H); 4.19 (s, 4H); 2.58 (t, $J = 7.5$ Hz, 2H); 1.55 (m, 2H); 1.33 (m, 2H); 0.93 (t, $J = 7.3$ Hz, 3H). ^{13}C-NMR: (62 MHz; $CDCl_3$): δ 143.20; 138.22; 129.64; 117.49; 114.65; 41.11; 34.57; 33.39; 22.11; 13.74. MS (FAB$^+$) *m/z* 227 [M$^+$]. Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.98%; H, 7.54%; N, 18.49%. Found: C, 73.78%; H, 7.54%; N, 18.63%.

1-(4-Butylphenyl)piperazine (**12**)

Dinitrile **11** (2.27 g, 10 mmol) was dissolved in anhydrous THF (40 mL). Borane-dimethylsulfide (5 mL, 50 mmol) was added and the mixture was heated to refluxed for 24 h. The mixture was hydrolyzed by cautious addition of methanol. The volatiles were removed in vacuo to give the crude piperazine. Yield: 2.0 g, 92%. GC–MS: 218 (M$^+$); 176; 162; 133; 118 (Which is a parallel series to the fragmentation pattern reported for phenyl piperazine).

2,2′-(4-Butyl-phenyl)diethyl-di-*p*-toluenesulfonate (**14**)

Diol (**13**) [16] (9.86 g, 41.54 mmol) was dissolved in anhydrous pyridine (80 mL) and the solution was cooled to −5 °C before addition of TsCl (17.42 g, 91.4 mmol) in one portion. The reaction mixture was stirred for 30 min at room temperature and then left over night at 5 °C. The reaction mixture was cooled to 0 °C before (careful) addition of water (200 mL). The mixture was extracted with CH_2Cl_2 (2 × 200 mL) and 2 M H_2SO_4 was added to the combined organic extracts until the aqueous phase had a pH of approximately 1–2. The phases were separated and the aqueous phase extracted with additional CH_2Cl_2 (2 × 75 mL). The combined organic phases were washed with water (100 mL), then saturated $NaHCO_3$ (100 mL) and then brine (100 mL). The organic phase was dried (Na_2SO_4), filtered through paper and evaporated to dryness in vacuo. The resulting oil was crystallized from EtOAc/heptane to yield the title compound as an off-white solid. Yield 15.0 g, 68%. Mp. 56–57°C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.62 (d, 4H), 7.18 (d, 4H), 6.88 (d, 2H), 6.45 (d, 2H), 4.02 (t, 4H), 3.50 (t, 4H), 2.41 (t, 2H), 2.38 (s, 6H), 1.44–1.50 (m, 2H), 1.25–1.35 (m, 2H), 0.86 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 145.2, 132.9, 130.1, 129.6, 129.2, 128.1, 126.2, 113.0, 66.9, 50.9, 34.7, 34.1, 22.6, 21.9, 14.2. MS (FAB$^+$): *m/z* 544.8 [M + H$^+$]. Anal. Calcd. for $C_{28}H_{35}NO_6S_2$ C, 61.63; H, 6.46; N, 2.57. Found: C, 61.45; H, 6.46; N, 2.55.

Results and discussion

Hosts

In previous work the tunability of the guest–host system was studied by varying both the host motif and the guest motif. In one study the length of the spacer connecting the tertiary amine and the urea moiety was varied from propyl to ethyl [9]. This variation generally led to lower association constants to the ureido-glycine based guest molecules ascribed to a better molecular fit of the propyl-based host with the guests, as the entropic cost for binding to a guest is higher for

the propyl host as compared to the ethyl host [9]. In another study the urea part of the host motif was changed to a thiourea moiety on large generation poly(propylene imine) dendrimers [22]. This led to slightly higher association constants as compared to the urea based host. It was argued that this effect was a result of a less tightly self associated host prior to the insertion of the guest.

Changing the host part of the guest–host system to an aryl amine instead of an alkyl amine provides a tool for studying the effect of the basicity of the host molecule. 4-*n*-Butyl aniline proved convenient as the aniline part of the host molecules as shown in Fig. 2 for a number of reasons. First of all it proved necessary to incorporate the *n*-butyl group to the host molecules to give the necessary solubility in chloroform. Chloroform is a convenient solvent for studying the guest–host interactions using NMR. The presence of the alkyl group in 4-*n*-butyl aniline could potentially induce liquid crystalline behavior in the guest–host system, and this was also a governing factor for choosing this component. Two different hosts based on 4-*n*-butyl aniline were prepared (Fig. 2), with different spacer lengths between the aniline nitrogen and the ureido moieties. Host $\mathbf{1}_i$ is equivalent to the binding motif of the periphery of the poly(propylene imine) dendrimers and host $\mathbf{2}_i$ simply has an ethylene spacer replacing the propylene spacer. Host $\mathbf{2}_i$ was prepared to study the flexibility of the host binding motif. In Fig. 2 the anthracene based hosts used in previous studies are also shown for comparison ($\mathbf{1}_t$ and $\mathbf{2}_t$) [9–11].

Guests

The design of the original type of guest motif has an ureido-glycine tail in the binding motif [5, 6]. This opens the path to several structural modifications to obtain tunability of the association constants. By changing the acid part from a carboxylic acid to a phosphonic acid and a sulfonic acid the association constants increased considerably [7, 10]. Removal of the urea part of the guest molecules also removes the ability to form hydrogen bonds, and it was shown that the hydrogen bonds have a considerable contribution to the binding strength [9–11]. Guest molecules based on C-terminal tripeptides have also been studied and some selectivity dependant on the nature of the amino acid side chains was observed [23].

In the present work, we have used the previously prepared series of chloroform soluble guest molecules bearing the above indicated binding motifs (Fig. 3) [9–11]. The *tris*-dodecyloxy benzoic acid part of the guest molecules induces solubility of the guests in chloroform which is the solvent of choice for this guest–host chemistry.

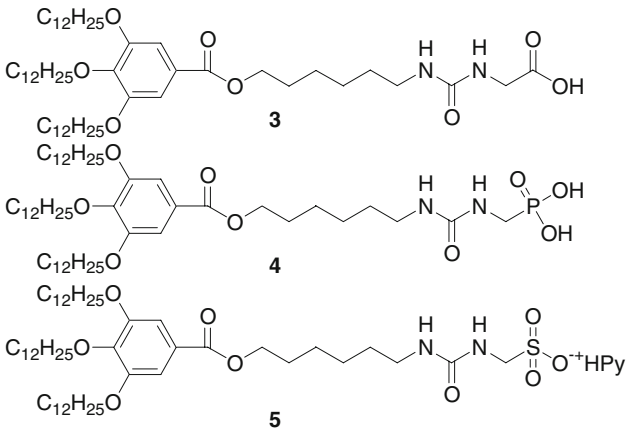


Fig. 3 Structure of the three ureido containing guest molecules **3**, **4** and **5**

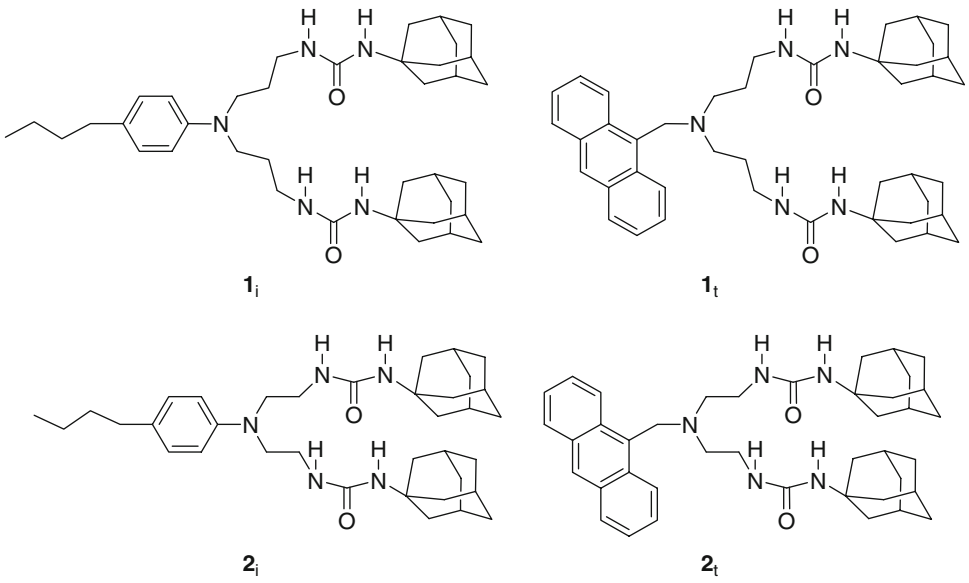


Fig. 2 Structure of the aniline hosts ($\mathbf{1}_i$ and $\mathbf{2}_i$) and the previously studied anthracene based hosts ($\mathbf{1}_t$ and $\mathbf{2}_t$)

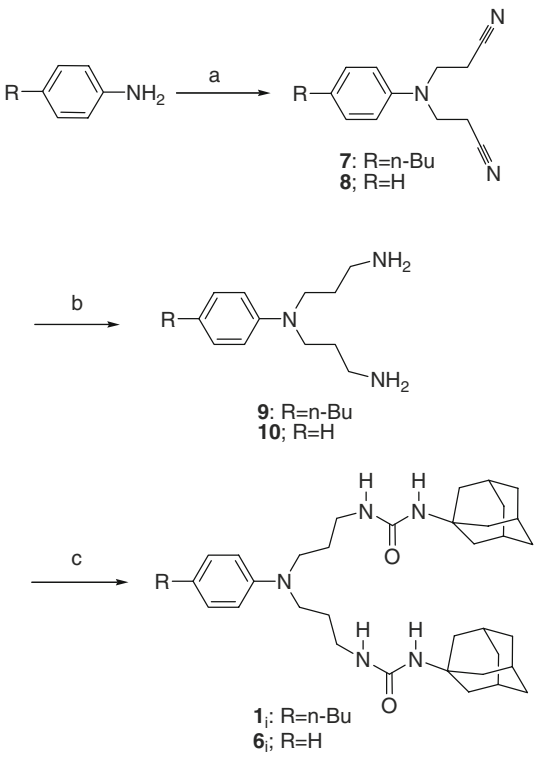
Synthesis

The synthesis of the three guest molecules (**3**–**5**) have been described previously [9–11, 22]. The synthetic procedures for the two new host molecules $\mathbf{1}_i$ and $\mathbf{2}_i$ are outlined in Schemes 1 and 3 respectively.

Host $\mathbf{1}_i$ was synthesized from 4-*n*-butyl aniline starting with a double Michael-type alkylation with acrylonitrile. The dinitrile (**7**) was reduced to the triamine in high yield using Raney nickel alloy in wet ethanol and NaOH as the base. The resulting triamine (**9**) was then treated with adamantyl isocyanate to give $\mathbf{1}_i$ in high yield. The synthesis of the host molecule without the 4-*n*-butyl group ($\mathbf{6}_i$) was conducted in a parallel fashion via the dinitrile **8** and the triamine **10**.

Attempts to synthesize the host $\mathbf{2}_i$ with the ethyl spacer groups via the corresponding dinitrile resulted in cyclization to the piperazine (**12**) through loss of NH_3 during the reduction reaction of the nitrile functionalities using a variety of reducing agents ($LiAlH_4$, AlH_3 and BH_3). This reaction has been optimized for the piperazine synthesis by catalytic hydrogenation by Mosher et al. [24] (Scheme 2).

Given the synthetic difficulties $\mathbf{2}_i$ was synthesized via the alcohol **13** as shown in Scheme 3. Diol **13** was prepared using a modification of the conditions of Liu et al. [16]. The hydroxy groups were tosylated using TsCl in anhydrous pyridine to yields the tosylate **14**. The following three steps were performed without intermediate purification and yielded the host $\mathbf{2}_i$ in high yield. The ditosylate was reacted with NaN_3 in anhydrous DMF to yield the corresponding diazide (**15**), isolated as a crude oil by an aqueous work up. The crude was reduced at 1 atmosphere H_2 in 96% ethanol using Pd/C as the catalyst. The crude triamine (**16**) was isolated as colorless oil. This was reacted with adamantyl isocyanate in CH_2Cl_2 to yield the host $\mathbf{2}_i$.



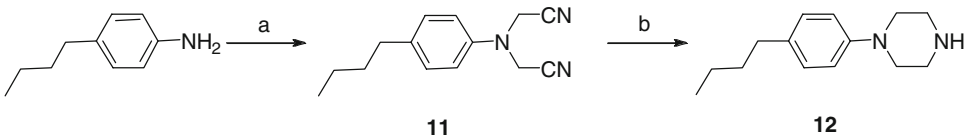
Scheme 1 Reagents and conditions: (**a**) Acrylonitrile, CuCl, 31% (**7**) (**b**) RaneyNi, EtOH, $NaOH_{(aq.)}$ (**c**) Ad-NCO, CH_2Cl_2, 38% ($\mathbf{1}_i$) (2 steps), 80% ($\mathbf{6}_i$)

1D NMR studies

The association constant between the two hosts ($\mathbf{1}_i$ and $\mathbf{2}_i$) and the three guests (**3**, **4** and **5**) were determined by ^{1}H-NMR titrations in $CDCl_3$ using the dilution method [3]. The upfield chemical shift of the ureido protons were followed as a function of the formal concentration of the complexes. The association constants for the complexes are given in Table 1. The binding constants for complexes between the previously described anthracene hosts ($\mathbf{1}_t$ and $\mathbf{2}_t$) and **3**, **4** and **5** are also included for comparison [9–11].

In general, the weaker base dialkyl aniline hosts ($\mathbf{1}_i$ and $\mathbf{2}_i$) interact less strongly with the acidic guest molecules than the trialkyl amine based hosts ($\mathbf{1}_t$ and $\mathbf{2}_t$). Some of the trends observed in previous studies are not observed in this study. First, the phosphonic acid guest (**4**) has the weakest interacting guest of the three. This is in variance with the previous studies on large dendrimers where the binding strengths clearly followed the acid strength of the guest (sulfonic acid > phosphonic acid > carboxylic acid). This illustrates that the strength of the guest–host complex rely on several simultaneous interactions and the acidity of the guest or the basicity of the host are not autocratically determining the association constant. To our surprise the strongest of the complexes was $\mathbf{1_i} + \mathbf{3}$ which is the carboxylic acid guest and the propyl-based host. In previous studies it was shown that the propyl-based host has a better 'fit' with the carboxylic acid guest than analog hosts with

Scheme 2 Reagents and conditions: (a) $(CH_2O)_n$, NaCN, AcOH, H_2SO_4, 46% (b) $BH_3{\cdot}Me_2S$, THF



Scheme 3 Reagents and conditions: (a) 2-chloro ethanol, $CaCO_3$ (b) TsCl, pyridine, 68% (c) NaN_3, DMF (d) H_2, Pd/C (e) Ad-NCO, CH_2Cl_2, 73% (3 steps)

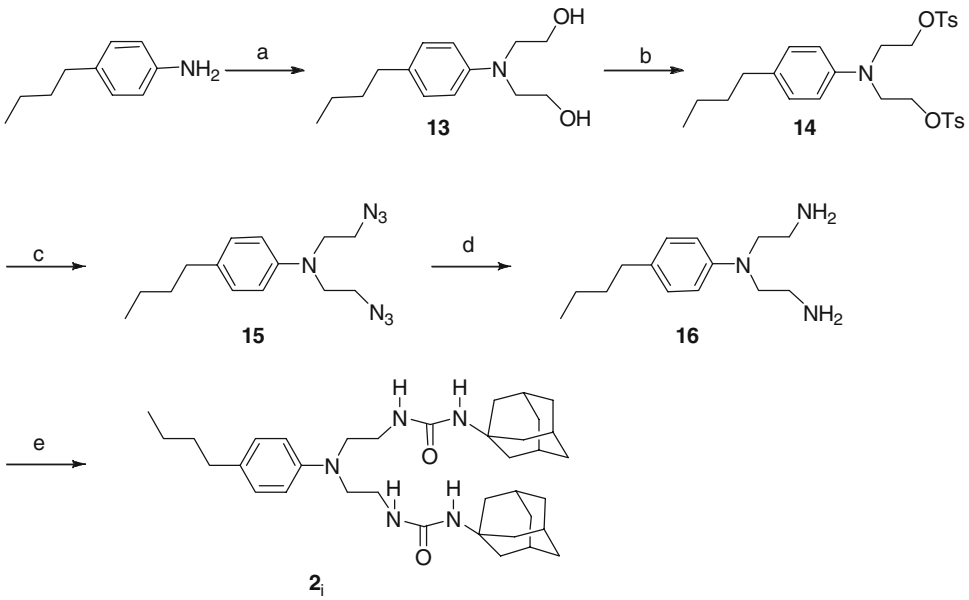


Table 1 Association constants ($\times 10^2$ M^{-1}) for the formed complexes in $CDCl_3$

Binding constants	1_i	1_t	2_i	2_t
3	33.00 ± 19.78	7.76 ± 0.43	5.39 ± 1.60	4.66 ± 0.27
4	1.52 ± 0.53	685 ± 125	2.71 ± 1.06	127 ± 9
5	10.57 ± 1.23	967 ± 57	10.29 ± 5.69	864 ± 282

ethyl spacers. This was confirmed here where the association constant is 6 times larger for $\mathbf{1}_i$ than $\mathbf{2}_i$ with guest **3**. More surprisingly was the fact that, the carboxylic acid guest (**3**) binds stronger than the phosphonic acid guest (**4**) (21 times) and the sulfonic acid guest (**5**) (3 times) to $\mathbf{1}_i$. Besides the difference in acidity of these three guests the geometry of the acidic moiety of the guests is another significant difference. The carboxylic acid is planar, while the sulfonic acid and the phosphonic acid are both tetrahedral and more space filling. This could influence a tightly bound guest–host binding motif significantly.

2D NMR studies

Both NOESY and COSY experiments were carried out on the $\mathbf{1}_i + \mathbf{3}$ complexes. The $\mathbf{1}_i + \mathbf{3}$ complex was chosen for studying the guest–host binding motif because it compares to the previous 2D NMR studies carried out on a guest–host complex with similar binding motif [8].

The urea protons have resonances at 6.40 and 6.00 ppm for both the protons in the guest and host molecules. In uncomplexed form the urea protons occurs at different resonances and the coinciding resonances for the set of urea protons have been established previously [8].

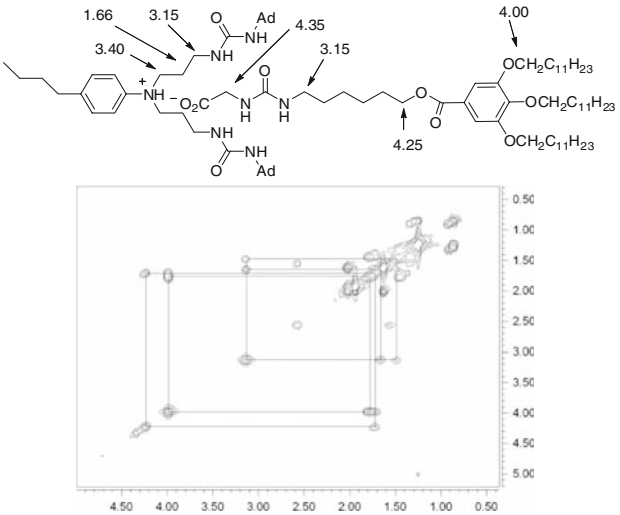


Fig. 4 ^{1}H-COSY spectrum of the guest-host complex $\mathbf{1}_i + \mathbf{3}$ in chloroform

From the ^{1}H-COSY spectrum (Fig. 4) and a ^{1}H-NMR spectrum it was possible to resolve the remaining resonances from the individual protons in the guest–host complex. Starting with the region centered at 4.35 ppm which was assigned to the methylene protons between the urea and carboxylic acid groups in the guest. This assignment was based on the integrals in the ^{1}H-NMR spectrum and the lack of any cross peaks for this resonance in the COSY spectrum. The resonance at 4.25 ppm has a cross peak showing coupling to a proton with resonance in the low-field region and correlating this with the integrals from the ^{1}H-NMR spectrum this resonance was assigned to the methylene protons next to the ester group in the guest. By a similar argumentation the resonances at 4.00 ppm was

assigned to the ether methylene protons in the guest. A resonance at 3.15 ppm is assigned to the methylene groups next to the urea groups for both the host and the guest molecules. This interpretation was supported by the presence of two cross peaks to low-field resonances and integrations in the ^{1}H-NMR spectrum. A broad resonance at 3.40 ppm was observed in the ^{1}H-NMR spectrum and by close inspection of the COSY spectrum this resonance has cross peaks to a resonance at 1.66 ppm allowing assignment of the resonances 3.40 ppm and 1.66 ppm to the remaining protons in the propyl spacer group in the host molecule. The resonance at 3.40 ppm was assigned to the protons next to the amine group. Broadening and up-field shift of this resonance in comparison to the uncomplexed host was expected as the adjacent amine gets protonated in the complexed form.

In the NOESY spectrum (Fig. 5) cross peaks between the urea protons and the resonances at 4.35 ppm was observed suggesting that binding occur. More important is the cross peaks between the 4.35 ppm and 3.15 ppm and between the 4.35 ppm and 1.66 ppm resonances. These are non-interchangeable protons, and the cross peaks show that

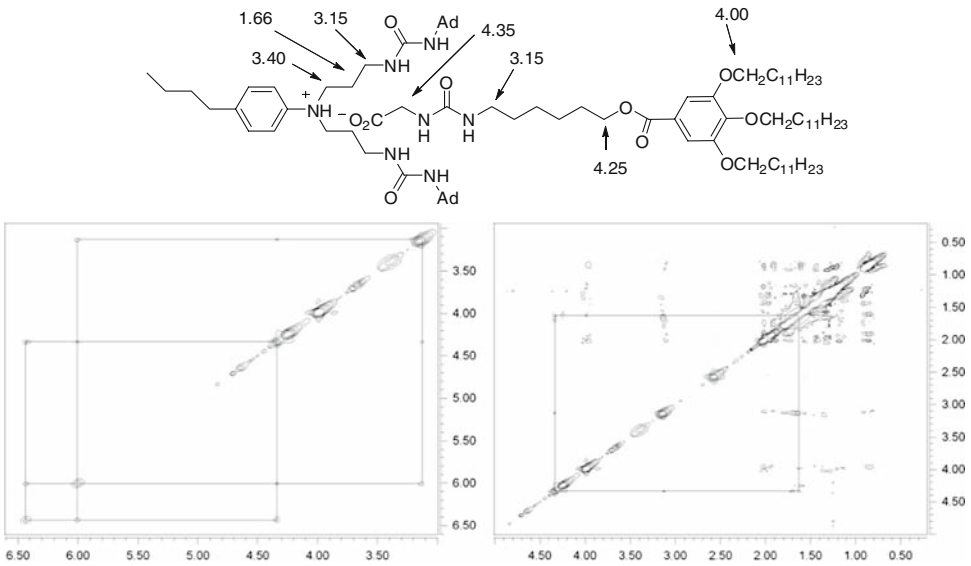


Fig. 5 ^{1}H-NOESY spectrum of the guest-host complex $\mathbf{1_i} + \mathbf{3}$ in chloroform

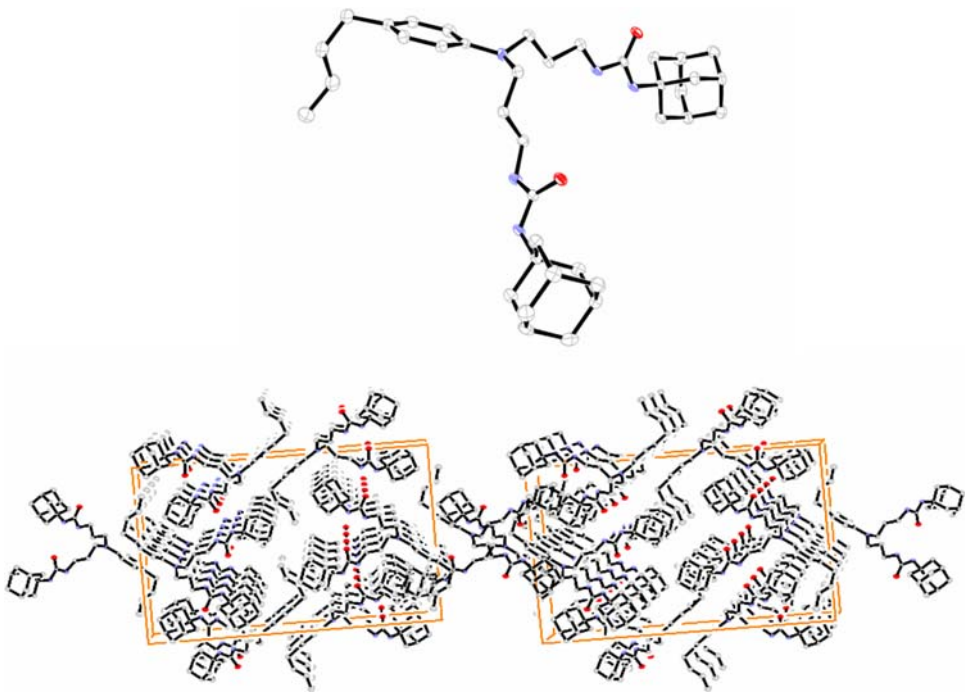


Fig. 6 Single crystal X-ray structure of host $\mathbf{1}_i$. Top: A single molecule of $\mathbf{1}_i$. Bottom: The packing of $\mathbf{1}_i$ illustrating the π-π stacking and the intermolecular hydrogen bonding

spatially specific binding between guest and host molecules according to the binding motif shown in Fig. 5.

Crystal structure studies

The single crystal X-ray structure of host molecule $\mathbf{1}_i$ was solved (Fig. 6). A single crystal of X-ray quality of the host ($\mathbf{1}_i$) was obtained by slow evaporation from a saturated solution of the compound in ethanol. The compound crystallizes in the monoclinic space group $P2_1/c$. In the solid state the dominating attractive force is intermolecular π–π stacking between two molecules of $\mathbf{1}_i$ and intermolecular hydrogen bonding. Distinct hydrogen bonding interactions between adjacent molecules are evident with N6 and N7 donating their hydrogens to O2, but no intramolecular hydrogen bonding is observed. This is presumably a consequence of the bulky nature of the adamantyl groups. This means that the binding site in the host is not pre-organized (in the solid state).

Conclusions

Two new receptors for supramolecular chemistry based on 4-*n*-butyl aniline have been designed and synthesized. Guest–host complexes with the three different guest molecules have been studied and it is clear that the stability of the formed complexes depend on several factors. In general, the weaker base aniline hosts interact less strongly with the acidic guest molecules. The results from this study is somewhat in variance with the previous studies on large dendrimers where the binding strengths clearly followed the acid strength of the guest (sulfonic acid > phosphonic acid > carboxylic acid). This illustrate that the strength of the guest–host complex rely on several simultaneous interactions and that the acidity of the guest or the basicity of the host are not autocratically determining the association constant.

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References

1. Lehn, J.M.: Supramolecular Chemistry. VCH, Weinheim (1995)
2. Atwood, J.L., Davies, J.E.D., Macnicol, D.D., Vögtle, F.: Comprehensive Supramolecular Chemistry. Elsevier Science Ltd, Oxford (1997)
3. Schneider, H.J., Yatsimirsky, A.K.: Principles and Methods in Supramolecular Chemistry. Wiley, New York (2000)
4. Chang, S., Hamilton, A.D.: Molecular recognition of biologically interesting substrates: synthesis of an artificial receptor for barbiturates employing six hydrogen bonds. J. Am. Chem. Soc. **110**, 1318 (1988). doi:10.1021/ja00212a065
5. Baars, M.W.P.L., Karlsson, A.J., Sorokin, V., de Waal, B.F.M., Meijer, E.W.: New dendrimer-peptide host–guest complexes: towards dendrimers as peptide carriers. Angew. Chem. **112**, 4432 (2000). doi:10.1002/1521-3773(20001201)39:23<4262::AID-ANIE4262>3.0.CO;2-Y
6. Baars, M.W.P.L., Karlsson, A.J., Sorokin, V., de Waal, B.F.M., Meijer, E.W.: Non-covalent synthesis of supramolecular dendritic architectures in water. Angew. Chem. Int. Ed. **39**, 4262 (2000). doi:10.1002/1521-3773(20001201)39:23<4262::AID-ANIE4262>3.0.CO;2-Y
7. Pittelkow, M., Christensen, J.B., Meijer, E.W.: Guest–host chemistry with dendrimers: stable polymer assemblies by rational design. J. Pol. Sci. A **42**, 3792 (2004). doi: 10.1002/pola.20276
8. Banerjee, D., Broeren, M.A.C., van Genderen, M.H.P., Meijer, E.W., Rinaldi, P.L.: An NMR study of supramolecular chemistry of modified poly(propyleneimine) dendrimers. Macromolecules **37**, 8313 (2004). doi:10.1021/ma049146z
9. Pittelkow, M., Nielsen, C.B., Broeren, M.A.C., van Dongen, J.L.J., van Genderen, M.H.P., Meijer, E.W., Christensen, J.B.: Molecular recognition: comparative study of a tunable host–guest system by using a fluorescent model system and collision-induced dissociation mass spectrometry on dendrimers. Chem. Eur. J. **11**, 5126 (2005). doi:10.1002/chem.200401230
10. Hermans, T.M., Broeren, M.A.C., Gomopoulos, N., Smeijers, A.F., Mezari, B., van Leeuwen, E.N.M., Vos, M.R.J., Magusin, P.C.M.M., Hilbers, P.A.J., van Genderen, M.H.P., Sommerdijk, N.A.J.M., Fytas, G., Meijer, E.W.: Stepwise non-covalent synthesis leading to dendrimer-based assemblies in water. J. Am. Chem. Soc. **129**, 15631–15638 (2007). doi:10.1021/ja074991t
11. Chang, T., Pieterse, K., Broeren, M.A.C., Kooijman, H., Spek, A.L., Hilbers, P.A.J., Meijer, E.W.: Structural elucidation of dendritic host-guest complexes by X-ray crystallography and molecular dynamics simulations. Chem. Eur. J. **13**, 7883–7889 (2007). doi:10.1002/chem.200700572
12. Broeren, M.A.C., van Dongen, J.L.J., Pittelkow, M., Christensen, J.B., van Genderen, M.H.P., Meijer, E.W.: Molecular recognition: comparative study of a tunable host-guest system by using a fluorescent model system and collision-induced dissociation mass spectrometry on dendrimers. Angew. Chem. **116**, 3579 (2004). doi:10.1002/anie.200453707
13. Broeren, M.A.C., van Dongen, J.L.J., Pittelkow, M., Christensen, J.B., van Genderen, M.H.P., Meijer, E.W.: Multivalency in the gas phase: the study of dendritic aggregates by Mass Spectrometry. Angew. Chem. Int. Ed. **3**, 3557 (2004). doi:10.1002/anie.200453707
14. Gillies, E.R., Frechet, J.M.J.: Dendrimers and dendritic polymers in drug delivery. J. Org. Chem. **69**(1), 46 (2004). doi:10.1021/jo035329s
15. Smith, P.A.S., Yu, T.: Some syntheses of compounds related to julolidine. J. Am. Chem. Soc. **74**, 1096 (1952). doi:10.1021/ja01124a524
16. Dimroth, K., Aurich, H. G.: Cyanomethylation of weakly basic amines. Chem. Ber. **98**, 3902 (1965). doi:10.1002/cber.19650981217
17. Liu, R.C.W., Fung, P., Xue, F., Mak, T.C.W., Ng, D.K.P.: Synthesis of mixed aza, oxa and thia crown ethers. J. Chem. Res. Miniprint **8**, 1744 (1998)
18. Duisenberg, A.J.M., Kroon-Batenburg, L.M.J., Schreurs, A.M.M.: Preparation and properties of some substituted Julolidines. J. Appl. Cryst. **36**, 220 (2003). doi:10.1107/S0021889802022628
19. Sheldrick, G.M.: An intensity evaluation method. Acta. Crysallogr. A **46**, 467 (1990). doi:10.1107/S0108767390000277

20. Sheldrick, G.M.: SHELXL97 Program for the Refinement of Crystal Structures. University of Göttingen, Germany, 1997
21. Mackey, S., Gilmore, C.J., Edwards, C., Stewart, N., Shankland, K.: MaXus Computer Program for the Solution and Refinement of Crystal Structures. Bruker Nonius. Macscience, Japan & The University of Glasgow, The Netherlands 1999
22. Boas, U., Karlsson, A.J., de Waal, B.F.M., Meijer, E.W.: Synthesis and properties of new thiourea-functionalized poly (propylene imine) dendrimers and their role as hosts for urea functionalized guests. J. Org. Chem. **66**, 2136 (2001). doi: 10.1021/jo001573x
23. Boas, U., Söntjens, S.H.M., Jensen, K.J., Christensen, J.B., Meijer, E.W.: New dendrimer-peptide host–guest Complexes: towards dendrimers as peptide carriers. ChemBioChem **3**, 433 (2002). doi:10.1002/1439-7633(20020503)3:5<433::AID-CBIC 433>3.0.CO;2-0
24. Mosher, H.S., Cornell J. Jr., Stafford, O.L., Roe T.J. Jr.: Synthesis of piperazines by reductive cyclization. Am. Chem. Soc. **75**, 4949 (1953). doi:10.1021/ja01116a020