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The Localization of Guests in Water-Soluble Oligoethyleneoxy-Modified Poly(propylene imine) Dendrimers**

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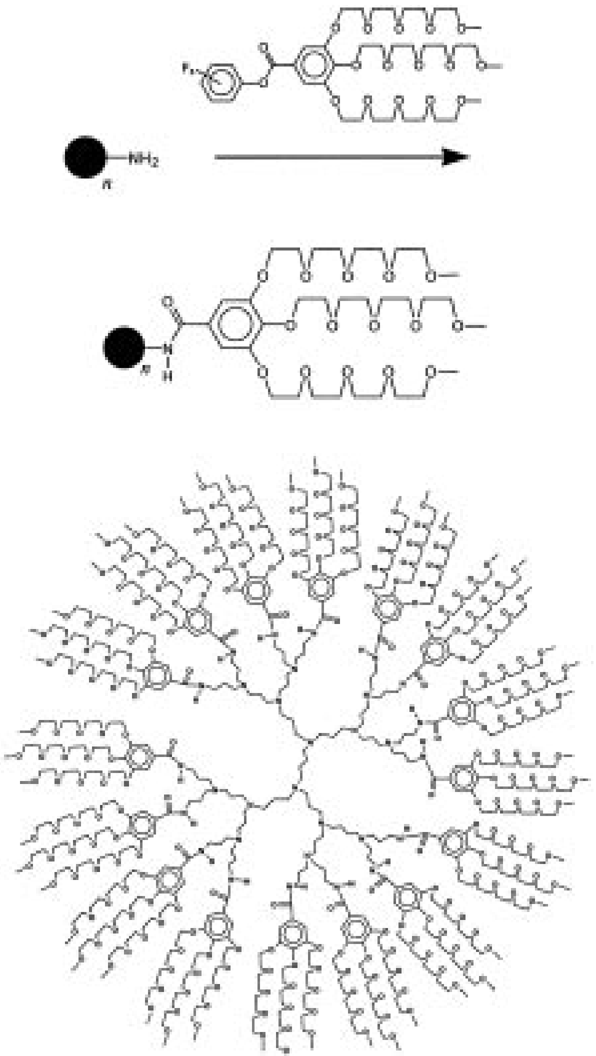
The highly branched, three-dimensional geometry of dendritic macromolecules[1] makes these new molecular architectures ideal container molecules.[2] It has been suggested that these molecules could be used in a number of applications including those related to the controlled release of pharmaceuticals.[3, 4] Several host–guest systems have already been developed, for example, dendritic hosts with unimolecular (inverted) micellar structures,[5] the "dendritic box",[6] crown ether dendrimers,[7] and cyclophane dendrimers.[8] A restricted number of guests, such as rose bengal, can be encapsulated in the "dendritic box", (a fifth generation poly(propylene imine) dendrimer modified with a dense shell of amino acids)[6] and released by simple chemical modification of the shell.[6c] Dynamic hosts in organic media[9a] or supercritical CO_2[9b] are based on hydrophobically modified poly(propylene imine) dendrimers and have proved to be efficient extractants of aqueous solutes. Recently, more attention has been focussed on water-soluble dendritic systems,[10] but their host–guest properties have not been addressed so far. Herein we present poly(propylene imine) dendrimers modified with 3,4,5-tris(tetraethyleneoxy)benzoyl units, which have a basic interior of tertiary amines and a hydrophilic periphery (Scheme 1). Titrations and small angle X-ray scattering



Scheme 1. Top: Synthesis of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers; $n = 4$: **1**; $n = 16$: **2**; $n = 32$: **3**, and $n = 64$: **4**. Bottom: Schematic structure of host **2**.

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

(SAXS) experiments show that unique interactions lead to the preferential location of guests in the core of these novel, unimolecular water-soluble dendritic hosts.

Four different generations of oligoethyleneoxy-functionalized poly(propylene imine) dendrimers (DAB-*dendr*-(NHCO-EG)$_n$, where EG represents the 3,4,5-tris(tetraethyleneoxy)-benzoyl unit and with $n = 4$: **1**, $n = 16$: **2**, $n = 32$: **3**, and $n = 64$: **4**) have been synthesized by reaction of the corresponding pentafluorophenyl ester with the amine-functionalized poly(propylene imine) dendrimers. Dendrimers **1**–**4** and all intermediates have been characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy as well as by mass spectrometry (ESI or MALDI-TOF). The functionalized dendrimers are monodisperse compounds, for example, a single peak is observed at $m/z = 13243$ in the mass spectrum of the third generation dendrimer **2**, which corresponds to the correct mass. The defects that are observed in the fourth and fifth generation can be attributed to defects already present in the amine-functionalized poly(propylene imine) dendrimers,[11] and are not a result of incomplete modification of the dendrimer end groups.

The host–guest properties of these dendritic structures were studied in buffered aqueous media at pH 7 using two anionic, water-soluble xanthene dyes as guest molecules (**I**: 4,5,6,7-tetrachlorofluorescein, **II**: rose bengal). Titration of a stock solution of **4** to a solution of guests **I** or **II** yielded a bathochromic shift in the wavelength of the maximum absorption (λ_{max}) in both cases, which is indicative of an interaction (complexation) between the dendrimer host and the xanthene guest. This complexation was studied by plotting the ratio of the absorptions corresponding to the complexed and free guest against the guest–host ratio (GHratio; Figure 1).[12] The complexation of guest **II** with the dendritic host is much stronger than for guest **I**, with association constants K_a of $(5.0 \pm 0.04) \times 10^5\,\mathrm{M}^{-1}$ and $(3.0 \pm 0.4) \times 10^4\,\mathrm{M}^{-1}$, respectively. Upon titration of **I** with **4** the absorption at the λ_{max} of the free dye decreases and there is an isosbestic point over the whole titration range, which is indicative of an equilibrium existing between the complexed and free dye. The single isosbestic point indicates that the λ_{max} of the complexed dye is independent of the number of dyes complexed. More information can be obtained from the titration of **II** with **4** (Figure 1, bottom right) where three different regimes and two inflection points (marked by arrows) at GHratios of 1 ± 0.5 and 40 ± 5 can be distinguished. Moreover, the UV spectra not only reveal complexation of the guest, but also the effect of dye–dye interactions inside a single host. Between $0 <$ GHratio < 1 a strong complexation of the guest takes place and a constant absorption spectrum is obtained (regime A). Between $1 <$ GHratio < 40 all the guests are strongly complexed, but as a result of dye–dye interactions of the guest within one host molecule a decrease in the ratio A_{563}/A_{547} is

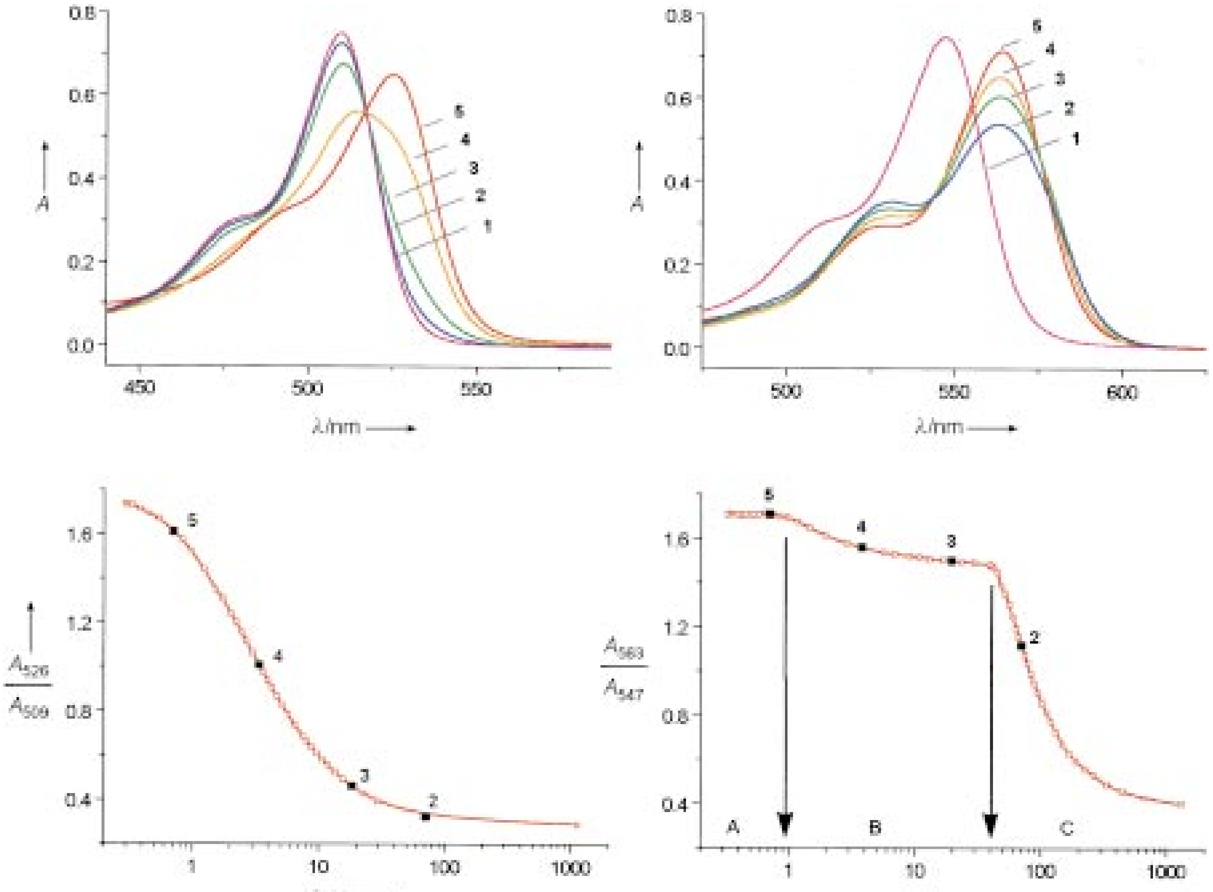

Figure 1. Top: UV/Vis spectra obtained from the titration of guest **I** (left) and **II** (right) with **4**. Typical UV/Vis spectra are marked from 1 to 5. Bottom: Ratio of the absorption of the complexed dye to the free dye as a function of the GHratio for guest **I** (left) and guest **II** (right). Numbers 2–5 are used to refer to the UV/vis spectra. Number 1 at infinite GHratio is omitted.

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observed (regime B). Finally, for a GHratio > 40 an excess of guest is present in equilibrium with complexed guest molecules (regime C).

The association between the host and guest described above is explained by acid–base interactions between the acidic functionality of the guest and the tertiary amine groups of the dendritic host, similar to previously reported host–guest systems[9a, 13] This argument is also supported by the association behavior of **I** being strongly pH dependent. The smaller pH-dependence of **II** suggests, however, that it is not only electrostatic interactions, but also the higher hydrophobicity of **II**[12] that plays an important role in the association process. The stability of the system is demonstrated by an ultrafiltration technique, in which a membrane with a molecular weight cut-off of approximately 10 kDa was used. We were able to distinguish between host–guest complexes formed with hosts **1** (3 kDa) and **4** (53 kDa). In the case of host **4**, all the guest molecules are retained in the filtration cell, which is indicative of the high molecular weight of the host and the strong host–guest association. This result is in contrast to a host–guest complex of **1**, which passes through the membrane.

The structure of dendrimer **4** in different solutions has been analyzed by SAXS measurements.[14] The oligoethyleneoxy-functionalized dendrimers are soluble in toluene, dichloromethane, tetrahydrofuran, acetonitrile, ethylene glycol monomethyl ether, ethanol, and aqueous media. Interactions between the dendrimers in dilute solutions are negligible and they reveal maximum dimensions of 5.1–5.6 nm.[15] Consequently, measurements have been performed on dilute solutions (concentrations approximately 10 $\text{mg}\,\text{mL}^{-1}$) of host **4** and guest **II** at different GHratios. In all cases the SAXS intensity at low scattering vector $\boldsymbol{q}$ is described using the Guinier approximation and displayed in Figure 2 (top).

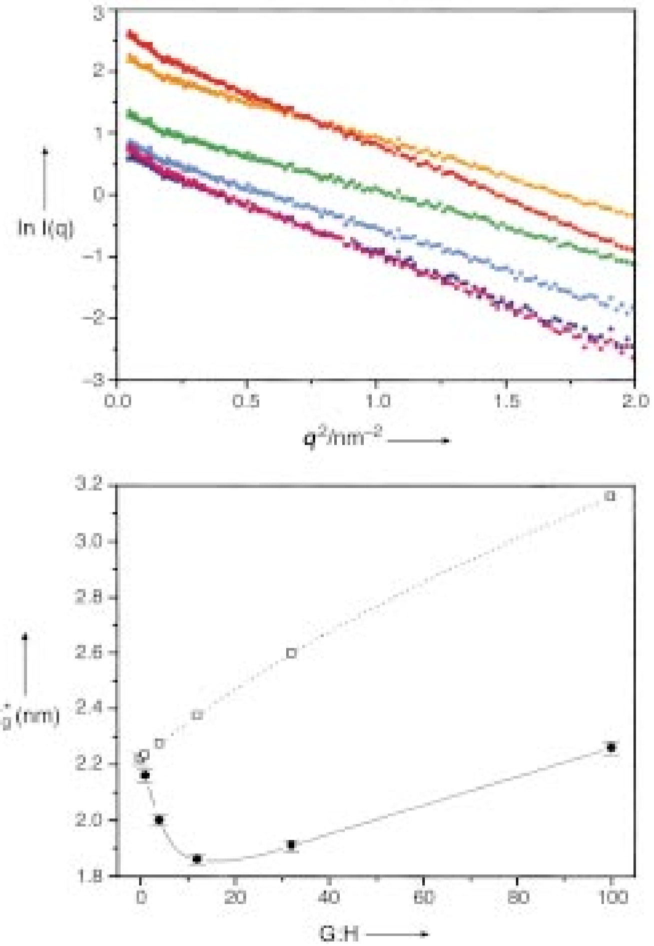

Figure 2. Top: Guinier plots for complexes of **4** and **II** for different GHratios; purple: no guest, dark blue: 1 guest, Light blue: 4 guests, green: 12 guests, yellow: 32 guests, red: 100 guests. Bottom: Radius of gyration of complexes (R_g*) of **4** and **II** as a function of the GHratio (•–•–). Expected radius of gyration of complex is included, and assumes a homogeneous distribution of guests (··□··).

This plot reveals three features: 1) the forward scattering intensity $I_h(\boldsymbol{q} \rightarrow 0)$ obtained by extrapolation and the invariant Q_h were derived in order to calculate the particle volume without absolute scaling of $\boldsymbol{q}$ [Eq. (1)].

$$V_h = \frac{2\pi^2 I_h(0)}{Q_h} \qquad (1)$$

This equation yields $V_h = 8.5 \times 10^{-26}\ \text{m}^3$ and the molar mass of the host $M_h = V\rho N_A$ is therefore 51.5 kDa when a density of 1000 $\text{kg}\,\text{m}^{-3}$ is assumed, whereas the actual molar mass is 53.5 kDa as measured by MALDI-TOF mass spectrometry. This result confirms that the SAXS pattern reflects the scattering from individual macromolecules. Additional scattering data, scaled to absolute intensities, are given in the Supplementary Information; 2) an increase in the forward scattering intensity $I(\boldsymbol{q} \rightarrow 0)$ with increasing amounts of dye molecules in the dendrimer, which not only reflects the change in molecular weight of the complex from addition of the guest molecules (1 kD) to the dendritic host (53 kD), but also a change in contrast $\Delta\rho$, since the guest molecules with chlorine and iodine atoms add a substantial amount of electrons to the system; 3) a change in the slope of the Guinier plots, which reveals a significant decrease in the radius of gyration (R_g^*) of the complex upon addition of the guest molecules (•–•–). If the dyes were uniformly distributed within the dendrimer molecules, a slight increase would be expected in both the radius of gyration of the complex (··■··) and the maximum dimensions as a result of the increase in the total molecular weight. In the present systems, however, the maximum dimensions are essentially unchanged, whereas the radius of gyration (Figure 2, bottom) decreases with an increasing number of guest molecules (up to a ratio of 12:1). Since the latter reflects the second moment of the (electron) density distribution $\rho^*(r)$ within the complex, and not $\rho(r)$ of the dendritic host, this in fact indicates that the dye molecules are preferentially accumulated in the central region of the dendritic hosts. If more guests are complexed to the dendritic hosts, the outer regions fill up and an increase in the R_g is observed. Surprisingly, with an excess of guest, that is, a GHratio of 100, the R_g equals that of the unloaded host (Figure 3).

In summary, we conclude that a new host–guest system has been developed and the interactions in aqueous media have been studied by UV/Vis titrations. A typical property of dendrimers, namely their retention in membranes as a result of their nanometer dimensions, has been shown by ultrafiltration. As there is no aggregation the SAXS measurements

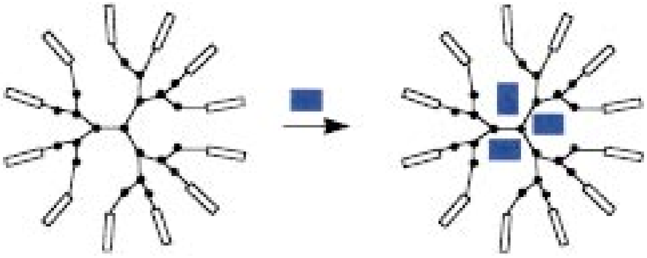

Figure 3. Schematic reprsentation of the preferential location of dye molecules in the dendrimer as the concentration of the dye is increased.

provide strong evidence for the preferential location of the guests in the interior of the dendrimer.

Experimental Section

A more extended description of the compounds, synthesis, and characterization are presented in the Supplementary Information. Moreover, experimental details and additional SAXS data are included in this section. Only a typical procedure for the synthesis of oligoethyleneoxy-modified poly(propylene imine) dendrimers is described here.

2: The pentafluorophenyl ester of 3,4,5-tris(tetraethyleneglycol)benzoic acid (8.82 g, 9.72×10^{-3} mol, 1.025 equiv per NH_2) was added to a solution of DAB-*dendr*-$(NH_2)_{16}$ (1.00 g, 5.93×10^{-4} mol) in CH_2Cl_2 (10 mL). After stirring the mixture overnight it was extracted with 0.1 M NaOH and excess active ester was removed by chromatography on biobeads (BioRad, SX1) to yield pure **2** (6.28 g, 80 %) as a viscous oil. Purity was confirmed by TLC (CH_2Cl_2/MeOH 95/5, $R_f = 0$). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (s, 16H, NHCO), 7.16 (s, 32H, Ar-H), 4.16–4.00 (96H, Ar-OCH_2), 3.80–3.45 (672H, OCH_2), 3.42 (32H, CH_2NHCO), 3.38 (144H, OCH_3), 2.60–2.30 (84H, NCH_2), 1.80–1.40 (60H, NCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.2$ (NHCO), 152.3 (Ar-C3,C5), 140.8 (Ar-C4), 129.7 (Ar-C1), 106.7 (Ar-C2,C6), 72.6/72.1/70.8/70.7/69.8/69.0 (OCH_2), 59.0 (OCH_3), 52.4–51.8 (NCH_2), 38.9 (CH_2NHCO), 27.5 ($NCH_2CH_2CH_2$NHCO); MALDI-TOF-MS: calcd. for $C_{632}H_{1136}N_{30}O_{256}$: 13251.9; found: 13243 $[M+H]^+$.

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Crystal Engineering of Metalloporphyrin Zeolite Analogues[**]

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Molecular self-assembly has emerged in recent years as an attractive approach to the fabrication of new materials.[1] This process involves the spontaneous aggregation of small molecular building blocks in solution that recognize each other through multiple molecular recognition sites to form extended architectures (while overcoming solvation forces and negative entropy effects), and it can be particularly effective in the design of nanoporous solids. However, such formula-

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