Communications to the Editor

Synthesis, Characterization, and Guest−Host Properties of Inverted Unimolecular Dendritic Micelles

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Dendrimers, being well-defined and highly-branched macromolecules, have become the subject of extensive studies,[1,2] because their multifunctionality and specific shape have been recognized as powerful tools in the synthesis of new structures. Applications of dendrimers in molecular architectures,[2] and the dendritic box,[3] show the versatility of these materials. In 1985, the use of dendrimers as unimolecular micelles was already proposed by Newkome.[4] Micellar behavior has been demonstrated by dissolving, e.g., organic molecules in dendrimers,[5a−e] whereas some dendrimers have been employed as micellar structures in electrokinetic capillary chromatography.[5f−h] In all of these cases, dendrimers are regarded as regular unimolecular micelles, which consist of an apolar core and a polar shell. In this communication we report on the synthesis of *inverted* unimolecular dendritic micelles, by the modification of the end groups of hydrophilic poly(propylene imine) dendrimers[6] (DAB-*dendr*-$(NH_2)_{4-64}$), with hydrophobic alkyl chains.

The modification consists of the conversion (in 60−95% isolated yield) of the 4− 64 primary amines of DAB-*dendr*-$(NH_2)_x$ into their amide analogues with a variety of long-chain alkyl acid chlorides ($ClCOC_n$ with $C_n = (CH_2)_{n-1}CH_3$ with $n = 5, 9-15$) in THF and in the presence of Et_3N as an external base (Scheme 1). Structural characterization of the dendritic amides (DAB-*dendr*-$(NHCOC_n)_x$) with ^{1}H-NMR, ^{13}C-NMR, IR, and MALDI-TOF spectroscopies showed that all of the dendrimer end groups were amidated.[7] Most remarkably, when the long-chain alkyl acid chlorides were used in the reaction with an excess of DAB-*dendr*-$(NH_2)_{4-64}$, two products were always isolated; water-insoluble fully reacted dendrimer (at least 90% of the end groups, as determined by ^{1}H-NMR) and water-soluble, totally unmodified dendrimers (no fatty acid amide functionality is observed by ^{1}H-NMR and IR) were obtained in the correct product ratios.[8] This effect proved to be independent with respect to solvent (THF or CH_2Cl_2), concentration of the reagents, and the degree of excess dendrimer used. The water (in)solubility of the products makes the separation and characterization very easy. However, this effect is not found for pivaloyl chloride, with which partially converted structures are prepared.[9] A reasonable explanation for the phenomenon observed is lacking at the present time.[10]

Evidence for the development of dendritic character (i.e., high packing of end groups) by increasing generation from DAB-*dendr*-$(NHCOC_n)_{4-64}$ was obtained by ^{1}H-NMR spectroscopy. A significant shift for the N*H*CO proton to lower fields with increasing generation was observed (Figure 1). The low-generations, DAB-*dendr*-$(NHCOC_n)_{4-16}$, also showed a concentration dependence of the N*H*CO position, which was absent for the two higher generations, DAB-*dendr*-$(NHCOC_n)_{32,64}$. The shift of the amide proton is a result of the change from predominantly concentration-dependent, but weak, intermolecular H-bonding for the lower generations to concentration-

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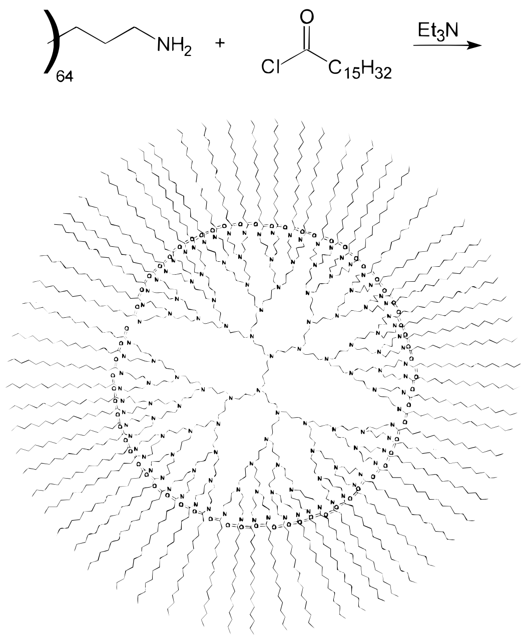
(7) . Typical preparation and characterization of an alkyl-modified dendrimer, DAB-*dendr*-$(palmitoyl)_8$: To a solution of 2.5 g DAB-*dendr*-$(NH_2)_8$ (1 equiv, 3.3 mmol) in 50 mL THF, 5.00 g triethylamine and 8.56 g palmitoyl chloride (1.10 equiv, 28.6 mmol) were added. After the mixture stirred for 20 h at room temperature, the solvent was evaporated. The mixture was heated under reflux in 50 mL of diethyl ether for 30 min and filtered, to remove excess palmitoyl chloride. To the residue, a solution of 2 g Na_2CO_3 in 50 mL H_2O was added, and the mixture was heated under reflux for 6 h, in order to remove residual ammonium salts and to deprotonate the dendrimers. The mixture was filtered, the residue was dried *in vacuo* at 40 °C, and the product was obtained as a white/yellow solid material (yield 76%). ^{1}H-NMR ($CDCl_3$): δ 0.90 (t, C*H*$_3$), 1.18−1.75 (m, C*H*$_2$−CH$_3$ + CH$_2$−C*H*$_2$−CH$_2$), 2.17 (t, NHCO−C*H*$_2$), 2.40 (m, C*H*$_2$−N−(CH$_2$)$_2$), 3.28 (q, C*H*$_2$−NHCO), 6.95 (t, N*H*CO) ppm. ^{13}C-NMR ($CDCl_3$): δ 14.10 (*C*H$_3$), 22.69 (*C*H$_2$−CH$_3$), 24.87 (N−CH$_2$−*C*H$_2$−*C*H$_2$−CH$_2$−N + N−CH$_2$−*C*H$_2$−CH$_2$−N), 25.96 (NHCO−CH$_2$−*C*H$_2$), 27.09 (N−CH$_2$−*C*H$_2$−CH$_2$−NH-CO), 29.37− 29.73 (CH$_2$−(*C*H$_2$)$_n$−CH$_2$), 31.93 (*C*H$_2$−CH$_2$−CH$_3$), 36.75 (NHCO−*C*H$_2$), 37.93 (*C*H$_2$−NHCO), 51.64 (N−*C*H$_2$−CH$_2$−CH$_2$−NHCO), 52.20 (N−*C*H$_2$−CH$_2$−CH$_2$−*C*H$_2$−N + N−*C*H$_2$−CH$_2$−*C*H$_2$−N), 173.59 (NH*C*O) ppm. IR: amide N−H stretch 3300.2 cm^{-1}, sec. amide N−H stretch 3083.8 cm^{-1}, C−H sat. 2918.1 cm^{-1}, sec. amide C═O 1638.9 cm^{-1}, N−H bend 1560.0 cm^{-1}. DSC: phase transition at 74.3 °C. MALDI-TOF: measurement of DAB-*dendr*-$(NHCOC_{15})_8$: 2683 g/mol, calcd 2678 g/mol.

(8) This phenomenon was observed for reactions between a 2-, 3-, and 4-fold excess of DAB-*dendr*-$(NH_2)_{4-64}$—based on the number of primary amine end groups—and palmitoyl and oleyl chloride. The workup procedure with the Na_2CO_3 solution resulted in separation between water-soluble DAB-*dendr*-$(NH_2)_{4-64}$ and modified DAB-*dendr*-$(NHCOC_n)_{4-64}$. Both products isolated were unambiguously identified with IR and NMR spectroscopies, and the melting points of the amidated products resembled those of the products made by using equimolar amounts of reactants. For experimental details, see the supporting information.

(9) It was found that 13 out of 64 end groups were amidated by using 0.21 equiv of pivaloyl chloride per equialent end group of DAB-*dendr*-$(NH_2)_{64}$. Workup was strongly hampered by the formation of emulsions, and some fractionation during dialysis was found. When equimolar amounts of pivaloyl chloride are used, no emulsions were observed, and the fully amidated structure was easily obtained in pure form (i.e., at least 95% of the end groups have reacted).

(10) For similar effects in calixarenes with 4−6 functional groups in one molecule, see: Shinkai, S.; Araki, K.; Shibata, J.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* **1989**, 195.

Scheme 1. Modification of DAB-*dendr*-$(NH_2)_{64}$ with Palmitoyl Chloride



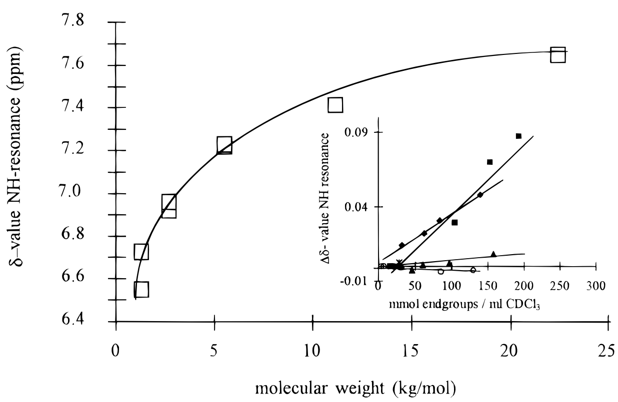


Figure 1. Generation dependence of the N*H*CO NMR resonance of DAB-*dendr*-$(NHCOC_{15})_x$ series, measured in $CDCl_3$. Inset: Concentration dependence of the N*H*CO NMR resonance of the series, measured in $CDCl_3$ (moles of alkyl amide end groups per liter): ■, $x = 4$; ◆, $x = 8$; ▲, $x = 16$; ○, $x = 32$; *, $x = 64$.

independent strong intramolecular H-bonding for the higher generations. Dynamic light scattering (DLS) also confirms the absence of clustering between DAB-*dendr*-$(NHCOC_{15})_{64}$ molecules: single particle behavior was observed with a hydrodynamic diameter of 2−3 nm in dichloromethane.

The first-generation dendrimers showed melting points (measured by DSC) that resemble those of the corresponding alkylamides, indicating that the first generation is a regular organic compound. Phase transitions observed for the higher generation dendrimers were independent of the number of end groups and fully determined by the alkyl chain length. The phase transition temperature increased continuously with increasing chain length (mp of DAB-*dendr*-$(NHCOC_n)_{8-64}$ varies from −1 °C for $n = 5$ to 75 °C for $n = 15$), and no odd−even behavior could be detected.[11,12]

Evidence for an inverted micellar structure of the alkyl amide-modified dendrimers was obtained by their capability to act as guest−host systems. DAB-*dendr*-$(NHCOC_{5,\ 9,\ 15})_{8,64}$ were used as dynamic hosts for guest molecules like Bengal Rose. The hydrophilic dye was trapped into the inverted unimolecular micelles by first dissolving micelle and dye in ethanol, allowing the dye to enter the dendritic core. Precipitation of the complex in acetonitrile, followed by an extensive washing procedure with acetonitrile until no coloration of solvent occurred, resulted in the removal of untrapped and adhered dye. The $x = 64$ compounds were further purified by dialysis with water. The number of dye molecules trapped (varying from an average of 1 for $x = 8$ to 7 for $x = 64$) was determined with UV spectroscopy.[13] It was possible to strongly improve the compatibility between Bengal Rose and an apolar solvent such as *n*-hexane by first encapsulating the dye into the inverted micelle. It was impossible to release the dye from the solution by washing with water; however, the addition of toluene to Bengal Rose@DAB-*dendr*-$(NHCOC_n)_{64}$ in *n*-hexane released the dye from the micelle. These guest−host systems also open routes toward compatibilization of apolar and polar materials using nanoscopic phase separation, as a result of the unique properties of dendritic macromolecules.[14]

Supporting Information Available: Synthetic procedures and spectroscopic properties of the palmitoyl-modified dendrimers and the yields after workup of all the fully modified structures (14 pages). See any current masthead page for ordering and Internet access instructions.

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(13) It is assumed that the absorption coefficients ϵ of "free" and encapsulated Rose Bengal, both measured in ethanol, are identical. The load of the dye is strongly dependent on both generation and fatty acid chain length. The highest number (seven) of molecules entrapped is found for DAB-*dendr*-$(NHCOC_9)_{64}$. The chain-length dependent barrier effect seems to have its optimum at C_9, in which case the hydrophobic shell favors trapping of the dye into the micelle instead of release or exclusion.

(14) Independently, Tomalia et al. prepared guest−host systems based on inverted unimolecular micelles from PAMAM dendrimers modified with fatty acids: D. A. Tomalia, personal communication.