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Amphiphilic Pyrene-Functionalized Dendrons: Synthesis and Intermolecular Interactions

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The synthesis of new functional amphiphiles **4** and **7** synthesized by DCC coupling of pyrenebutyric acid with first- and second-generation Newkome-type aminodendrons is reported. The crystal structure of the free amphiphilic tricarboxylic acid **4** exhibits efficient and cooperative usage of all possible hydrogen-bonding sites as well as π-stacking interactions. In contrast, no face-to-face π-stacking is observed in the single-crystal structure of the *tert*-butyl-protected precursor molecule **3**. As determined by DOSY-NMR spectroscopy, the second-generation amphiphile **7** forms small micelles in aqueous solutions with a diameter of about 4 nm. Absorption and fluorescence spectroscopic investigations show that amphiphile **7** is able to promote the transfer of the apolar perylene dye **8** into the aqueous phase.

Introduction

We have recently reported on the first examples of shape-persistent[1] micelles[2] whose defined three-dimensional structures could be resolved with molecular precision. The controlled self-assembly of specific amphiphilic molecules, leading to stable and precisely defined micelles, not only represents an enormous challenge for fundamental research but has also potential nanotechnological applications, such as the development of high-performance drug-delivery capsules.[3] The key to the achievement of this goal is the proper design of the corresponding amphiphilic building blocks, since the information determining their specific supramolecular assembly must be encoded in their molecular architecture. As amphiphiles for the assembly of shape-persistent micelles we used comparatively rigid and T-shaped fullerene- and calixarene-based molecules carrying Newkome-type dendrons as hydrophilic part and a couple of hydrophobic aliphatic chains.[1] In this study we report on a new type of amphiphilic dendrons where we connected the same hydrophilic Newkome-type dendrons to pyrene which serves both as a hydrophobic component capable of undergoing π-stacking interactions as well as a reporter unit due to its absorption and emission properties. The incentive was to provide new labeled amphiphiles which can be used for the investigation of the assembly and disassembly of micelles and liposomes as well as of the layer-by-layer assembly of oligoelectrolytes.[4] Of special interest in this contribution are the X-ray crystal structures of the first-generation representatives. Here the intermolecular packing of the amphiphiles is determined by the efficient and cooperative use of π-stacking and all possible H-bonding interactions, resembling situations seen in biomolecules such as proteins and DNA.

Results and Discussion

Synthesis of the Amphilic Pyrene-Labeled Dendrons

The first-generation pyrene-labeled dendron **4** was synthesized by DCC coupling of 4-(1-pyrene)butyric acid (**1**) with the first-generation Newkome-type dendron **2**[5] in CH_2Cl_2 followed by subsequent deprotection of the precursor molecule **3** with formic acid (Scheme 1). Purification of **3** was achieved by flash chromatography on silica gel with hexanes/ethyl acetate (2:1) and subsequent recrystallisation from hexanes/ethyl acetate. The final yield of **3** was 39%. The quantitative deprotection of **3** was carried out by treatment with formic acid. The amphiphilic tricarboxylic acid **4** was purified by recrystallisation from acetone.

The second-generation pyrene-labeled dendron **6** was synthesized accordingly by connecting 4-(1-pyrene)butyric acid (**1**) with the second-generation Newkome-type dendron **5**[6] in DMF using DCC and 1-HOBT as coupling agents (Scheme 2). The crude product was purified by flash chromatography on silica gel with hexanes/ethyl acetate (2:1). The reaction product **6** was obtained in analytically pure form in 76% yield. Quantitative deprotection of **6** was carried out by treatment with formic acid (Scheme 2). The amphiphilic nonacarboxylic acid **7** was obtained in 96% yield as a beige powder.

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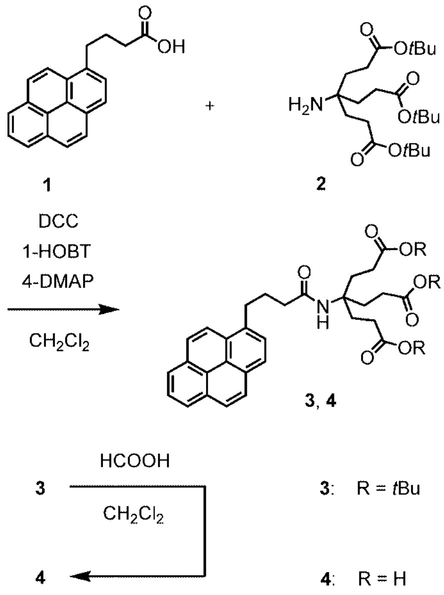
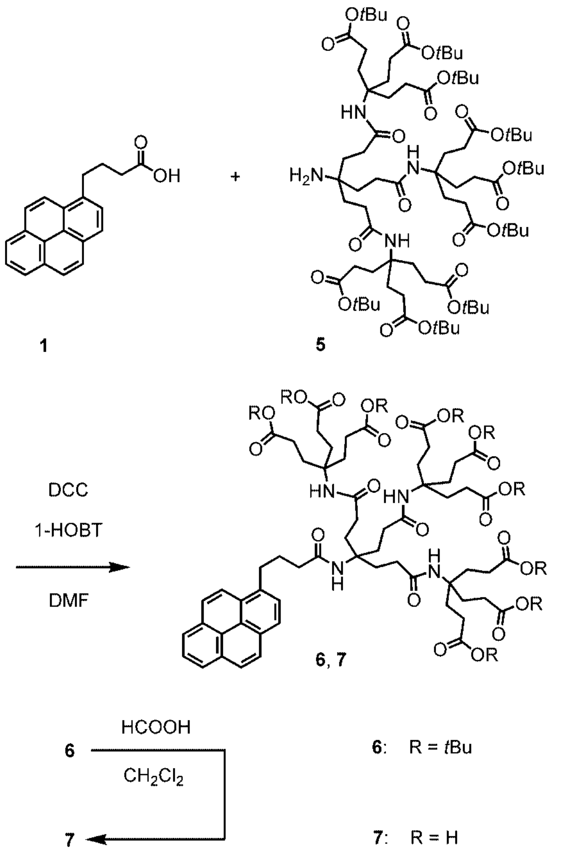


Scheme 1. Synthesis of the first-generation pyrene-functionalized dendrons **3** and **4**.



Scheme 2. Synthesis of the second-generation pyrene-functionalized dendrons **6** and **7**.

Crystal Structure of Dendron 3

The structure of **3** was determined by single-crystal X-ray analysis. The compound crystallizes in the monoclinic space group $P2_1/c$. Each unit cell contains four molecules.

No face-to-face stacking of the pyrene moieties is observed. Instead, edge-to-face stacking between two neighbouring pyrene units takes place (Figure 1).[7,8] The angle between the pyrene planes is 57.1°. Next to this π-stacking interaction a classical hydrogen bond between the amide proton and carbonyl oxygen atom of the amide bonds as well as a CH/O hydrogen bond are found in each pair of neighbours.

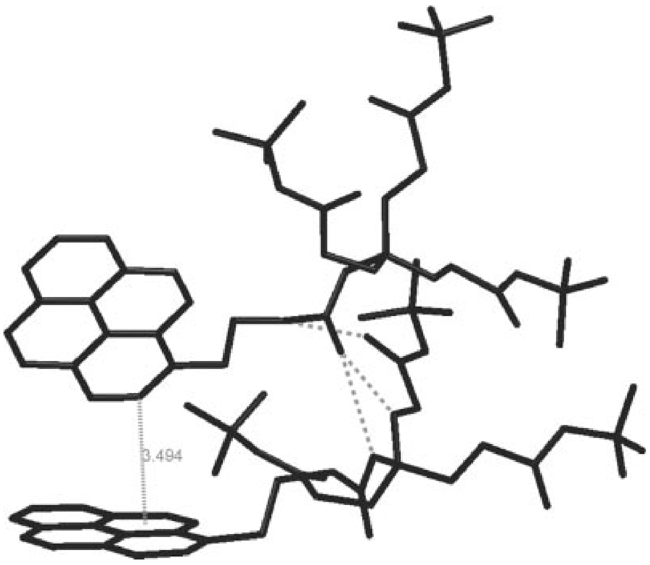


Figure 1. Edge-to-face stacking and hydrogen bonding between two adjacent molecules of **3**. The CH/π contact between a pyrene carbon atom and the centroid of a benzene ring of the adjacent pyrene unit and the hydrogen bonds between CO and NH and CO and CH_2 groups of the dendron are indicated by dashed grey lines.

Crystal Structure of Dendron 4

The amphiphilic first-generation dendron **4** crystallizes in the triclinic space group $P1$. Each unit cell contains two molecules. The hierarchically ordered arrangement of the molecules can be described by a sequence of inverted layers (Figure 2). The pyrene moieties are located on parallel planes. Each pyrene unit forms a face-to-face arrangement with an adjacent pyrene moiety located in the neighbouring plane (Figure 2). The distance between the aromatic planes in each pair of π-stacked pyrene units is 3.420 Å and thus similar to the interplanar distance in graphite (3.354 Å).[9] This can be interpreted as evidence for the existence of strong interplanar π-stacking interactions.

Significantly, each CO, OH and NH group of the carboxyl and amide residues of **4** is involved in a hydrogen bond with adjacent molecules. Since each molecule has three carboxylic groups and one amide group a three-dimensional network of hydrogen bonds is formed, which extends throughout the whole crystal (Figure 2). Each pair of π-stacked molecules is connected to twelve next neighbours by hydrogen bonding and each individual molecule to six next neighbours (Figure 2).

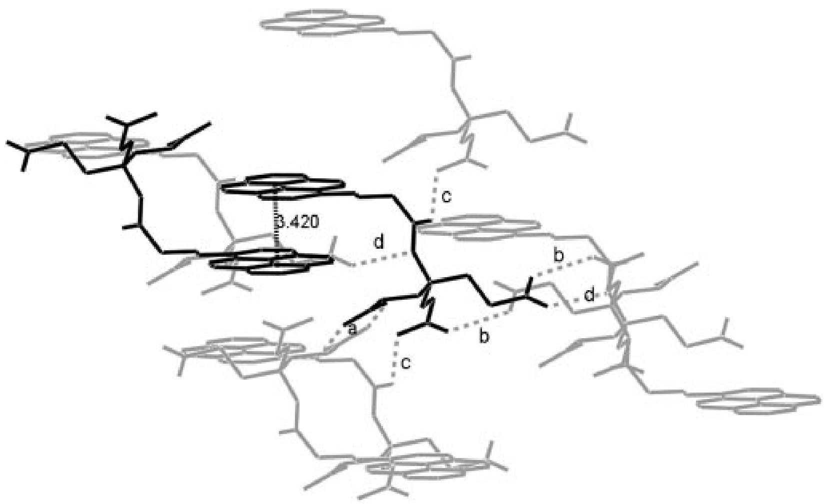


Figure 2. Two π-stacking molecules (black) of compound **4** with an interplanar distance of 3.420 Å (as indicated by dashed black line) between pyrene units. Each molecule of **4** is connected (as indicated by dashed grey lines) to six direct neighbours (grey) by four different types (a–d) of classical hydrogen bonds (shown only for one molecule).

The carboxylic and amide groups are connected by four different types of classical hydrogen bonds (types a–d; Figures 2 and 3).

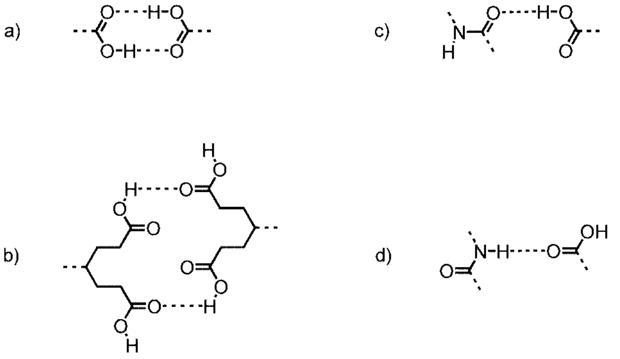


Figure 3. The four different types (a–d) of hydrogen bonds being involved in the crystal packing of compound **4**.

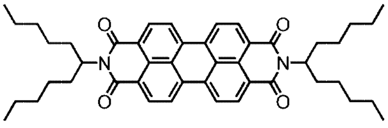
The molecular organization within the crystal structure of **4** displays striking similarities with the intermolecular inclusion of pyrene and ethanol as guest molecules in the channels formed by 1,3,5-benzenetricarboxylic acid (trimesic acid, TMA).[10] In an analogous way, the crystal structure of compound **4** can be described as an intramolecular host–guest structure, created by the inclusion of the pyrene moieties of **4** as guests in the channels (880 × 1290 pm) of the network formed by the interactions of the one amide and the three carboxylic acid moieties of the dendritic branches of compound **4**, thus stabilizing the network by filling this void space. According to Kitaigorodskii's principle of close crystal packing,[11] channels that are formed in a structure by the interaction of functional groups (for example the dimerisation of carboxylic acid groups) are only stable, if this void space is filled either by interpenetration of networks or by incorporation of guest molecules, like in the structures of trimesic acid[12] and adamantane-1,3,5,7-tetracarboxylic acid.[13] In addition to the π-stacking interactions already mentioned, the structure of compound **4** is stabilized by further noncovalent bonding interactions. This is indicated by a number of short contacts that were found in the X-ray crystal structure of **4**. Examples for these interactions are CH/O hydrogen bonds and non-directional C/H interactions.

Investigation of the Aggregation Properties of the Amphiphilic Dendron 7 in Water

To investigate the formation of micelles of the amphiphilic dendrons **4** and **7** in water, DOSY (diffusion-ordered spectroscopy) NMR[14] experiments were performed in aqueous buffer solution at pH = 7. The translational diffusion coefficient D [$\mathrm{m^2\,s^{-1}}$] of molecular species can be estimated by the Stokes–Einstein equation: $D = k_\mathrm{B}T/(6\pi\eta R)$, where T is the temperature, η the viscosity of the solvent, R the hydrodynamic radius of the molecule or aggregate and k_B the Boltzmann constant. According to this equation, the D value is inversely proportional to the hydrodynamic radius R of a molecule or an aggregate. Thus, the average sizes of the micelles of **4** and **7** could be determined from their diffusion coefficients; R values of 5.7 Å for the aromatic signals of **4** and 19.6 Å for the aromatic signals of **7** were observed. Those results indicate that at pH = 7 in aqueous solution small aggregates of compound **7** are formed, whereas under the same conditions no aggregation of compound **4** takes place.

A classical way to demonstrate the micelle formation behaviour of amphiphilic molecules is to show their ability to encapsulate apolar molecules and transfer them into the water phase.[15] Amphiphile **7** is only sparingly soluble in water in its fully protonated form. However, water solubility can be increased after deprotonation with bases. In a typical procedure, this was accomplished by treatment of a 10^{-3} M suspension of the nonacarboxylic acid **7** in water with

9 equiv. of $KHCO_3$. As apolar guest for the inclusion experiments we chose the red perylenedicarboximide derivative **8**, which is completely insoluble in water. In order to promote encapsulation, **8** was dissolved in diethyl ether and added to the amphiphile **7**. After sonication for 2 h, the aqueous phase took a faint orange-red colour. The UV/Vis spectrum of the aqueous phase shows absorptions of the perylene moiety between 400 and 600 nm (Figure 4). The slightly yellowish solution of the pyrene amphipile **7** displays absorptions only below 370 nm. However, compared to the spectrum of **8** recorded in CH_2Cl_2 (Figure 4), the absorptions of the perylene dye molecules encapsulated by **7** are considerably broadened. Also the relative intensities of the absorption bands are significantly changed. Now the transition at 470 nm is the most intensive one.



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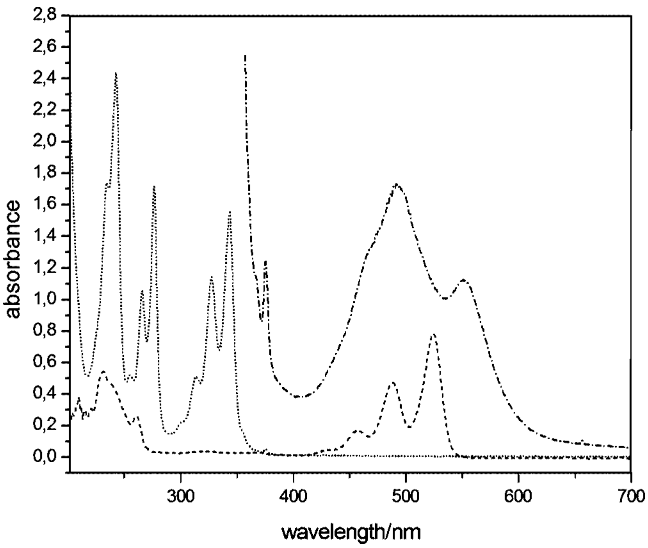

Figure 4. UV/Vis spectra of the amphiphilic dendron **7** in water (dotted line), the perylene dye **8** in CH_2Cl_2 (dashed line) and the solution of the phase-transfer experiment (dashed-dotted line).

We assume that this is an indication for π-stacking interactions between the perylene units and/or between the perylene and pyrene units within the micelles. The absorption properties of perylenebis(imide) dyes are scarcely dependant upon the environment, i.e. little solvatochromism is observed for these dyes.[16] However, it has been reported that aggregation of apolar perylene dyes in organic solvents has a pronounced influence on the optical spectra.[17–20] Indeed, the absorption spectra of such aggregated π-stacks of perylenebis(imides) are the same that we find here (Figures 4 and 5). In order to address the question whether the π-stacking occurs between perylene or between perylene and pyrene moieties, we investigated the encapsulation of perylene dye **8** in various concentrations by **7** at a fixed concentration of the amphiphile. We could not see an indication of concentration dependence in the absorption spectra (Figure 5), since the typical features for π-stacked perylene dyes are still seen upon decreasing the concentration of **8** by a factor of 10. Especially, no development of typical monomer perylenebis(imide) spectra like that of **8** in CH_2Cl_2 with a well-resolved vibronic structure is observed. This is in contrast to the concentration dependence found in the absorption spectra of many apolar perylene dyes in organic solvents, where a continuous change to the absorption features of the monomeric species is observed upon dilution.[16,21] Instead, the absorption spectra of **8** encapsulated in the micelles (Figure 5) exhibit drastically decreased absorption coefficients, and shifts (32 nm) of the absorption maxima, indicative of a close face-to-face stacking.[19a,22]

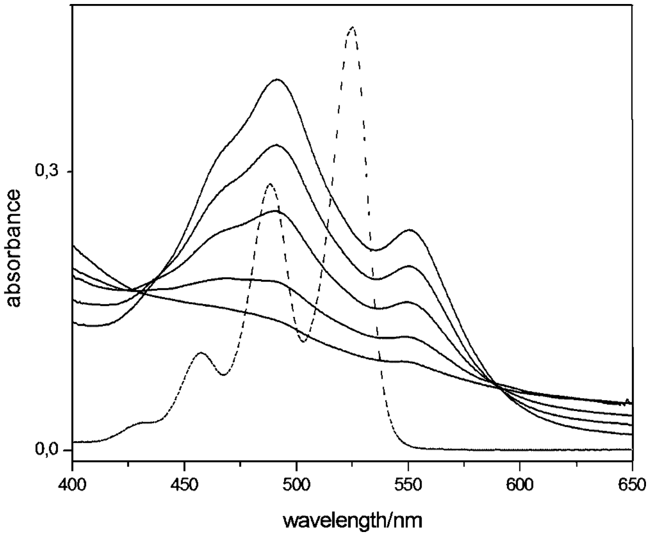

Figure 5. Absorption spectrum of perylenebis(imide) **8** in dichloromethane (dashed line) and concentration-dependent UV/Vis spectra (solid lines) of **8** encapsulated by micelles of **7** in water measured at different concentrations of **8** (c_0, $7.5\times10^{-1}\,c_0$, $5.0\times10^{-1}\,c_0$, $2.5\times10^{-1}\,c_0$, $7.5\times10^{-2}\,c_0$, the initial concentration c_0 of **8** was 6.4×10^{-6} M).

More characteristic than the changes to the UV/Vis absorption spectra upon decreasing the concentration of **8** are those of the fluorescence emission spectra (Figure 6) and the concomitant colour changes of the perylene dye.

Würthner and co-workers reported colour changes for the luminescence of perylene dyes, depending on the ratio α_{agg} of aggregated vs. total perylene dye molecules, from red ($\alpha_{agg} > 0.9$) to orange ($\alpha_{agg} = 0.8$), yellow ($\alpha_{agg} = 0.7$) and green ($\alpha_{agg} < 0.3$).[16] They observed red colour for a 10^{-2} M solution of perylene dye in toluene.[16] In our phase-transfer experiment we observed such a red colour for a much lower concentrated ($c_0 = 6.4\times10^{-6}$ M) aqueous solution of **8** in the presence of micelles of **7**. As the spectra revealed, this colour change was accompanied by the occurrence of a broad aggregate emission band at 580 to 780 nm. Similar emission features were observed for aggregates of π-stacked apolar perylene dyes in organic solvents.[21,23,24] Interestingly, the very low concentration of **8** in the presence of

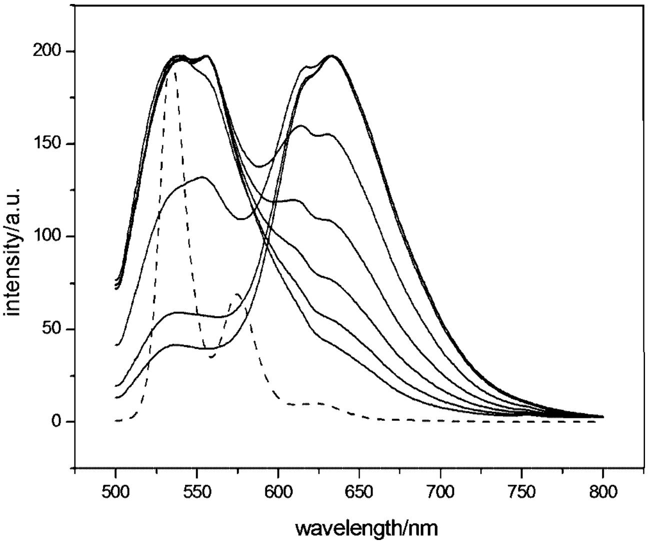

Figure 6. Fluorescence spectrum (excitation at 469 nm) of perylenebis(imide) **8** in dichloromethane (dashed line) and normalized concentration-dependent fluorescence spectra (excitation at 469 nm) of **8** (7.5×10^{-1} c_0 to 1.0×10^{-3} c_0) in micelles of dendrimer **7** in water (solid lines). The initial concentration c_0 of perylene dye **8** was 6.4×10^{-6} M.

micelles of **7** in water was visible to the eye as red colour, whereas much higher concentrations of **8** dissolved in dichloromethane appeared colourless to the eye. This serves as an additional indication for a strong aggregation of **8** inside the micelles of amphiphile **7**. Since the dye molecules **8** have to pass the water phase, before entering the micelles, pre-aggregation might occur, with the result that even at low concentrations of **8** the dye is transferred to the micelles of **7** as an aggregate rather than as a monomer. The transfer of the perylene dye **8** from organic solvents to the aqueous phase is considered to be a partition equilibrium between the organic phase and the micelles. Obviously, only a small fraction is transferred into the micellar phase. On the other hand, if the aqueous phase with **8** encapsulated by the micelles of **7** is treated with an organic solvent, the perylene dye is re-extracted from the micelles into the organic phase. After extraction of **8**, for example with diethyl ether, the organic phase exhibited a green fluorescence, indicative of an increased ratio of de-aggregated perylene units ($a_{\mathrm{agg}} < 0.3$), even at the same concentration as previously established in the micellar phase. Würthner and co-workers observed a green fluorescence for solutions of low concentrations (10^{-5}–10^{-6} M) of perylene dyes in toluene.[16] This result can serve as a rough estimate of the amount of perylene dye that is encapsulated by the micelles. A more accurate determination was carried out by calculating the concentration of **8** from the absorbance measured in the UV/Vis spectrum of the aqueous phase and the absorption coefficient $\varepsilon(490\ \mathrm{nm}) = 52240\ \mathrm{M}^{-1}\mathrm{cm}^{-1}$ that was determined by Langhals[25] for a solution of **8**. With this, the concentration of the red solution of **8** encapsulated by the micelles of **7** in water was calculated to be 3.3×10^{-5} M. Fluorescence spectra recorded in water at different concentrations of **8** encapsulated by the micelles of **7** (Figure 6, solid lines) exhibit a strong aggregate band (575–775 nm) and only weak nonresolved bands in the wavelength area of the monomer emission (500–575 nm). On diluting the solution, the intensity of the aggregate band slowly decreases and the band in the region of the monomer emission increases, but in contrast to Würthners results,[21] there is no sharp resolution of the vibronic structure of the monomer band (the emission spectrum of non-aggregated dye **8** in dichloromethane with a well-resolved vibronic structure is shown as dashed line in Figure 6). This could be an indication for π-stacking between the perylenebis(imide) guests and the pyrene moieties of **7**. The fact that the absorption and emission features of the pyrene unit in **7** are not affected by the presence of the perylene unit is most likely due to the fact that most micelles are empty, since the molar ratio between **8** and **7** in micellar solutions does not exceed 1:30. However, at these upper limits the perylenebis(imide) forms intermolecular stacks already, as demonstrated by the absorption and emission investigations (Figures 5 and 6).

Conclusions

A new type of functional amphiphiles involving first- and second-generation Newkome-type amide dendrons and a pyrene unit has been synthesized. In these molecular architectures the pyrene moiety serves both as hydrophobic part and as photoactive reporter unit. In the single crystal of the first-generation dendron **4** the intermolecular packing is determined by the efficient and cooperative use of all possible hydrogen-bonding sites as well as π-stacking interactions. This closely resembles the supramolecular packing situations found in secondary structure motifs of biomolecules such as proteins and DNA. The second-generation amphiphile **7** forms small micelles in aqueous solutions with a diameter of about 4 nm as determined by DOSY NMR experiments. Amphiphile **7** is able to promote the transfer of the apolar perylene dye molecules **8** into the aqueous phase. Here the perylene units are preferably arranged within intermolecular π-stacks encapsulated by the micelles. Pyrene-functionalized amphiphiles such as **4** and **7** are of interest for labeling experiments of biotic and abiotic membranes. Moreover, after being deprotonated, those fluorescence-labeled compounds can serve as reporter units for the layer-by-layer assembly of oligo- and polyelectrolytes in new hierarchically organized surface architectures. Work along these lines is currently underway in our laboratory.

Experimental Section

General Remarks: Reactions requiring dry or oxygen-free conditions were carried out under nitrogen (Schlenk conditions). Dichloromethane was dried by distillation from lithium aluminum hydride. Dry DMF and 4-(1-pyrene)butyric acid were purchased from Acros. Perylenebis(imide) dye **8** was prepared according to the method given by Langhals and co-workers.[25] First- and second-generation Newkome-type aminodendrons were prepared according to literature procedures.[5,6] TLC was performed on F_{245} silica gel 60 plates (Merck); detection was effected by 366 nm UV light or by treatment with 1% potassium permanganate in water and subsequent heating. Products were isolated by flash column chromatography (FC) (silica gel 60, particle size 0.040–0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were recorded with JEOL JNM EX 400 and JEOL JNM GX 400 spectrometers. The chemical shifts are given in ppm relative to the appropriate solvent peak as standard reference. The resonance multiplicity is indicated as s (singlet), d (doublet), t (triplet) or m (multiplet). Mass spectra were measured with a Micromass Zab (FAB) using a Finnigan MAT 900 spectrometer with 3-nitrobenzyl alcohol as the matrix. IR spectra were recorded with an ASI React IR-1000 spectrometer. The spectra were measured as a film. Elemental analyses were carried out using an EA 1110 CHNS from CE Instruments. X-ray crystallographic data were collected with a Nonius KappaCCD area detector. Calculations were carried out using SHELXS-97 and SHELXL-97 software.[26] The graphics were generated using the Mercury 1.3 program.

Di-*tert*-Butyl 4-[2-(*tert*-Butoxycarbonyl)ethyl]-4-[4-(pyrene-1-yl)butyrylamino]heptanedioate (3): Under Schlenk conditions, 4-(1-pyrene)butyric acid (**1**) (1.50 g, 5.20 mmol) and amino compound **2** (3.24 g, 7.80 mmol) were dissolved in dry CH_2Cl_2 (100 mL), and the mixture was cooled to 0 °C. DMAP (95 mg, 0.80 mmol) and DCC were added and the resulting mixture was stirred at 0 °C for 2 h and afterwards at room temperature for 7 d. Progress of the reaction was monitored by TLC. Precipitated DCU was removed by filtration, and the solvent was removed under vacuum. The yellow residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 2:1). The solvent was removed in vacuo. At room temperature, the residue was dissolved in ethyl acetate (8 mL), and then hexanes (24 mL) were added. After 3 d at room temperature, crystals were collected and washed with hexanes. Title compound **3** (1.40 g, 2.04 mmol, 39%) was obtained as greenish-yellow crystals (m.p. 128 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.38 (s, 27 H, CH_3), 1.99 (t, ^3J = 7.7 Hz, 6 H, $C\mathit{H}_2$-CH_2), 2.16 (m, 2 H, CH_2), 2.23 (m, 8 H, CH_2, CH_2-$C\mathit{H}_2$), 3.33 (t, ^3J = 7.15 Hz, 2 H, CH_2), 5.90 (s, 1 H, NH), 7.82–8.27 (m, 9 H, pyrene) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C): δ = 27.38 (CH_2), 27.90 (CH_3), 29.79, 29.88 (CH_2–CH_2), 32.68 (CH_2), 36.68 (CH_2), 57.27 [$\mathit{C}(CH_2–CH_2)_3$], 80.51 [$C(CH_3)_3$], 123.24, 124.59, 124.62, 124.69, 124.83, 124.93, 125.65, 126.48, 127.24, 127.32, 128.59, 129.57, 130.76, 131.24, 135.77 (pyrene), 171.96 (CONH), 172.77 [$\mathit{C}OOC(CH_3)_3$] ppm. IR: $\tilde{\nu}$ = 3354, 3316, 3258, 3046, 2976, 2937, 2872, 2822, 1725, 1657, 1648, 1606, 1540, 1455, 1420, 1366, 1316, 1235, 1212, 1146, 1108, 1042, 1011, 992, 961, 930, 892, 845, 826, 784, 757, 722, 672, 622, 587, 556, 521, 494, 467, 429 cm^{-1}. FAB-MS (NBA): *m*/*z* = 686 [MH^+]. $C_{42}H_{55}NO_7$ (685.89): calcd. C 73.55, H 8.08, N 2.04; found C 73.11, H 8.06, N 2.09.

4-[2-(Hydroxycarbonyl)ethyl]-4-{[4-(pyrene-1-yl)butyryl]amino}-heptanedioic Acid (4): Compound **3** (630 mg, 0.92 mmol) was dissolved in CH_2Cl_2 (5 mL). To the stirred solution formic acid (98%, 10 mL) was added. After stirring for 48 h, solvent and formic acid were removed under vacuum. Toluene (50 mL) was added to the residue and distilled off in a rotary evaporator. This procedure was repeated five times to remove any traces of formic acid. The residue was dissolved by boiling it with acetone (50 mL). After standing at room temperature for 3 d, almost colourless crystals formed which were separated from the solution and washed with hexanes. To the solution toluene (50 mL) was added and, after standing for 3 d, a second crop of almost colourless crystals (m.p. 214 °C) was collected. The total yield of title compound **4** was 438 mg (0.84 mmol, 92%) The tricarboxylic acid **4** is almost insoluble in water, but very soluble in a mixture of acetone/water (5:1), where the solubility is higher than 250 mg/mL. ^{1}H NMR (400 MHz, [D_6]acetone/D_2O, 5:1, 25 °C): δ = 2.03 (m, 8 H, CH_2, $C\mathit{H}_2$-CH_2), 2.29 (t, ^3J = 8.2 Hz, 6 H, CH_2-$C\mathit{H}_2$), 2.36 (t, ^3J = 7.2 Hz, 2 H, CH_2), 3.28 (t, ^3J = 7.9 Hz, 2 H, CH_2), 7.83–8.28 (m, 9 H, pyrene) ppm. ^{13}C NMR (100.5 MHz, [D_6]acetone/D_2O, 5:1, 25 °C): δ = 28.49 (CH_2), 28.65 (CH_2–CH_2), 33.07 (CH_2), 36.75 (CH_2), 57.61 [$C(CH_2–CH_2)_3$], 124.00, 125.12, 125.20, 125.31, 125.37, 125.46, 126.56, 127.03, 127.81, 127.90, 128.04, 129.02, 130.23, 131.36, 131.79, 137.11 (pyrene), 174.23 (CONH), 176.21 (COOH) ppm. IR: $\tilde{\nu}$ = 3327, 3046, 1216, 1185, 1162, 2984, 2941, 2907, 2791, 2636, 2617, 2548, 2513, 1984, 1945, 1706, 1664, 1602, 1552, 1455, 1424, 1366, 1305, 1282, 1262, 1131, 1112, 1058, 1015, 919, 899, 842, 776, 706, 679, 614, 575, 548, 529, 498, 471, 436 cm^{-1}. FAB-MS (NBA): *m*/*z* = 519 [MH^+]. $C_{30}H_{31}NO_7$ (517.57): calcd. C 69.62, H 6.04, N 2.71; found C 69.97, H 6.00, N 2.61.

9-Cascade:[4-(1-Pyrene)butyryl]aminomethane[3]:(3-Oxo-2-azapentylidyne):*tert*-Butyl Propionate (6): Under Schlenk conditions, compound **1** (144 mg, 0.50 mmol) and amino compound **5** (1080 mg, 0.75 mmol) were dissolved in dry DMF (20 mL), and the mixture was cooled to 0 °C. 1-HOBT (101 mg, 0.75 mmol) and DCC (155 mg, 0.75 mmol) were added and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for 7 d. Progress of the reaction was monitored by TLC. Precipitated DCU was removed by filtration and the solvent was removed under vacuum. The yellow residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 2:1). The solvent was removed in vacuo. Title compound **6** (646 mg, 0.38 mmol, 76%) was obtained as a colourless foam (m.p. 128 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.34 (s, 81 H, CH_3), 1.89 (t, ^3J = 7.8 Hz, 18 H, $C\mathit{H}_2$-CH_2 2nd gen), 1.97 (m, 8 H, CH_2, $C\mathit{H}_2$-CH_2 1st gen), 2.13 (m, 24 H, CH_2-$C\mathit{H}_2$ 1st gen + 2nd gen), 2.28 (t, ^3J = 7.1 Hz, 2 H, CH_2), 3.34 (t, ^3J = 7.6 Hz, 2 H, CH_2), 6.1 (s, 3 H, NH), 7.59 (s, 1 H, NH), 7.85–8.29 (m, 9 H, pyrene) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$, 25 °C): δ = 27.49 (CH_2), 27.91 (CH_3), 29.66, 29.70 (CH_2–CH_2 2nd gen), 31.65, 31.80 (CH_2–CH_2 1st gen), 32.86 (CH_2), 36.93 (CH_2), 57.33 [$\mathit{C}(CH_2–CH_2)_3$ 2nd gen], 57.40 [$\mathit{C}(CH_2–CH_2)_3$ 1st gen], 80.42 [$\mathit{C}(CH_3)_3$], 123.39, 124.56, 124.72, 124.87, 124.92, 125.57, 126.38, 127.20, 127.30, 127.38, 128.61, 129.70, 130.81, 131.25, 136.05 (pyrene), 172.55 (CO 2nd gen), 172.84 (CO 1st gen), 172.96 (CO) ppm. IR: $\tilde{\nu}$ = 3320, 3223, 3049, 2980, 2937, 1725, 1679, 1656, 1536, 1455, 1420, 1393, 1366, 1312, 1251, 1216, 1146, 1104, 953, 845, 757, 722, 683, 622, 591, 548, 529, 498, 471, 429 cm^{-1}. FAB-MS (NBA): *m*/*z* = 1710 [MH^+]. $C_{96}H_{148}N_4O_{22}$ (1710.22): calcd. C 67.42, H 8.72, N 3.28; found C 67.19, H 8.70, N 3.36.

9-Cascade:[4-(1-Pyrene)butyryl]aminomethane[3]:(3-Oxo-2-azapentylidyne):Propionic Acid (7): Compound **6** (246 mg, 0.144 mmol) was dissolved in CH_2Cl_2 (10 mL). To the stirred solution, formic acid (98%, 10 mL) was added. After stirring for 48 h, solvent and formic acid were removed under vacuum. Toluene (20 mL) was added to the residue and distilled off in a rotary evaporator. The procedure was repeated five times to remove any traces of formic acid. Title compound **7** (166 mg, 0.137 mmol, 96%) was obtained as a beige powder (m.p. 118 °C). ^{1}H NMR (400 MHz, [D_6]acetone/D_2O, 5:1, 25 °C): δ = 1.96 (m, 24 H, $C\mathit{H}_2$-CH_2 1st gen + 2nd gen), 2.04 (m, 2 H, CH_2), 2.23 (m, 24 H, CH_2-$C\mathit{H}_2$ 1st gen + 2nd gen), 2.37 (t, ^3J = 7.3 Hz, 2 H, CH_2), 3.35 (t, ^3J = 7.7 Hz, 2 H, CH_2), 7.93–8.38 (m, 9 H, pyrene) ppm. ^{13}C NMR (100.5 MHz, [D_6]acetone/D_2O, 5:1, 25 °C): δ = 28.37 (CH_2), 29.21 (CH_2–CH_2 2nd gen), 31.58 [(CH_2–CH_2) 1st gen], 33.22 (CH_2), 36.93 (CH_2), 57.70 [$\mathit{C}(CH_2–CH_2)_3$ 2nd gen], 58.22 [$\mathit{C}(CH_2–CH_2)$ 1st gen], 124.26, 125.29, 125.37, 125.44, 125.66, 126.66, 127.11, 127.95, 128.18, 128.28, 129.19, 130.38, 131.55, 131.95, 137.33 (pyrene), 163.68 (CO), 174.68 (CO 1st gen), 175.99 (CO 2nd gen) ppm. IR: $\tilde{\nu}$ = 3323, 3038, 2934, 2853, 2617, 2177, 2108, 2088, 2038, 1996, 1702, 1625, 1540, 1455, 1413, 1285, 1185, 1100, 895, 845, 730, 695, 622, 602, 560, 533, 502, 471, 429 cm^{-1}. FAB-MS (NBA): m/z = 1205 [MH$^+$]. $C_{60}H_{76}N_4O_{22}$ (1205.29): calcd. C 59.79, H 6.36, N 4.65; found C 59.82, H 6.45, N 4.39.

Crystallography: The crystals were taken directly to a Nonius KappaCCD diffractometer (Mo-K_α-Radiation, $\lambda = 0.71073$ Å) for data collection. Cell parameters were obtained from 10 frames using a 10° scan. Lorentz, polarization, and absorption corrections[27] were applied. The space groups were determined from systematic absences and subsequent least-squares refinement. The structures were solved by direct methods. The parameters were refined with all data by full-matrix least squares on F^2 using SHELX-97.[26] Non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were fixed in idealized positions using a riding model. Scattering factors were taken from the literature.[28]CCDC-641653 and -641654 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

X-ray Crystal Structure of 3: A greenish-yellow crystal of **3** (linear dimensions ca. 0.25 × 0.20 × 0.15 mm) was obtained by slow diffusion of hexane into a solution of **3** in ethyl acetate. Crystal data at 173(2) K for $C_{42}H_{55}NO_7$ (685.87). Monoclinic, space group $P2_1/c$, $D_c = 1.192$ g cm^{-3}, $Z = 4$, $a = 20.7459(3)$ Å, $b = 18.5123(6)$ Å, $c = 10.0844(5)$ Å, $\alpha = 90°$, $\beta = 99.192(2)°$, $\gamma = 90°$, $V = 3823.2(2)$ Å^3, $\mu = 0.080$ mm^{-1}. Number of measured and unique reflections: 16812 and 8727 ($R_{int} = 0.0456$), respectively. Final $R_1 = 0.0471$, $wR_2 = 0.1017$ for 460 parameters and 4812 reflections with $I > 2\sigma(I)$ and an index range of $2.20° < \theta < 27.49°$ (corresponding R values based on all 8727 reflections are 0.1109 and 0.1224, respectively).

X-ray Crystal Structure of 4: An almost colourless crystal of **4** (linear dimensions ca. 0.20 × 0.20 × 0.20 mm) was obtained by slow diffusion of toluene into a solution of **4** in acetone. Crystal data at 173(2) K for $C_{30}H_{31}NO_7$ (517.56). Triclinic, space group $P\bar{1}$, D_c = 1.322 g cm^{-3}, $Z = 2$, $a = 8.4759(2)$ Å, $b = 9.4471(4)$ Å, $c = 16.7553(6)$ Å, $\alpha = 84.355(2)°$, $\beta = 84.888(2)°$, $\gamma = 77.465(2)°$, $V = 1300.14(8)$ Å^3, $\mu = 0.094$ mm^{-1}. Number of measured and unique reflections: 10971 and 5880 ($R_{int} = 0.0226$), respectively. Final $R_1 = 0.0558$, $wR_2 = 0.1427$ for 343 parameters and 4166 reflections with $I > 2\sigma(I)$ and an index range of $2.22° < \theta < 27.48°$ (corresponding R values based on all 5880 reflections are 0.0819 and 0.1576 respectively).

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