Notes

Novel Functionalized Poly(amido amine) (PAMAM) Dendrimers: Synthesis and Physical Properties

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Received March 25, 1997
Revised Manuscript Received September 8, 1997

Introduction

As a class of new materials, dendrimers have generated great interest throughout the scientific community.[1] Despite synthetic difficulties,[2,3] a wide range of these new materials have been produced and characterized.[4−6] However, the study of their properties is still in its infancy (relative to classical polymers) and there remain large gaps in our knowledge that must be filled if the potential uses of these materials are to be realized.

Our interest in dendrimers stems from their mesoscopic physical scale and well-defined overall size.[7] Control of the size and geometry of molecular structures at dimensions on the order of 10 nm may offer an opportunity to observe new physical phenomena specifically related to the boundaries imposed by the molecular structure. Restriction to a well-defined molecular region of either discrete charge carriers or of extended electronic excitations, for example, may result in novel phenomena not observable at other size scales. Such effects would require some degree of correlation between substructures in the molecule such as interaction between closely spaced surface functional groups.[8,9]

Our work has yielded a range of functionalized poly(amido amine) (PAMAM) dendrimers. These contain either dipolar, nonlinear optical, or fluorescent groups. Initial evaluation of these systems has been undertaken, including attempts to characterize the molecules using fluorescence spectroscopy and electric field induced second harmonic generation (EFISH).

Experimental Section

PAMAM Dendrimer and Model Compound Synthesis. PAMAM dendrimers derived from an ammonia core[10] (such compounds will be referred to as "AG*x*" in the text, where A denotes the ammonia core, G*x*, the generation number and $x = 1-7$) and the model compounds 2-naphthylamide (NAM) and 1,2-bis(amidonaphth-2-yl)ethane[11] (DINAM) were prepared by literature methods. PAMAM dendrimers derived from an ethylenediamine core (such compounds will be referred to as "EG*x*" in the text, where E denotes the ethylenediamine core) were purchased from Aldrich. All solvents used were Aldrich HPLC grade, and all chemicals were used as received from Aldrich without further purification, except for tetracyanoquinodimethane (TCNQ), which was purchased from Lancaster Synthesis Ltd.

General Procedure for Synthesis of 2-Naphthoyl-Functionalized Dendrimers, Series I.[11] A water/acetonitrile solution of 2-naphthoyl chloride was added dropwise to a stirred solution of aqueous sodium hydroxide and PAMAM dendrimer. The resulting mixture was stirred for 48 h under nitrogen and then washed thoroughly with ether to remove excess 2-naphthoyl chloride. The water was removed by rotary evaporation, and the remaining white solid was crystallized from water/methanol. Subsequent recrystallizations from methanol gave a white powder in yields that varied from 30 to 40%. Characterization was achieved by proton and carbon NMR, infrared, and UV/visible spectroscopy. Data for compound IAG1: IR (KBr disk) ν_{CO}1633, 1538 cm^{-1}; UV/vis (methanol) λ 235, 280, 329 nm; ^{1}H NMR (DMSO-d_6, ppm) δ 1.31 (triplet, broad, 2H), 1.78 (triplet, broad, 2H), 2.42, 2.48 (multiplet, broad, partially obscured DMSO, 4H), 6.69 (quintet, 2H), 7.08 (doublet, 4H), 7.53 (singlet, broad, 1H), 7.60 (singlet, 1H), 7.88 (triplet, broad, 1H). ^{13}C data for compound IEG5 (DMSO-d_6): δ 30.71, 33.31 (broad), 36.91, 37.00, 37.21, 49.59 (broad), 52.16 (broad), 124.18, 126.09, 126.65, 127.01, 127.52, 127.79, 128.80, 131.77, 132.11, 134.08, 166.49, 171.34, 171.83, 172.22. GPC analysis was also carried out on this series.

General Procedure for Synthesis of *p*-Nitrobenzyl-Functionalized Dendrimers, Series II.[12] A DMF solution of PAMAM dendrimer was added dropwise to a stirred mixture of 4-nitrobenzyl chloride and sodium hydrogen carbonate in DMF under nitrogen. The reaction was warmed at ~50 °C for 2 h and then stirred at room temperature for 48 h. Sodium hydrogen carbonate was removed by filtration and the DMF was removed by rotary evaporation, yielding a red oil, which was stirred vigorously with a large volume of ether overnight to remove excess 4-nitrobenzyl chloride to yield the crude product as an orange powder. This was separated by filtration and subsequently dissolved in dichloromethane; the resulting solution was filtered and crystallized from acetone/ether (higher generations were precipitated by the addition of a DMF solution to a large volume of acetone), yielding a yellow/orange powder in yields of 30−43%. Product characterization was achieved using infrared, UV/visible, and proton and carbon NMR spectroscopy. This series of functionalized dendrimers were also studied by GPC. Data for compound IIAG1: IR (KBr disk) ν_{CO} 1642, 1517 cm^{-1}; ν_{NO_2} 1558, 1344 cm^{-1}; UV/vis (DMF) λ_{max} 277 nm; ^{1}H NMR (CD_2Cl_2 ppm) δ 2.23 (triplet, 2H), 2.50 (triplet, 2H), 2.65 (triplet, 2H), 3.22 (quartet, 2H), 3.63 (singlet, 4H), 6.51 (triplet, 1H), 7.51 (doublet, 4H), 8.11 (doublet, 4H); ^{13}C NMR (CD_2Cl_2 ppm) δ 35.68, 38.72, 51.23, 55.38, 59.71, 125.40, 131.33, 148.87, 149.06, 173.92.

General Procedure for Synthesis of TCNQ-Functionalized Dendrimers, Series III.[13] A solution of PAMAM dendrimer in DMF (dimethylformamide) was added to a warmed, stirring solution of TCNQ (tetracyanoquinodimethane) under nitrogen. After stirring for 48 h, the DMF was removed by rotary evaporation and the resulting solid was dissolved in aqueous sodium hydroxide; the resulting solution was filtered and then acidified with dilute hydrochloric acid, which brought about precipitation of a black/purple solid. This was collected by filtration, washed with water, and dried under vacuum. The products were characterized by proton NMR, infrared, and UV/visible spectroscopy. Data for compound IIIAG2: IR (KBr disk) ν_{CO} 1654, 1576, ν_{CN} 2172, 2123; UV/vis (DMF) λ 368, 446 nm.

Spectroscopic Measurements. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AC250 or a Varian VXR-200 spectrometer. Infrared spectra were measured by a Perkin-Elmer 1600 series FT-IR spectrometer. UV/vis spectra were recorded using a Perkin-Elmer Lambda 19 spectrophotometer. Fluorescence spectra were obtained by use of a Perkin-Elmer LS5OB luminescence spectrometer. GPC was performed on a PL gel 5 μm mixed C polystyrene, 300 × 7.5 mm column

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S0024-9297(97)00411-7 CCC: $14.00

Scheme 1. Outlined Synthesis Schemes for the Dendrimers Studied

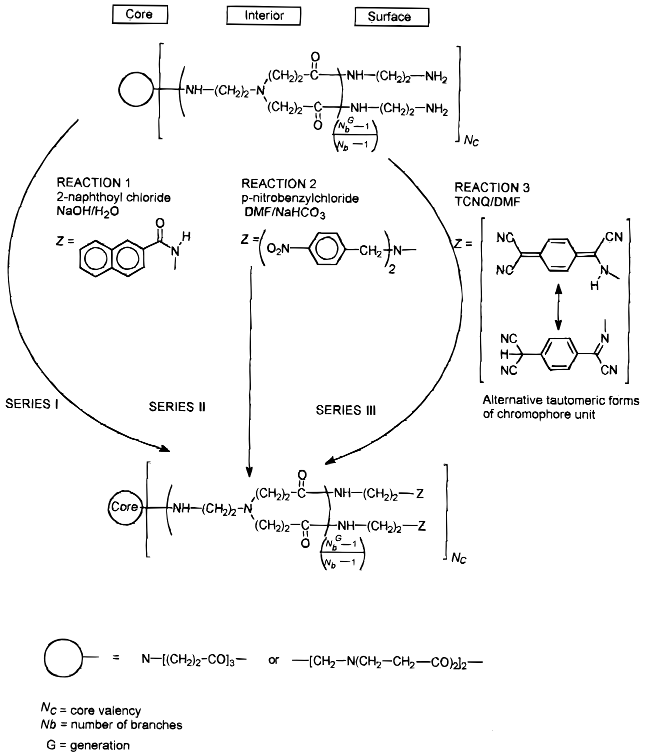

Table 1. Extinction Coefficient per Dendrimer Molecule (Series I, 237 nm; Series II, 276 nm) Obtained for the Functionalized Dendrimers Studied[a]

compd	ϵ (L mol^{-1} cm^{-1})	N
IAG1	11 000	3
IAG2	17 000	6
IEG1	10 000	4
IEG2	15 000	8
IEG3	35 000	16
IEG5	140 000	64
IIAG1	58 000	3
IIAG2	98 000	6
IIEG1	130 000	8
IIEG2	270 000	16
IIEG3	500 000	32
IIEG5	4 700 000	64

[a] N is the number of chromophores per molecule.

Table 2. GPC Data Obtained for the Functionalized Dendrimers Studied

sample	M (expected)	$\bar{M}_w$ (found)	M_w/M_n
IEG1	1133	1900	1.2
IEG2	2663	4600	1.2
IEG3	5722	6890	1.2
IEG4	11837	11000	1.5
IIAG1	1169	1200	1.3
IIAG2	2663	2600	1.2
IIEG1	1597	1500	1.5
IIEG2	3590	5000	1.9
IIEG3	7576	11000	
IIEG5	31495	30000	

with NMP (*N*-methylpyrrolidinone) and lithium chloride (~0.1% by weight) as the eluent. The operating temperature was 80 °C, the pressure was 5 MPa, the flow rate was 1 mL min^{-1}, and the sample injection coil size was 20 μL. A Pye Unicam 4011 pump with a 4030 controller, a 4810 integrator, and a 4020 UV detector were used.

Results and Discussion

Initially, both functionalization of "whole" generation (NH$_2$ terminated) and "half" generation (CO$_2$ terminated) PAMAM dendrimers was attempted, of which the amine chemistry was found to be more immediately successful. Scheme 1 illustrates the three most successful reactions investigated and discussed herein. Two types of PAMAM dendrimer; one type possessing an ammonia (NH$_3$) core and the other having an EDA (ethylenediamine, H$_2$NCH$_2$CH$_2$NH$_2$) core were investigated. In all three reaction series studied, a large excess of functionalization reagents was used (typically 2 molar equiv per dendrimer reactive site) and extended reaction times were employed to ensure complete reaction of the dendrimer end groups.

IR data obtained from the compounds of series I (IAG1, IAG2, IEG1, IEG2, IEG3, IEG4, IEG5, and IEG7), showed the absence of the peak at 1750 cm^{-1}, due to the carbonyl stretch of the starting 2-naphthoyl chloride compound, and strong peaks due to the carbonyl stretch of the amide groups, which shifted to higher wavenumbers in higher generations, indicative of increased hydrogen bonding within the structure. In higher generations (compounds IEG4, IEG5, and IEG7) a strong, unidentified peak at 1399 cm^{-1} was observed. Structured peaks attributed to C–H and N–H stretching in the 3500–2500 cm^{-1} region were observed in the lower generations, which tended to broaden into two single peaks in higher generations. ^{1}H NMR showed the expected peaks due to the CH$_2$ groups of the dendrimer (the CH$_2$ next to the newly formed amide bond was shifted downfield), the aromatic naphthyl unit, and discrete amide resonances. At higher generations, however, the ^{1}H NMR became increasingly broad; nevertheless, the relative proportions of alkyl–aromatic protons were still obtainable from the integration. This crude analysis was complicated by the presence of the peak due to the incompletely deuterated solvent and also to residual methanol contained within the sample, which could not be removed even by prolonged drying procedures (over 1 week in a vacuum desiccator). Elevated temperatures were not employed, as decomposition was observed on occasions. Greater reliance was therefore placed on ^{13}C NMR. In the case of IEG5 an additional carbon resonance was observed at δ 172.22 ppm, indicative of a dislocation in the dendrimer structure.[1,2] Examination of UV/vis data shown in Table 1, of the compounds of series I, showed the expected increase of the extinction coefficient on moving to higher generations. This indicated that the dendrimer end groups were fully functionalized. In GPC traces obtained from this series, sharp peaks of low polydispersity were observed for the lower generations. Samples IEG3 and IEG4 displayed an additional peak. Disagreement between experimental and theoretical molar masses (Table 2) will be exacerbated by the use here of poly(vinylpyridine) standards, whose linear structure is a poor model of branched dendritic architectures. Initial work, showing unexpected high molecular mass peaks in the GPC trace, suggested that aggregation of dendrimer molecules was occurring even at the low working concentrations of the experiment. The addition of lithium chloride (~0.1% by weight) to NMP solvent prevented this.

Of series I, compound IEG7 was too insoluble to carry out NMR or GPC analysis and only ir and poor quality UV/vis spectra could be obtained. Compound IEG5 was not sufficiently soluble in the GPC eluent to obtain a significant trace, but ^{13}C NMR data were obtained in DMSO-d_6.

IR data obtained from the compounds of series II (IIAG1, IIAG2, IIEG1, IIEG2, IIEG3, and IIEG5) showed

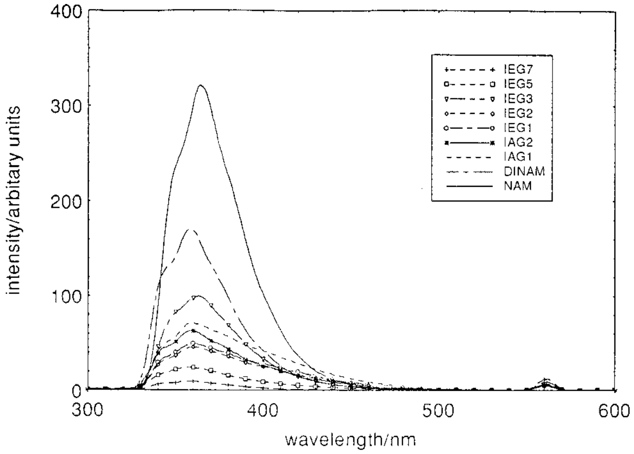

Figure 1. Fluorescence emission spectra (λ_{ex} = 280 nm) of series **I**.

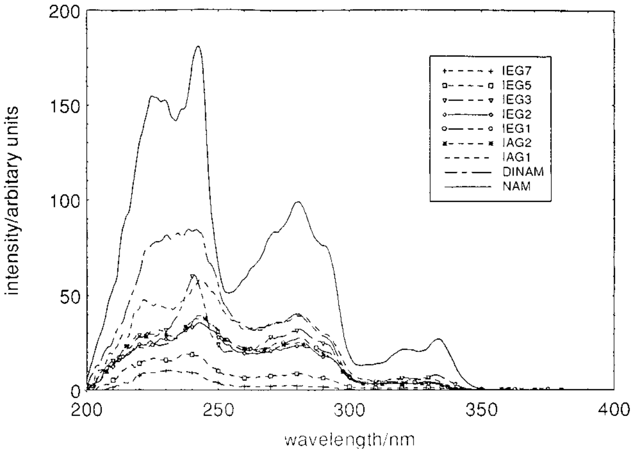

Figure 2. Fluorescence excitation spectra at 400 nm of series **I**.

the expected strong peaks due to the carbonyl of the amide group and the nitro group of the chromophore unit. Similar shifts in the peaks due to the amide carbonyl stretching and broadening of the N−H and C−H stretching signals were observed as described previously for series I. ^{1}H NMR spectra of early generations showed the expected structure, with the benzylic CH_2 group shifted upfield in the product as compared to the starting 4-nitrobenzyl chloride. Problems of line broadening and solvent (DMF) entrapment became significant in higher generations. ^{13}C NMR spectra also exhibited the expected resonances. The UV/vis data shown in Table 1 were also consistent with full dendrimer end group functionalization. Samples IIAG1, IIAG2, IIEG1, and IIEG2 exhibited single, sharp peaks in the GPC spectrum which comprised >85% of the sample. The remainder of the sample appeared in the form of a low molecular weight "tail" to the main peak. IIEG3 exhibited two poorly resolved peaks in the GPC trace; IIEG5 showed multiple peaks (major peak 60% of the sample), indicative of growing imperfection in the dendrimer structure.

Of the compounds of series II, compound IIEG7 was only superficially characterized by IR spectroscopy, due to its insolubility in organic solvents, which precluded the use of GPC or NMR or UV/vis spectroscopy.

The insolubility of the G7 compounds of series I and II may be indicative of the approach of the de Gennes dense-packed generation[14] for these types of functionalized dendrimers.

Due to the low solubility of the adducts of series III, proton NMR spectra were of a poor quality but indicated the presence of the two tautomeric forms of the desired product. Two such functionalized dendrimers were produced, IIIAG1 and IIIAG2, but due to their poor solubility (only soluble in DMF and DMSO) even at low generation, they were deemed unsuitable for further study and were not pursued.

Fluorescence Measurements. Emission and excitation fluorescence spectra of the 2-naphthyl-functionalized dendrimers, series I were measured and are displayed in Figures 1 and 2. The spectra of IEG7 are also shown, but as this material was found to be extremely insoluble, only an unknown, trace amount was dissolved in solution. The model compound 2-naphthylamide (NAM) and 1,2-bis(amidonaphth-2-yl)ethane (DINAM) were also studied. The compounds all exhibited two main absorption peaks in their UV/visible spectra (237 and 280 nm) and a third weak absorption at ~320 nm. For the fluorescence studies, solutions were prepared that exhibited an absorbance of 0.1 at 280 nm. It can be seen from the emission spectra that, relative to NAM, quenching is occurring in the dendrimer systems. This indicates that nonradiative pathways not available to the model chromophore in methanol solution are open to the dendrimer molecules. This is assumed to be attributable to intramolecular associations. Chromophores on each of the dendrimer molecules may be held closer and are less solubilized than the free chromophores. Further, a broadening of the low-energy side of the emission peak is observed in the lower generation dendrimers. This may be due to the formation of excimer species, made possible in the lower generations by the flexible branches, which could allow the necessary conformation to occur. Similar quenching effects and the observation of excimer species have recently been reported in naphthyl-terminated polyether dendrons.[15]

EFISH Measurements. The study of mesoscopic molecules using the technique of EFISH[16] represents a new area of interest. The recent study of 4-(dimethylamino)benzenecarboxamide-functionalized poly(propylenimine) dendrimers by hyper-Rayleigh scattering[17] showed the expected flexible, averaged spherelike structure at lower generations, which tends toward a rigid spherical morphology at higher generations.

The two molecules studied here were IIAG1 and IIEG1, each in dichloromethane solution. Dendrimer IIAG1 contains six terminal nitrobenzyl groups whereas IIEG1 contains eight terminal groups. Incident pulses of 8 ns duration at a wavelength of 1.064 μm were used and the second harmonic was detected by a photomultiplier tube filtered with a 532 nm interference filter.

The EFISH technique uses electric fields to polarize a liquid or solution, thus breaking the symmetry and allowing coherent generation of second harmonic light in response to an incident optical beam. Normal material refractive dispersion leads to a phase mismatch between the coupled fundamental and harmonic fields. A coherence length, l_c, may then be defined as

$$l_c = \frac{\lambda}{4(n_\omega - n_{2\omega})} = \frac{\lambda}{4(\Delta n)}$$

where λ is the wavelength of the fundamental light and n is the refractive index of the solution at the fundamental ω and second harmonic 2ω frequencies, respectively. Translation of a wedged sample cell across the beam produces fringes of second harmonic light (Maker fringes) spaced by $2l_c$.

Interestingly, in comparison of Maker fringes obtained from IIAG1 in dichloromethane and the pure solvent, the spacing between the fringes for the solution are longer than for the pure solvent. This indicates an increase in coherence length (approximately 22 μm compared with 17 μm obtained for dichloromethane). A similar, and larger, effect was seen for IIEG1, where the coherence length extended to 28 μm despite the molar concentration being lower than for IIAG1 (although the weight fraction is the same).

We will not attempt to provide a detailed analysis of these results, but it is clear that the addition of dendrimer to dichloromethane lowers the dispersion of the solution (Δn is lower) rather than raises it, as is usual in EFISH studies (due to the addition of a strongly dispersive solute). We ascribe the present observations to reductions in solution density on solubilizing these mesoscopic molecules in a dichloromethane solution, whereupon the normal dispersion of the components is partially canceled.

Conclusions

We have successfully produced a range of chromophore-functionalized dendrimers. Naphthalene moieties reacted with the dendrimer terminal amine groups produced dendrimers with fluorescent properties, while reaction of the dendrimer with *p*-nitrobenzylic functions yielded dendrimers with nonlinear optical chromophores attached. Highly dipolar groups derived from the reaction of TCNQ with the dendrimer were also incorporated into the dendrimer structure. GPC and NMR studies of the naphthyl and *p*-nitrobenzylic functions indicated that at higher dendrimer generation, the regular branched structure of the starburst was disrupted to a small degree with minor dislocations evidenced by an additional peak due to a carbonyl type group in the ^{13}C NMR and the presence of a second, small, poorly resolved peak in the GPC trace. Naphthyl-functionalized dendrimers, investigated by fluorescence spectroscopy, showed the expected feature of increased energy transfer with higher generation, indicated by the decrease of the intensity of the fluorescence emission spectra.

We have examined in a preliminary way the electric field induced second harmonic generation (EFISH) of solutions of a dipolar-terminated dendrimer. The observation that the coherence length is increased with increasing dendrimer concentration suggests that care must be taken in further work to take account for the volume fraction of dendrimer molecules in solution. In particular, it will be essential to correlate EFISH data with solution density studies.

Acknowledgment. We wish to acknowledge EPSRC for the financial support for this work, Dr. A. Beeby for use of the fluorescence spectrometer, and Dr. P. Adams for GPC work.

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MA9704119