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Preparation, MALDI-TOF analysis, and micelle-like behavior of alkyl-modified poly(propylene imine) dendrimers

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Summary

MALDI-TOF mass spectral analysis was used to characterize the novel unimolecular micelles that result from functionalization of the chain ends of poly(propylene imine) dendrimers with C_{10} alkanoyl or C_{12} alkyl groups.

Introduction

Dendrimers, as a novel class of materials, have attracted considerable interest in the scientific community since they appeared in mid-1980s (1). Compared to conventional linear polymers, dendrimers contain highly branched structure, offer better control of molecular architecture, size and shape, and possess a multiplicity of chain ends that can be functionalized. Dendrimers have found applications in many areas due to their unique structure and properties (1).

One interesting application of dendrimers is the construction of dendritic unimolecular micelles (2-6). It has been demonstrated that dendrimers with amphiphilic moieties exhibit micelle-like properties in solutions. For example, we have reported earlier that poly(aryl ether) dendrimers bearing carboxylic groups as chain ends were able to solubilize pyrene in water (2). In contrast to conventional micelles that are thermodynamic aggregates of amphiphilic molecules, the hydrophobic and hydrophilic moieties in dendritic micelles are linked covalently, therefore, they are unimolecular micelles and the micellar structure is maintained in all concentration range. So far, both normal (2-4) and reversed (5,6) dendritic unimolecular micelles have been reported.

Starting from poly(propylene imine) dendrimers (7), we prepared two different types of unimolecular micelles based on poly(propylene imine) dendrimers with C_{10} alkanoyl or C_{12} alkyl chain ends, and have characterized them using MALDI-TOF MS.

Experimental

Materials and Characterization

Poly(propylene imine) dendrimers (G-1 to G-5) were purchased from DSM. All other chemicals were purchased from Aldrich and used without further purification. ^{1}H-NMR spectra were recorded on a Bruker AMX-300 (300 MHz) spectrometer in $CDCl_3$ with the solvent proton signal as the standard. Infrared samples were prepared as KBr discs or as

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thin films (neat) on silicon wafers and measured on a Nicolet IR/44 spectrophotometer. MALDI-TOF mass spectra were obtained on a Perseptive Biosystems Voyager-DE instrument in positive ion mode using trans-3-indoleacrylic acid as the matrix.

General Procedure for the preparation of decanoyl-modified dendrimers

The procedure used was a modification of that of Meijer et al (5) for the amidation of similar dendrimers. To a solution of poly(propylene imine) dendrimer in CH_2Cl_2, triethylamine was added, followed by addition of decanoyl chloride (1.1 equiv. per terminal amino group). After stirred for 3 hrs, the solvent was removed and 0.5 M HCl aq. solution was added. The solid formed was washed with 0.5 M HCl aq. solution and acetone (for G-1, G-2 and G3) or ethyl ether (for G-4 and G-5). The solid was then partitioned between CH_2Cl_2 and sat. Na_2CO_3 aq. solution. The organic layer was separated, dried and evaporated to afford the product as a white/yellow solid.

General Procedure for the preparation of dodecyl-modified dendrimers

To a solution of poly(propylene imine) dendrimer in CH_2Cl_2 over 4 Å molecular sieves, dodecyl aldehyde (1.05 equiv. per terminal amino group) was added, and the mixture was stirred for 3 hrs. Then tetrabutylammonium cyanoborohydride was added, followed by addition of HCl (1.0 M solution in ethyl ether). The resulting solution was stirred overnight and the solvent was removed. To the residue, 0.5 M HCl aq. solution was added and stirred. The solid formed was filtered and washed with ether (for G-2 and G-3) or acetone (for G-4 and G-5). The solid was then partitioned between CH_2Cl_2 and sat. Na_2CO_3 aq. solution. The organic layer was separated, dried and evaporated, affording the product as a yellow liquid.

Results and Discussion

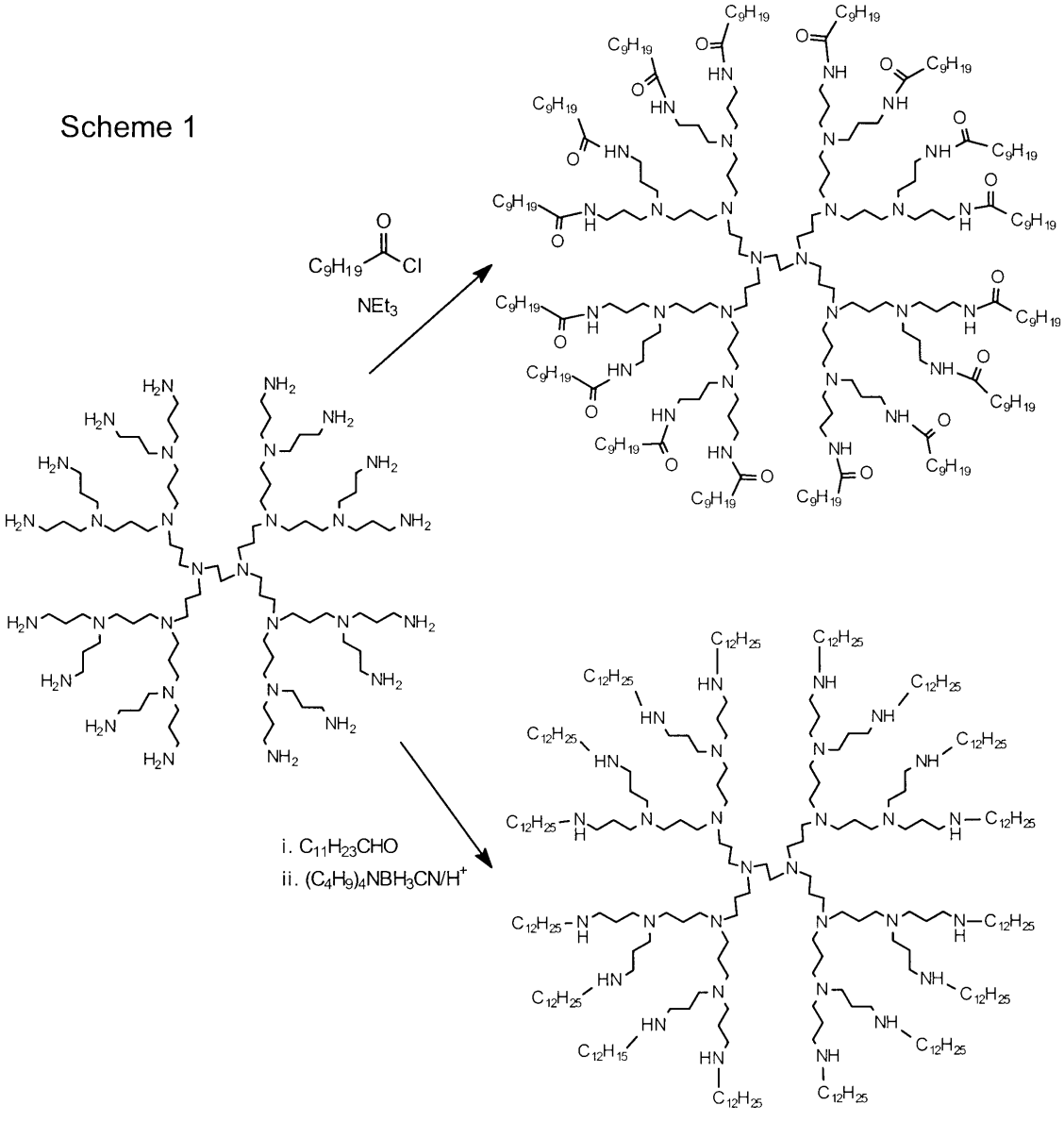
Five different generations of poly(propylene imine) dendrimers with 4 to 64 amino end groups were used as starting materials for the synthesis of alkyl-modified dendrimers. Two synthetic routes shown in Scheme 1 were attempted, i) amidation of amino groups with an aliphatic acid chloride (5), and ii) condensation with an aliphatic aldehyde followed by reduction.

1. MALDI-TOF characterization of poly(propylene imine) dendrimers

Dendrimers are frequently claimed as monodisperse, and this may be true for those prepared by the convergent approach. Structural defects indeed exist for almost all dendrimers prepared by the divergent approach, especially for higher generations of dendrimers. For example, Meijer and coworkers (8) have analyzed in detail the structure of poly(propylene imine) dendrimers by electrospray mass spectrometry, and found that two types of structural defects existed: i) missing $CH_2CH_2CH_2NH_2$ segments due to incomplete Michael addition (defect structure A), and ii) formation of cyclic structures with loss of a NH_3 molecule as a result of the cyclization of two surface arms during hydrogenation (defect structure B).

MALDI-TOF MS is a very useful technique for the characterization of dendrimers. While it does not replace common techniques such as size exclusion chromatography or light scattering, it is extremely useful to uncover fine structural details. For example, MALDI-TOF MS may be used to detect structural defects that arise during the

preparation or modification of the parent poly(propylene imine) dendrimers. Therefore, we analyzed poly(propylene imine) dendrimers by this technique. The G-1 dendrimer is too small to be differentiated from matrix peaks, and the G-5 dendrimer is too large and no signal could be observed under the condition of our analysis. Good MALDI spectra were easily obtained for G-2 to G-4 dendrimers as shown in Figure 1. In all the spectra, a major peak (H^+ adduct) corresponding to the "perfect" dendrimer is observed, and a few minor peaks corresponding to the defect structures are also observed. For example, in Figure la, the peak with MW = 687.6 (M^+ - 57) is likely due to a molecule missing a segment of $CH_2CH_2CH_2NH_2$ (defect structure A), and the peak with MW = 727.5 (M^+ - 17) results from defect structure B.



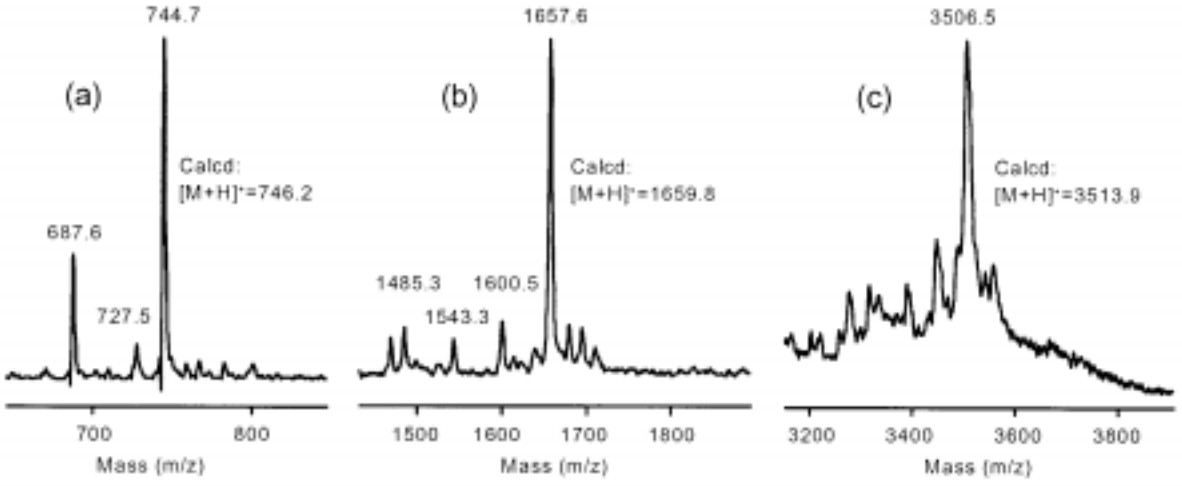


Figure 1. MALDI-TOF spectra of poly(propylene imine) dendrimers: G-2 (a), G-3 (b), and G-4 (c).

2. Reaction with decanoyl chloride

The modification reaction consists of the conversion of the terminal primary amino groups to amides in the presence of triethylamine (5). As expected, the coupling reaction worked very well affording the desired products in good yields. Characterization with ^{1}H-NMR, FTIR and MALDI-TOF showed that all amino end groups were amidated. FTIR data show the absence of a peak at 1802 cm^{-1} that would correspond to the carbonyl stretching of the starting decanoyl chloride. A strong absorption at 1640 cm^{-1} due to the carbonyl stretching of the newly formed amide bond is observed; this does not change much from generation to generation. A peak attributed to N-H stretching is observed at 3299 cm^{-1}. ^{1}H-NMR shows the expected signal at 3.2-3.4 ppm for the CH_2 groups of the dendrimers that are located next to the amide bonds. An interesting feature of the ^{1}H-NMR spectra is the downfield shift and broadening of the N-H peaks as the dendrimer generation increases. This is the result of the change from intermolecular H-bonding for lower generations to intramolecular H-bonding for higher generations (5).

MALDI-TOF MS was found to be useful to analyze the modified dendrimers with molecular weights lower than 10,000. Figure 2 shows the MALDI-TOF spectra of decanoyl-modified dendrimers (G-1 to G-4). In all of these spectra, two major peaks (H^+ and Na^+ adducts) corresponding to the fully modified dendrimers were observed. For G-1 and G-2, the observed molecular weights are in good agreement with the expected values, but for G-3 and G-4, there is a small difference between the observed and expected MW's (10 for G-3 and 27 for G-4). Good resolution was easily obtained for the first three generations. But for the larger G-4 dendrimers, higher laser power had to be used in order to obtain the spectrum. This led to peak broadening and an increase in baseline noise. In addition to the major peaks, each spectrum also exhibited a few minor peaks in the lower MW region. These peaks can be attributed to the defects in the starting dendrimers (8). For example, in Figure 2b, a peak with MW = 1922 (M^+ - 57) is due to a missing segment of $CH_2CH_2CH_2NH_2$ in the starting G-2 dendrimer (defect structure A in Figure 3). Note that this type of defect does not prevent the incorporation of the full complement of decanoyl groups since acylation of the secondary amine can take place. Another peak at MW 1807, which is 172 less than that of expected dendrimer, is due to the structural defect B in the starting dendrimer. This type of defect leads to one "missing" decanoyl group in the final structure.

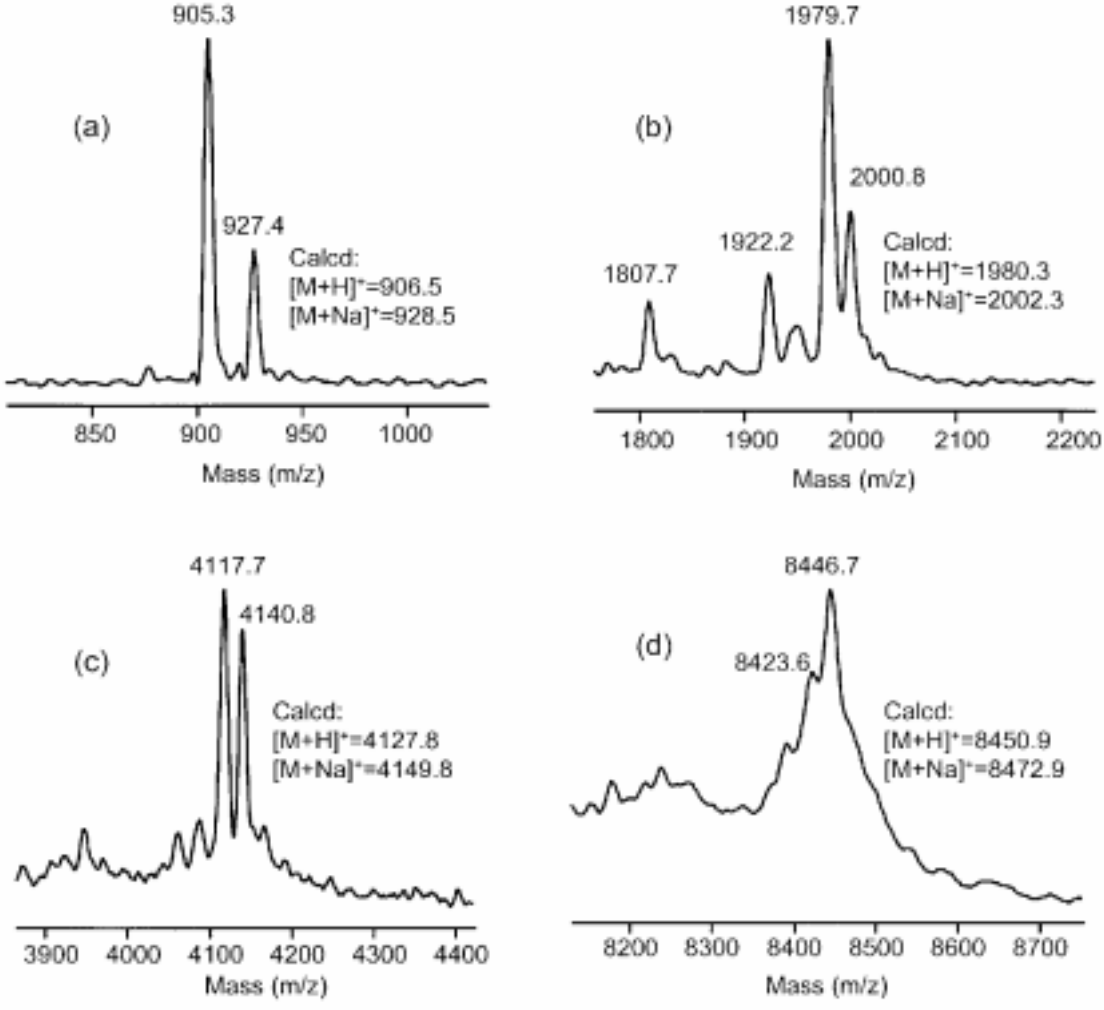


Figure 2. MALDI-TOF spectra of decanoyl-modified dendrimers: G-1 (a), G-2 (b), G-3 (c), and G-4 (d).

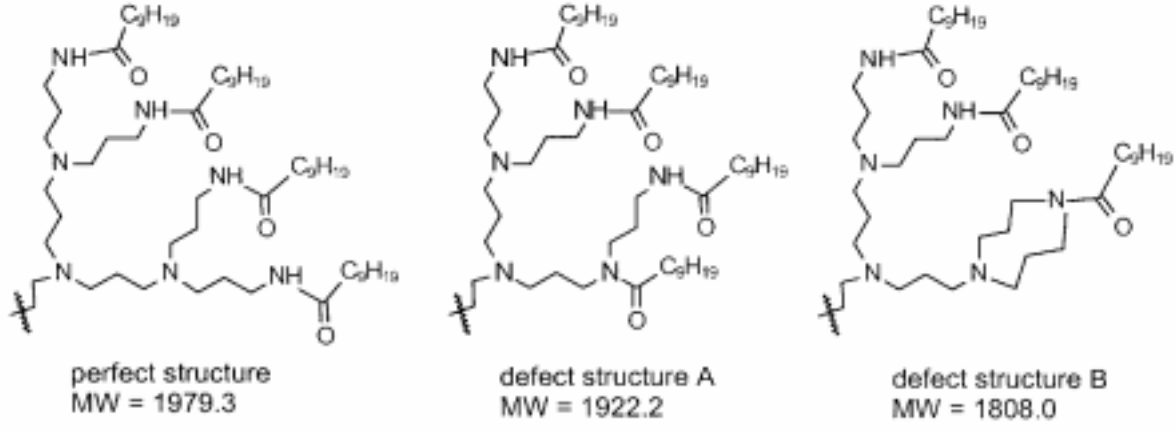


Figure 3. Structural defects in decanoyl-modified G-2 dendrimer.

3. Reaction with aldehyde

To explore the variety of reactions that may be carried out on the surface of poly(propylene imine) dendrimers, we attempted the reaction of a long-chain aldehyde with the terminal amino groups of the dendrimers. This reaction was performed in two steps: imine formation followed by reduction. The dendrimer and aldehyde were mixed in the presence of molecular sieves. The molecular sieves are used to absorb the water produced in the reaction and drive the formation of imine. The resulting imine was immediately stabilized by reduction to a secondary amine using tetrabutylammonium cyanoborohydride. This reaction sequence was monitored by FTIR. A strong absorption was observed at 1671 cm^{-1} after the amine dendrimer and the aldehyde were mixed, confirming the formation of C=N double bonds. Once the reducing agent was added, this peak disappeared. After purification, the modified dendrimers were obtained in good yields. However, examination of the products by MALDI-TOF MS revealed the occurrence of a side reaction. In the MALDI-TOF spectrum (Figure 4), three major peaks were observed and the peak with expected MW had the lowest MW of the three. The mass difference between two adjacent peaks was 168, which corresponds to the formula weight of one alkyl chain. That suggests that, in addition to the fully modified dendrimer, species with one or two additional dodecyl chains were also attached to the dendrimer. This phenomenon is explained by the occurrence of an aldol condensation that follows the formation of the imine bonds (9).

Dodecyl-modified dendrimers have good solubility in most common organic solvents, such as THF, CH_2Cl_2, $CHCl_3$ or ether. They are even soluble in hexane.

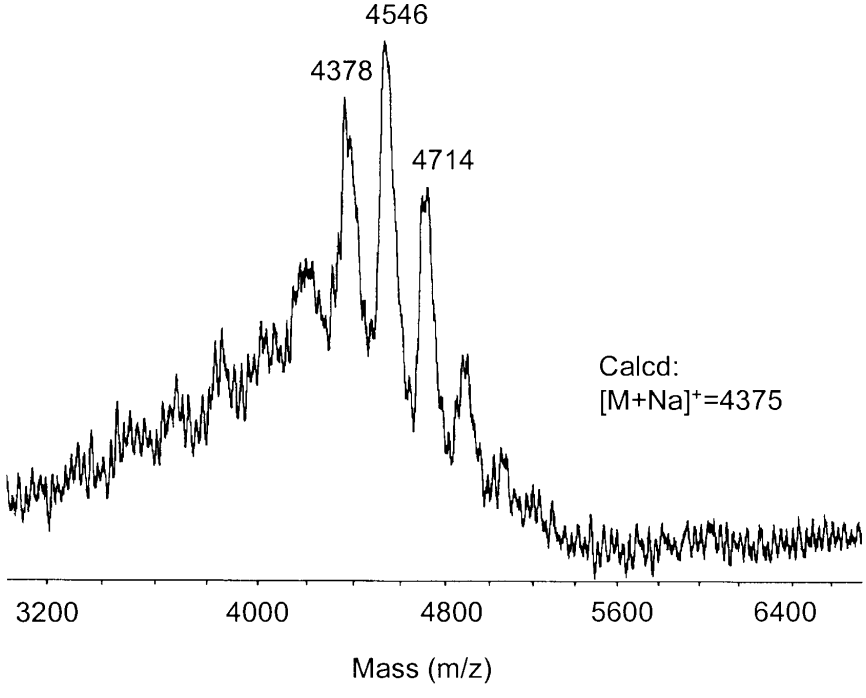


Figure 4. MALDI-TOF MS spectrum of dodecyl-modified G-3 dendrimer.

4. Solubilization test

The alkyl-modified dendrimers have a hydrophilic interior and a hydrophobic exterior. This type of amphiphilic molecules is structurally reminiscent of reversed micelles. If these macromolecules behave as reversed micelles, they should be able to solubilize polar molecules in non-polar solvents (10). A solubilization test was therefore performed to demonstrate the ability of the modified dendrimers to act as reversed micelles. Fluorescein was used as the probe molecule and hexane as the non-polar solvent. Dodecyl-modified G-5 dendrimer was used because it is quite soluble in hexane. In the absence of the modified dendrimer, fluorescein is totally insoluble in hexane and no coloration or UV-vis absorption can be detected. After the addition of the modified dendrimer, the hexane solution turned from colorless to yellow, and UV-vis measurement indicated a strong absorption at 512 nm, and the absorbance increased with the dendrimer concentration. The change in the saturated concentration of fluorescein with changes of the concentration of the modified dendrimer is shown in Figure 5. As can be seen, the concentration of fluorescein in hexane corresponding to saturation increases with the concentration of modified dendrimer in the solution. The modified dendrimer is capable of solubilizing fluorescein in hexane at concentrations as low as 6×10^{-7} mol dm^{-3}. However, it seems that there is no linear relationship between the concentration of fluorescein and the concentration of dendrimer, and the apparent solubilizing power of each dendrimer molecule increases with concentration. A possible explanation for this phenomenon is that the modified dendrimer molecules form aggregates at higher concentration, therefore, more fluorescein molecules can be encapsulated inside the larger aggregates. This test demonstrates that the alkyl-modified dendrimers can act as reversed micelles.

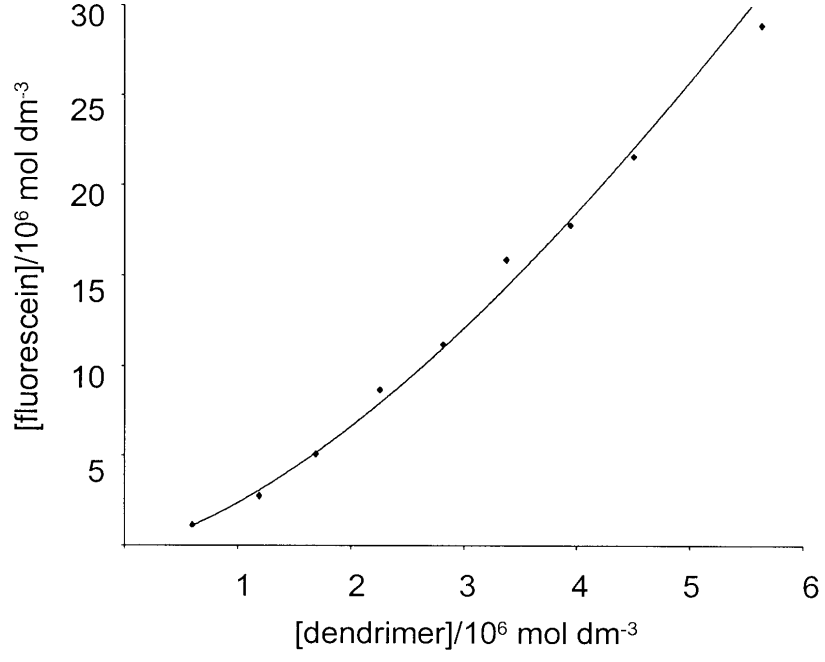


Figure 5. Solubility of fluorescein as a function of the concentration of dodecyl-modified G-5 dendrimer.

Acknowledgment
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