Pronounced Hydrogel Formation by the Self-Assembled Aggregates of *N*-Alkyl Disaccharide Amphiphiles

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Six disaccharide amphiphiles were synthesized and their hydrogel-forming behavior was extensively studied. These amphiphiles were based on maltose and lactose. Since the gels formed from some of these systems showed the ability to "trap" water molecules upon gelation, these gels were described as "hydrogels". When these gels were heated to ~70 °C, the samples turned into clear, isotropic fluids, and upon gradual cooling, the hydrogels could be reproduced. Thus these systems were also "thermoreversible". The low molecular mass (MW 565) of the gelators compared to that of a typical polymeric gelator forming substance implies pronounced aggregation of the disaccharide amphiphiles into larger microstructures during gelation. To discern the aggregate textures and morphologies, the specimen hydrogel samples were examined by high-resolution scanning electron microscopy (SEM). A possible reason for the exceptionally high water gelating capacities (>6000 molecules of water per gelator molecule) exhibited by these *N*-alkyl disaccharide amphiphiles is the presence of large interlamellar spaces into which the water molecules get entrapped due to surface tension. In contrast to their single-chain counterparts, the double-chain lactosyl and maltosylamine amphiphiles upon solubilization in EtOH−H_2O afforded hydrogels with reduced mechanical strengths. Interestingly, the corresponding microstructures were found to be quite different from the corresponding hydrogels of their single-chain counterparts. Rheological studies provided further insights into the behavior of these hydrogels. Varying the chain length of the alcohol cosolvent could modulate the gelation capacities, melting temperatures, and the mechanical properties of these hydrogels. To explain the possible reasons of gelation, the results of molecular modeling and energy minimization studies were also included.

Introduction

Due to their excellent mechanical and surface properties, the gels based on synthetic polymers and biopolymers are widely employed in various materials applications.[1,2] To achieve similar gelation in various organic solvents, numerous low molecular mass gelators have also been described recently.[3,4] However, examples are indeed rare for nonpolymeric hydrogel formers.[5] The hydrogels are useful as these materials are used as a transport medium for dissolved species (such as drugs) and as a link between the body fluids and the synthetic implants. Unfortunately, however, the methods of preparation of polymer-based hydrogels are often subject to constraints imposed by their thermosetting nature, and consequently, they often lack the benefits associated with thermoplastic processing.[6] In addition, many hydrogels of this class are mechanically weak and do not have adequate water retention capacity, which limits their usefulness.

Self-assembly provides an excellent route to creation of novel organizations.[7] Due to our continuing interest in the design of novel amphiphilic self-assemblies,[8] we sought to develop molecules that would aggregate in water and related polar solvents to produce supramolecular networks with gelation properties.[4] We thought that the amphiphilic carbohydrate analogues might be

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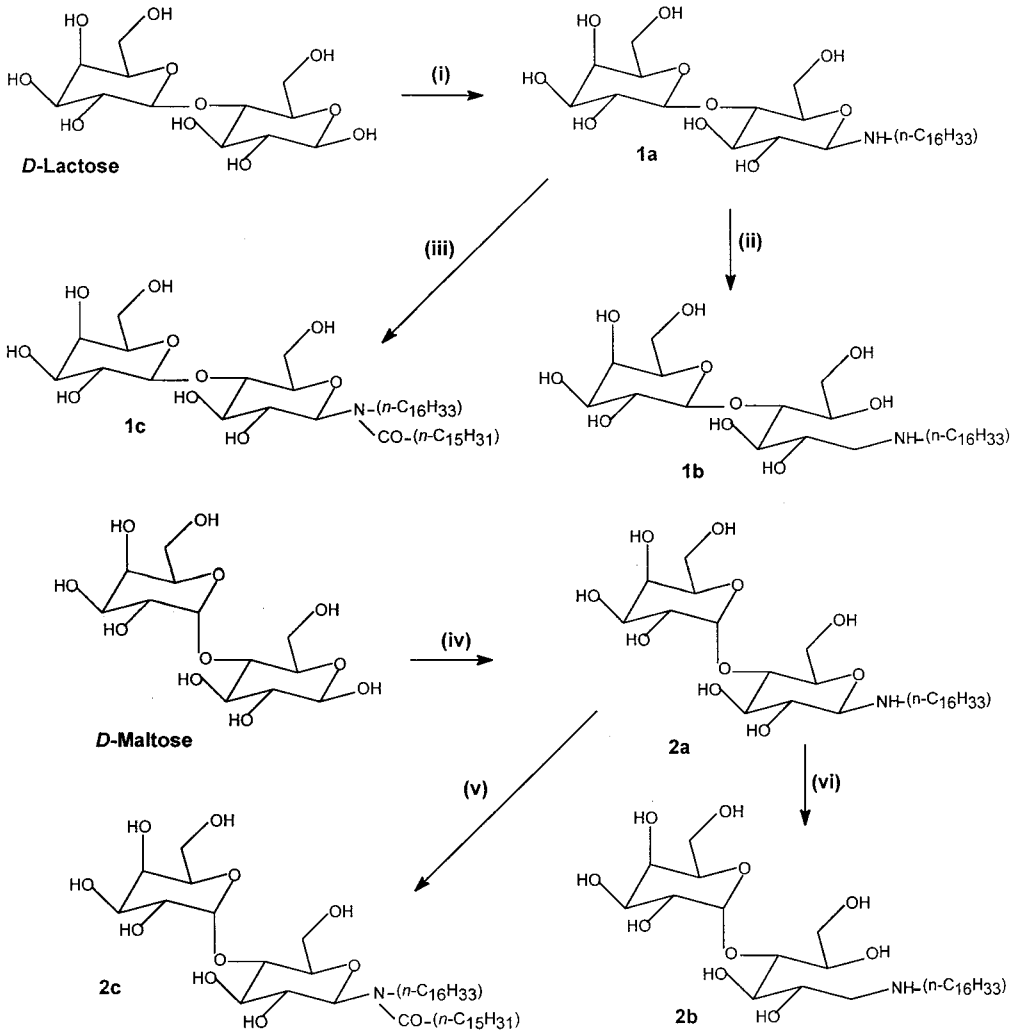
Scheme 1[a]



[a] Conditions: (i) n-$C_{16}H_{33}$-NH_2, 2-propanol, stir, 24 h, 60 °C; (ii) $NaBH_4$, in MeOH, rt, stir, 30 min; (iii) n-$C_{15}H_{30}COCl$ in DMF, rt, stir 24 h; (iv) n-$C_{16}H_{33}$-NH_2, 2-propanol, stir, 24 h, 60 °C; (v) $NaBH_4$, in MeOH, rt, stir, 30 min; (vi) n-$C_{15}H_{30}COCl$ in THF/DMF, Na_2CO_3, rt, stir, 24 h.

appropriate candidates, in that a carbohydrate is a naturally occurring biocompatible substance. In addition, sugar-based surfactants are being produced on a commercial scale and both the hydrophobic and the polar segments of these surfactants stem from renewable raw materials.[9] As opposed to synthetic materials, polysaccharides are highly hydrophilic and have also been used as matrixes for enzyme immobilization.[10]

In view of the above, we chose to prepare a few easily synthesizable, nonpolysaccharide amphiphile systems. Altogether six compounds **1a**−**c** and **2a**−**c** (Scheme 1) were synthesized. These contain selected structural subunits and were prepared as described in the Experimental Section. Herein, we report on the impressive hydrogel-forming abilities of some of these molecules and discuss possible reasons for hydrogel formation.

Results and Discussion

Considerations in the Choice of Molecules. We are interested in developing new molecular systems that self-assemble in water by making use of the noncovalent interactions such as hydrogen bonding and hydrophobic interactions. These forces promote the formation of supramolecularly held three-dimensional networks in which solvent molecules could be retained. In this context the amphiphilic sugar derivatives are of interest because of their significance in areas of self-assembly and molecular recognition in biosystems. Cyclic sugars are conformationally more defined and also have multiple as well as directional hydroxyl groups compared to their acyclic analogues. Consequently, the formation of strong cooperative hydrogen-bonding networks between the amphiphiles bearing cyclic sugar residues is expected. In addition, due to the cyclic nature of the sugar part of the headgroup, a rigid character is

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imparted to the headgroup of the amphiphile. Long alkyl chains force amphiphilic molecules to form self-organized arrays in order to minimize the interface between water and the hydrophobic chains.

In our endeavors to design and synthesize molecules which contain the above-mentioned functional elements, we chose cyclic disaccharides as the headgroup as these are biocompatible, readily available, commercially inexpensive, and naturally occurring and can be obtained in natural chiral form. In addition, these sugars contain an anomeric hydroxyl group, which can be readily chemically transformed into lipophilic aldosylamines.

On the basis of these considerations, we selected D-lactose and D-maltose as the core, since they fulfill most of the necessary requirements, i.e., contain directional hydroxyl groups, rigid backbone, and, of course, chiral centers. Altogether six compounds, **1a**−**c** and **2a**−**c**, were synthesized (Scheme 1) with D-lactose in **1a**−**c** and D-maltose in **2a**−**c**, and we studied in depth their self-assembly behavior to form macroscopic superstructures in water.

Synthesis. The synthesis began by converting the commercially available D-lactose and D-maltose to *N*-hexadecyl-D-lactosylamine (**1a**) and *N*-hexadecyl-D-maltosylamine (**2a**) in 85% and 65%, respectively, on reacting with 1-aminohexadecane (cf. Scheme 1). Compounds **1a** and **2a** were converted into *N*-hexadecyl-D-lactitol (**1b**) and *N*-hexadecyl-D-maltitol (**2b**) in 86% and 80%, respectively, by treatment with $NaBH_4$ in MeOH. Also **1a** and **2a** were reacted separately with hexadecanoyl chloride to afford *N*-hexadecanoyl-*N*-hexadecyl-D-lactosylamide (**1c**) and *N*-hexadecanoyl-*N*-hexadecyl-D-maltosylamide (**2c**) in 55% and 47% yields, respectively. All the compounds, isolated as solids after evaporation of solvents, were recrystallized and kept in a refrigerator. Each gave expected analytical and spectroscopic data consistent with their given structures (cf. Experimental Section).

Aggregation Behavior. To examine the aggregation properties in aqueous media, a solution of 0.1 mmol of either **1a**−**c** or **2a**−**c** in a minimum volume of ethanol (200 μL) and 12 mL of water were prepared in a test tube (20 mL). The resulting mixture was heated to ∼75 °C to produce a clear homogeneous solution that on cooling to ambient temperature over a period of ca. 30 min afforded soft, yet firm, opalescent masses for **1a** and **2a**. By turning the tube upside down, the small excess of unabsorbed solvents could be decanted; however, neither the solidlike mass nor the solvent molecules retained with it flowed under the influence of gravity. Therefore, the mass produced was due to the gelation of either **1a** or **2a** in water.

Gelation Behavior. The gels formed from **1a** and **2a** showed the ability to "trap" water molecules upon gelation; hence, these gels may be described as "hydrogels". When these gels were heated to ∼70 °C, the samples turned to clear, isotropic fluids, and upon gradual cooling, the hydrogels could be reproduced. Thus, these systems may be considered "thermoreversible". While similar gels could also be produced from **1c** and **2c**, they were mechanically weaker than those of **1a** and **2a**.

Ethanol was used since **1a** or **2a** tended to form crystalline precipitates from pure water. Thus, formation of this mixture depends on a delicate balance between gelation and precipitation. Notably, the hydrogel formation with **1a** or **2a** could also be effected by using several other polar solvents rather than ethanol. The results of the gelation experiments with various solvents and the minimum component concentration necessary for gelation with **1a** and **2a** are summarized in Table 1. The respective temperatures, at which such gels are converted to their sol-like fluid states, are also included in Table 1. In a given homologous series of cosolvents, e.g. alcohols, the properties of the hydrogel could be modulated by the chain length of the alcohol. Thus the gelation capacity becomes optimal as the chain length of the cosolvent alcohol gets shorter, while the gel "melting" temperature reaches a maximum with *n*-propanol as a cosolvent (Figure 1a,b).

Table 1. Summary of Hydrogel-Forming Properties of *N*-Hexadecyl-D-lactosylamine (1a) and *N*-Hexadecyl-D-maltosylamine (2a)[a]

entry	cosolvent[b] (vol, mL)	wt of H_2O[c] (g)	no. of H_2O molecules gelated[d] per molecule of amphiphile	T_m[e] (°C)
	1a as Amphiphile			
1	methanol (0.2)	11.2	6220	64
2	ethanol (0.2)	10.6	5890	68
3	1-propanol (0.2)	10.2	5670	74
4	2-propanol (0.2)	9.6	5330	66
5	1-butanol (0.2)	9.7	5440	70
6	2-butanol (0.15)	5.6	3110	68
7	1-pentanol (0.2)	7.4	4110	64
8	1-hexanol (0.1)	5.6	3110	64
9	benzyl alcohol (0.2)	4.1	2280	74
10	ethylene glycol (0.05)	9.6	5330	78
11	glycerol (0.4)	9.4	5220	82
12	tetraethylene glycol (0.1)	9.1	5060	84
13	DMF	2.3	3151	70
14	DMSO	2.9	3718	76
	2a as Amphiphile			
15	methanol (0.2)	10.4	5780	65
16	ethanol (0.2)	10.9	6060	63
17	1-propanol (0.2)	9.8	5450	74
18	2-propanol (0.2)	9.4	5330	66
19	1-butanol (0.2)	9.8	5500	71
20	2-butanol (0.15)	6.8	3780	64
21	1-pentanol (0.2)	6.1	3390	64
22	1-hexanol (0.1)	4.8	2670	64
23	benzyl alcohol (0.2)	4.5	2500	68
24	ethylene glycol (0.05)	8.8	4890	72
25	glycerol (0.4)	9.8	5440	76
26	tetraethylene glycol (0.1)	8.6	4780	84
27	DMF	2.6	3560	66
28	DMSO	3.1	3970	68

[a] See text for the details of hydrogel preparation. [b] Amount of cosolvent required to solubilize **1a** or **2a** prior to hydrogel formation. [c] Weight of water trapped with per 0.1 mmol of **1a** or **2a** (0.0565 g). [d] Ratio of number of moles of water trapped to the number of mol of **1a** or **2a**. [e] The temperature (±1 °C) at which a preformed hydrogel "melts" into a sol.

In the case of **1b** or **2b**, no gelation was observed even after 24 h, while **1c** and **2c** formed gels that were rather weak and susceptible to phase separation. The gelation capacities of **1c** or **2c** were also small, i.e., ∼800 molecules of water per gelator molecule.

Stability of the Gels. The hydrogels were found to be reasonably stable for several days when kept in a closed container. The fact that similar aldosylamines undergo hydrolysis[11] to alkylamine and aldose in aqueous media prompted us to examine the extent of hydrolysis of **1a** or **2a** in the hydrogel state. We examined the hydrolysis of **1a** in hydrogel form by

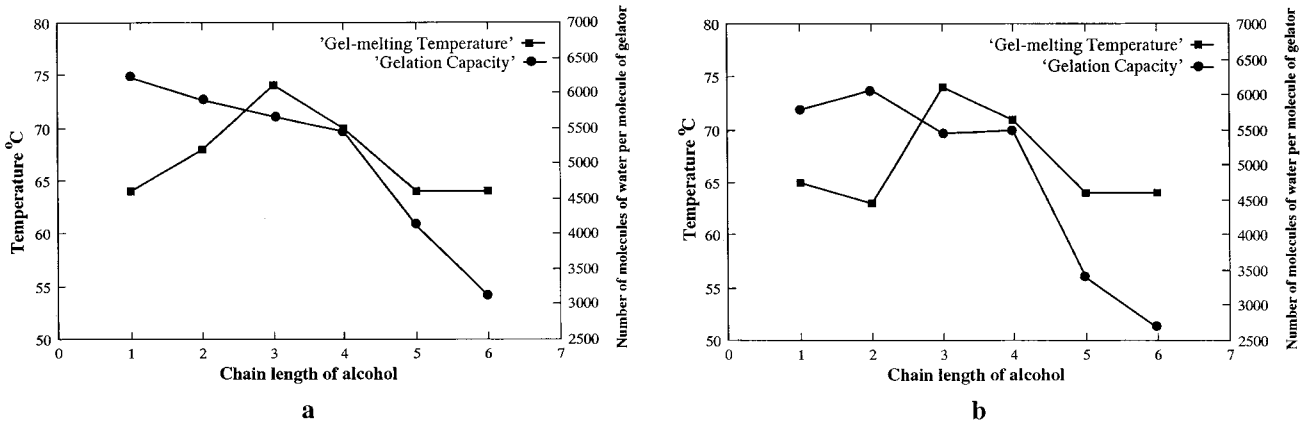

Figure 1. Effect of cosolvent and alcohol chain length on the water gelation capacities and the gel melting temperatures.

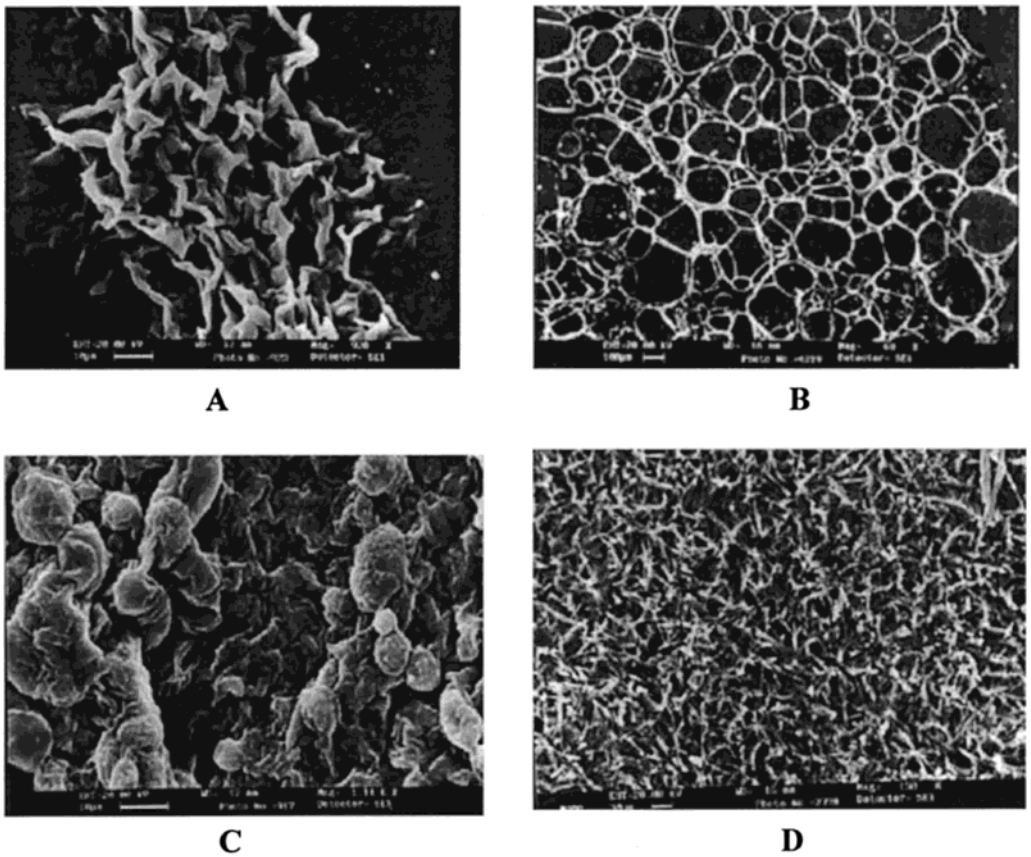

Figure 2. Scanning electron micrograhpic images: (A) wet gel of **1a**, (B) "dried" gel of **1a**, (C) wet gel of **2a**, and (D) "dried" gel of **2a**.

taking samples (2 mg) at various time intervals (every 15 min in the beginning up to the first couple of hours and then once every hour). Examination of these samples by HPLC and ESI-MS indicated that hydrolysis of **1a** occurred even when it was in the form of a hydrogel. However, the extent of hydrolysis did not surpass ~25%, even after keeping the hydrogel at ambient conditions for ca. 48 h. However, at lower pH, rapid (15 min) and substantial hydrolysis was observed. Notably, the gelation could not be initiated by solubilization of a physical mixture of 1:1 of hexadecylamine and D-lactose in EtOH/H_2O.

Characterization of Gels. The low molecular mass (MW 565) of the gelators (for **1a** and **2a**) compared to that of a typical polymeric gelator forming substance implies pronounced aggregation of the disaccharide amphiphiles into larger microstructures during gelation. To discern the aggregate textures and morphologies, the specimen hydrogel samples were examined by high-resolution scanning electron microscopy (SEM). SEM of each of these hydrogel formulations revealed the existence of a range of micron-scale protrusions and surface patterns (Figure 2). A collection of wrung clothlike intertwined fibrous microstructures was seen from the

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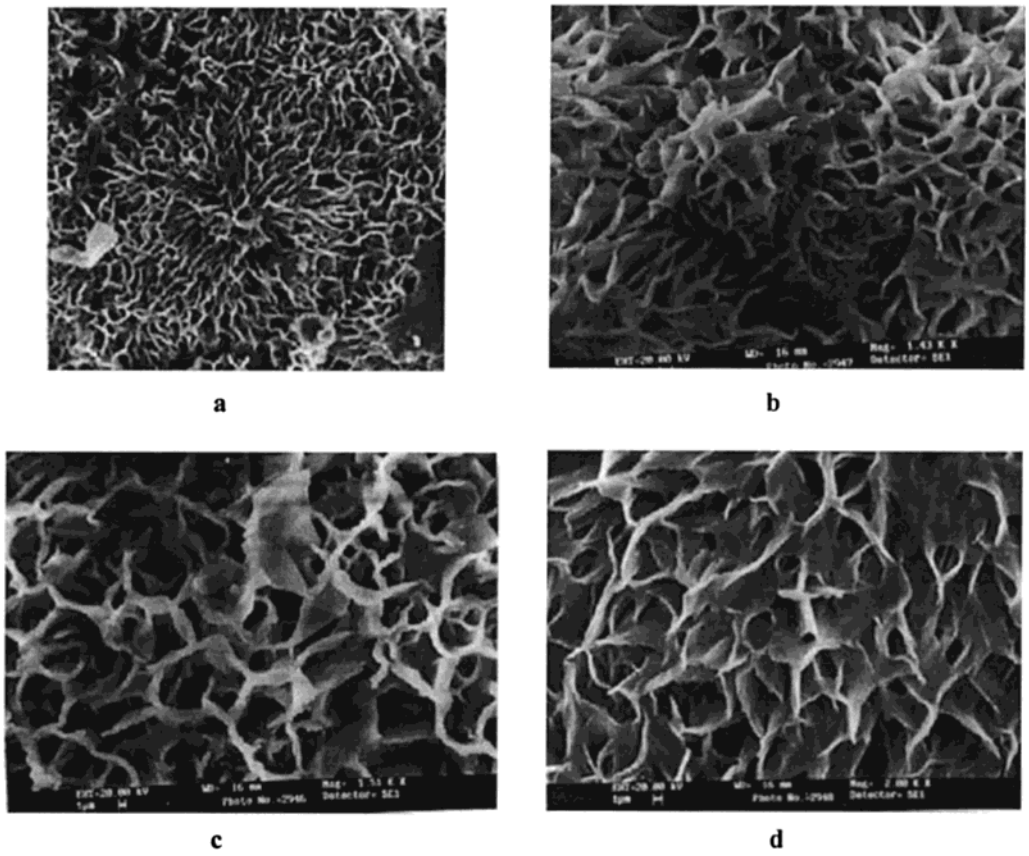


Figure 3. Scanning electron micrographic images of aged hydrogels of **1a**.

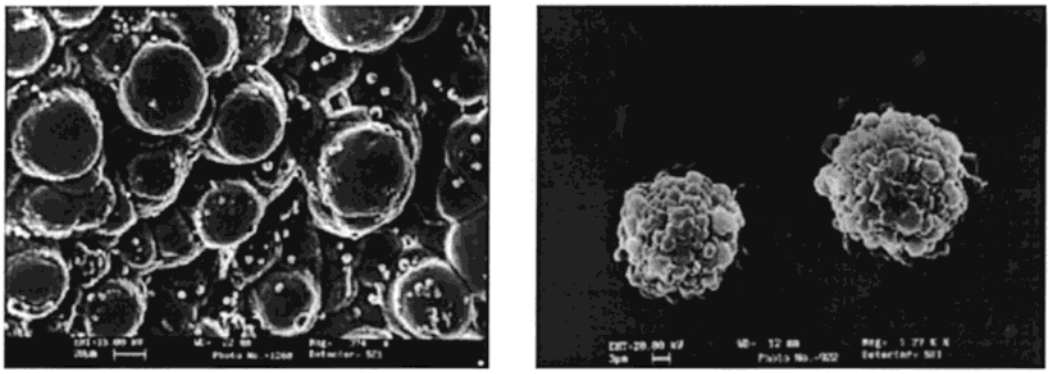
hydrogels of lactosyl-*N*-hexadecylamine, **1a** (Figure 2A). Typical widths of these fibers were 5 μm and the lengths spanned beyond 20 μm. The same hydrogel when subjected to partial drying under high vacuum at 25 °C, afforded a scaly mass which showed the existence of pumicelike porous networks (Figure 2B) under SEM. The typical diameters of these "pores" ranged from ~20 μm to several hundred microns. The dried material on resolubilization in 1.75% EtOH−H_2O, regenerated the features seen from original hydrogels as shown in Figure 2A. This observation is suggestive of the fact that the "pores" might provide pockets for water molecules to be included by surface tension for achieving optimal solvation and swelling necessary for hydrogelation. Similar examination of the hydrogels formed from maltosyl-*N*-hexadecylamine (**2a**) showed the existence of rolled, wrinkled, wet, clothlike textures under SEM (Figure 2C). Their average widths were between 5 and 10 μM. Upon partial drying (0.1 mTorr, 25 °C), the same hydrogel lost most of the solvents and produced a scale which on SEM examination revealed the existence of microstructures such as "sawdust" with a large number of interfibrous spaces and cavities (Figure 2D).

An aged sample of **1a** under SEM examination has shown the presence of corallike or spongelike structures with large channels (Figure 3A−D). From this evidence it can concluded that the solvent water molecules are entrapped into these large channels due to surface tension and capillarity, yielding gels which exhibit exceptionally high gelation capacities (Table 1).

In contrast to their single-chain counterparts, the double-chain lactosyl and maltosylamine amphiphiles (**1c** and **2c**) upon solubilization in EtOH−H_2O afforded hydrogels with reduced mechanical strengths. Interestingly, the corresponding microstructures were found to be quite different from the corresponding hydrogels of their single-chain counterparts. Thus, the SEM of a gel sample of *N*-hexadecyl-*N*-hexadecanoyl lactosyl amides showed the existence of snowballlike microspheres, the diameters of which ranged from 20 to 60 μm (Figure 4A). On the other hand, surface-patterned, clumped, and textured spheroids (diameter 6−8 μm) were seen from the SEM of the corresponding double-chain maltosyl amide (Figure 4B).

When we dissolved **1b** or **2b** in any of the solvent mixtures given in Table 1, no gel formation was seen. This is consistent with the observation of no gelation with **1b** or **2b**. The corresponding samples upon drying showed only amorphous flakes devoid of any microstructures or organization.

Rheological Studies. Rheological studies of gelated samples of **1a** and **2a** provide further insights into the behavior of these hydrogels. Representative plots of the viscosity changes for the hydrogels of **1a** or **2a** as a function of temperature are given in Figure 5. These show that the viscosity of the complex **1a** or **2a** begins to decrease on heating. The flat decreases in the plateau regions at $T < 48$ °C for **1a** and ~58 °C for **2a** (~8−10 Pa) are gradual, whereupon the viscosity of the sample drops abruptly at ~62 °C (for **1a**) as soon as the gel-to-sol conversion is complete. The resulting liquid has a viscosity typical of low molecular mass systems rather than that of a polymer. On a reverse run, when the sol was cooled from 80 to 25 °C with a temperature ramp of 3 °C/min, the viscosity suddenly increased at ~64 °C for both **1a** and **2a**. Thereafter, however, the increase



a **b**

Figure 4. Scanning electron micrographs of (a) hydrogel of **1c** (b) hydrogel of **2c**.

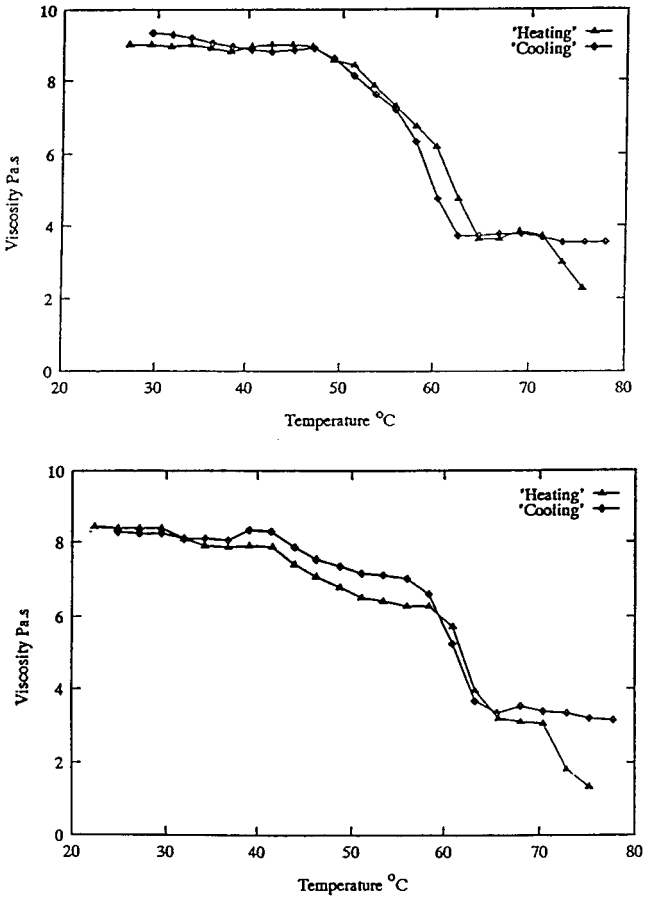


Figure 5. Rheological plot of viscosity against temperature showing the thermoreversiblility of the hydrogels of **1a** (upper panel) and **2a** (lower panel).

in the viscosity was gradual till the temperature reached 25 °C.

The viscosity of an aqueous solution of **1a** was also measured during gelation. A 0.1 wt % aqueous solution of **1a** containing 1.75 wt % of methanol prepared at ~80 °C was transferred to a viscometer at ~25 °C, and the viscosity was measured at various shear rates as the solution transformed into a hydrogel. At the onset of gelation, the viscosity showed pseudoplastic behavior and then quickly increased as the solution gelled. The elapsed time was 20 min.

Molecular Basis for Gelation. What could be the possible reasons for such pronounced hydrogel formation with **1a** or **2a**? It is apparent that while **1a** and **2a** form impressive hydrogels with excellent water retention capacities, the corresponding reduced analogues **1b** and **2b** fail to produce any gelation, and **1c** and **2c** are also inferior gelators. Clearly, the structural parameters of these molecules such as chirality, rigidity of the carbohydrate residues at the level of headgroup, and the number of the lipophilic tails in a monomeric amphiphile determine the efficiency of the gelation. It is proposed that, in water, these amphiphiles form fibrous assemblies and planar lamellae by hydrogen-bonded networking.

Indeed energy minimization studies using the Insight programs of Biosym (Discover) suggest that **1a** and **2a** aggregate through the formation of self-assembled networks[12] of *intermolecular* hydrogen bonds between N−H and carbohydrate OH groups among each of the amphiphile monomers. The presence of specific chirality at the anomeric position in these molecules makes the array of the amphiphiles "curl" away from planarity. The existence of β-anomeric conformations in aldosylamines have already been shown to be responsible for the induction of chiral aggregates.[11d] Notably in the case of **2b** and **3b**, the open chain sugar moiety disturbs the formation of an ordered array, as a result of which no aggregate or gel formation was observed. In addition, the presence of long hydrocarbon chains is an important contributor to the aggregation process. However, with the incorporation of two chains per monomer (**1c**, **2c**), the delicate balance between the hydrogen bonding at the polar interfaces and hydrophobic association necessary for gelation is disturbed.

Conclusions

From the present study there seems to be a few structural criteria that these low molecular weight *N*-alkyl disaccharide amphiphiles should possess in order to self-assemble to exhibit the property of gelation. First, the headgroup should contain a rigid backbone. Second, there should be a balance between the alkyl chains and the rigid headgroup. These structural requirements are necessary for **1a** and **2a** to self-assemble to form stable macroscopic aggregates.

The gels formed by **1a** and **2a** are interesting due to the low concentration of **1a** or **2a** required for formation

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of the gel and its thermal reversibility. The physical properties of these gels were characterized by SEM, DSC, and rheological studies. The SEM results suggest the formation of intertwined ribbons and fibers, which hold solvent molecules due to surface tension in the gel. In addition, the presence of coral- or spongelike architectures in the aggregate with large channels is responsible for the exceptionally high gelation capacities observed. Clearly, the hydrogen-bonding interactions between the OH residues of the disaccharide moiety, the rigidity of the headgroup, and the van der Waals interactions of the long hydrocarbon segments are essential driving forces for gelation and its mechanical stability. To further understand the structural features and directive forces influencing the gelation behavior of these molecules, energy minimization studies were also carried out. The fact that these hydrogel-forming systems retain in excess of ca. 6000 molecules of water per gelator molecule but do not dissolve in water makes these systems particularly attractive. Varying the chain length of the alcohol cosolvent could modulate the gelation capacities, melting temperatures, and the mechanical properties of these hydrogels. In addition, the monomeric sugar-based amphiphiles that form hydrogels are recyclable, biodegradable, and inexpensive, unlike their polymeric analogues.

In summary, the presently described hydrogels are simple and interesting. Although these are low molecular mass gelators, a typical equilibrium swelling ratio of >800 is observed with these hydrogels. The pore sizes of these hydrogel samples are macroporous. We can in fact incorporate ~1 wt % sugar such as D-glucose in these hydrogel samples, and the thermal and the shelf life stabilities of the resulting hydrogels were not affected to any significant extent under these conditions. We are now exploring the entrapment of suitable enzyme or protein such as cytochrome *c* oxidase or bacteriorhodopsin.

Experimental Section

All reagents and compounds were purchased either from Aldrich or Fluka and were used without further purification. Silica gel (Merck) 60−120 mesh was for column chromatography. ^{1}H NMR spectra were recorded at 400 MHz (Bruker Instrument). Chemical shifts are given in parts per million downfield from an internal standard (tetramethylsilane, TMS). Mass spectra were recorded on a JEOL GC−MS mass spectrometer. SEM studies were conducted on a JEOL stereoscan S-360 scanning electron microscope and TEM studies were performed on a JEOL 200 CX transmission electron microscope. Melting points were recorded in an open capillary and are uncorrected. Descriptions of other instruments used for various characterizations have been published.[13]

Viscometric Measurements. This experiment employed a Haake viscometer model Rotovisco RV 20 with a measuring system (MV) and a cup and cone rotor sensor system (SV-Din) in the shear rate range from 0 to 120 s^{-1}. The flow curve was recorded with a Haake Model xy-t ns recorder of zero shear. A 0.1 wt % aqueous solution of **1a** containing 1.75 wt % of CH_3OH was prepared at ~80 °C and quickly transferred into the viscometer cup at ~25 °C; the viscosity was measured at various shear rates as the solution transformed into a hydrogel. The viscosity of the solution of **1a** was measured during its gelation.

Rheological Measurements. These experiments were performed on a CARRIMED CSL Rheometer CSL-500 with a cone and plate geometry [steel cone (4 cm), 4°, diameter (4 cm) with a truncation (i.e., gap between the plate and cone) of 52 μm]. The warmed isotropic fluid was introduced between the cone and plate of the rheometer and cooled gradually to 25 °C. The instrument was set to a flow-step mode with a ramp duration of 20 min starting from 20 to 80 °C and the reverse with a constant shear rate of 50 rps. The data plot (Figure 5) shows that there is a drastic change in viscosity at ~60−62 °C.

Electron Microscopy. A small piece of the gel was transferred on to a cover slip and sputtered with gold. This sample was then introduced into the SEM (Oxford Stereoscan), and the micrographs were recorded.

Modeling Parameters. The modeling studies were conducted with BIOSYM software running on a Silicon Graphics Indigo workstation. The molecules were built using standard amino acid templates, bond lengths, angles, and side chain dihedral angles. The atoms within each molecule were assigned their proper hybridization, charge, and bond order utilizing the Builder module of Insight (version 2.3.5). The CVFF force field provided by the Discover module was chosen for the minimization constraints. This force field was applied to the constructed amino acid derivative and evaluated with conjugate gradient method. The interaction number for the conjugate gradient method was 200. The derivative (or convergence criterion) was chosen as 0.001 kcal mol^{-1}. The conformational preference of each molecule was determined in the following manner: the peptide underwent ca. 1000 steps of a dynamic simulation at 300 K with a time interval of 1.0 fs. The resulting lowest energy conformation was selected as the minimum for this parameter set.

Synthesis. *N-Hexadecyl-D-lactosylamine (**1a**).* To a solution of (25 mmol) hexadecylamine in 50 mL of 2-propanol was added to a solution of D-lactose monohydrate (15 mmol, 5.4 g) in 30 mL of water. The mixture was stirred for 24 h with periodic heating to ~60 °C at regular intervals as and when the solution turned turbid. At the end of this period, a precipitate was formed, which was separated from the solvent by filtration. The crude residue was dried first under vacuum and then recrystallized from EtOH and then again freeze-dried to eliminate traces of water to avoid hydrolysis of **1a** on prolonged storage (7.2 g, 85%): ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.79 (t, 3H), 1.17 (m, 28H), 2.2 (br s, 1H), 2.5 (m, 1H), 2.8 (m, 2H), 3.07 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.65 (m, 2H), 4.1 to 4.8 (m, 4H). Anal. Calcd for $C_{28}H_{55}O_{10}N\cdot H_2O$: C, 57.61; H, 9.84; N, 2.4. Found: C, 57.36; H, 10.03; N, 1.95.

*N-Hexadecylamino-1-deoxylactitol, (**1b**).* A solution of *N*-hexadecyl-D-lactosylamine (1 mmol, 565 mg) in water (50 mL) was cooled in an ice bath. A solution of $NaBH_4$ (1.2 mmol) in MeOH (15 mL) was added dropwise. The mixture was stirred for 30 min and then treated with active carbon. After filtration on Celite, the water was evaporated to leave a residue, which was taken up in methanol and evaporated five times in succession. A white flaky powder was obtained on freeze-drying (486 mg, 86%): ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.79 (t, 3H), 1.17 (m, 28H), 2.2 (br s, 1H), 2.5 (m, 1H), 2.8 (m, 2H), 3.07 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.65 (m, 2H), 4.1 to 4.8 (m, 4H). Anal. Calcd for $C_{28}H_{57}NO_{10}\cdot H_2O$: C, 57.41; H, 10.15; N, 2.39. Found: C, 57.39; H, 10.20; N, 2.55.

*N-Hexadecyl-D-maltosylamine (**2a**).* A similar procedure as described for **1a** was followed for the synthesis of **2a**, except that D-maltose was used (5.5 g, 65%): ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.80 (t, 3H), 1.18 (m, 28H), 2.21 (br s, 1H), 2.50 (m, 1H), 2.8 (m, 2H), 3.12 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.65 (m, 2H), 4.1 to 4.8 (m, 4H). Anal. Calcd for $C_{28}H_{55}O_{10}N\cdot H_2O$: C, 57.61; H, 9.84; N, 2.4. Found: C, 57.81; H, 10.21; N, 2.45.

*N-Hexadecylamino-1-Deoxymaltitol (**2b**).* A similar procedure as described for **1b** was followed for the synthesis of **2b**: yield 80%; ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.82 (t, 3H), 1.15 (m, 28H), 2.2 (br s, 1H), 2.5 (m, 1H), 2.8 (m, 2H), 3.07 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.65 (d m, 2H), 4.1 to 4.8 (m, 4H).

(13) (a) Bhattacharya, S.; De. S.; Subramanian, M. *J. Org. Chem.* **1998**, *63*, 7140. (b) Bhattacharya, S.; Snehalatha, K.; George, S. K. *J. Org. Chem*. **1998**. *63*, 27.

Anal. Calcd for $C_{28}H_{57}NO_{10}$, 1.5 H_2O: C, 56.54; H, 10.17; N, 2.36. Found: C, 56.55; H, 10.08; N, 2.62;

*N-Hexadecanoyl-N-hexadecyl-D-lactosylamide, (**1c**).* To a solution of **1a** (1 mmol, 565 mg) in 100 mL of dry THF containing sodium carbonate (117 mg, 1.1 mmol) was added dropwise a solution of hexadecanoyl chloride (1 mmol, 275 mg) in 10 mL of DMF at 0 °C, with stirring over a period of 45 min. The stirring was continued at 0 °C for 3 h and then for an additional 24 h at room temperature. The solvent was removed under vacuo, the residue washed with water, and the solid collected on filtration. The crude residue was dried first under pump and was purified by column chromatography on silica gel (442 mg, 55%): ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.81 (t, 6H), 1.20 (m, 56H), 2.2 (br s, 1H), 2.5 (m, 1H), 2.8 (m, 2H), 3.07 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.70 (d m,2H), 4.1 to 4.8 (m, 4H). Anal. Calcd for $C_{44}H_{85}NO_{11}$: C, 65.75; H, 10.67; N, 1.74; found C, 65.51; H, 10.9; N, 1.97.

*N-Hexadecanoyl-N-hexadecyl-D-maltosylamide, (**2c**).* To a solution of **2a** (1 mmol, 565 mg) in 100 mL of dry THF containing sodium carbonate (117 mg, 1.1 mmol) was added dropwise a solution of hexadecanoyl chloride (1 mmol, 275 mg) in 10 mL of DMF at 0 °C, with stirring over a period of 45 min. The stirring was continued at 0 °C for 3 h and then for an additional 24 h at 25 °C. The solvent was removed in vacuo and the solid was washed with water and collected on filtration. The crude residue was dried first under vacuum and was purified by column chromatography on silica gel (378 mg, 47% yield): ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 0.81 (t, 6H), 1.20 (m, 56H), 2.2 (br s, 1H), 2.5 (m, 1H), 2.8 (m, 2H), 3.07 (m, 2H), 3.23 (m, 1H), 3.37 (m, 1H), 3.70 (d m, 2H), 4.1 to 4.8 (m, 4H). Anal. Calcd for $C_{44}H_{85}NO_{11}$: C, 65.75; H, 10.67; N, 1.74; found C, 65.55; H, 10.61; N, 1.94.

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