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Amphiphiles Based on D-Glucose: Efficient Low Molecular Weight Gelators

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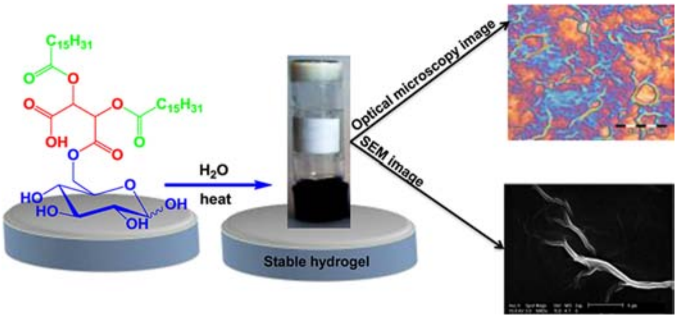
ABSTRACT



A series of novel amphiphiles were synthesized based entirely on renewable resources. Besides their efficacy as supramolecular gelators in a wide variety of organic solvents and also water, their surface properties as surfactants and emulsifiers have been determined. A methodical study revealed that the length of the hydrocarbon chains has a dramatic and decisive influence on the thermal stabilities of the obtained hydrogels.

Chemists are intrigued in forming numerous new synthetic strategies for the synthesis and development of nanoscale functional materials.[1a] Low-molecular weight gelators[1b] (LMWGs) represent one example of such functional architecture and have continued to evoke considerable interest as an important class of materials on account of their unique features and potential applications for new soft organic materials,[2] for template synthesis,[3] drug delivery,[4] cosmetics,[5] food processing,[5] tissue engineering,[6] and medical implants.[7] Most supramolecular gels are composed of long nanofibers that are self-assembled through supramolecular interactions such as H-bonding, van der Waals, hydrophobic, $\pi-\pi$ stacking, coordination, and donor–acceptor and/or charge–transfer interactions.[8] The one-dimensional (1-D) self-assembly of these gelling agents with fiber-like structures eventually entangles to form a three-dimensional (3-D) network followed by entrapment and immobilization of the solvent molecules inside the interstices of the 3-D network by surface tension[1b,9] and/or capillary forces,[10] to induce gelation in that particular solvent. Compounds with various structural diversities, such as derivatives of carbohydrates,[11] amino acids,[12] urea,[9a,13,19e,21a,b] and cholesterol,[10b,14]

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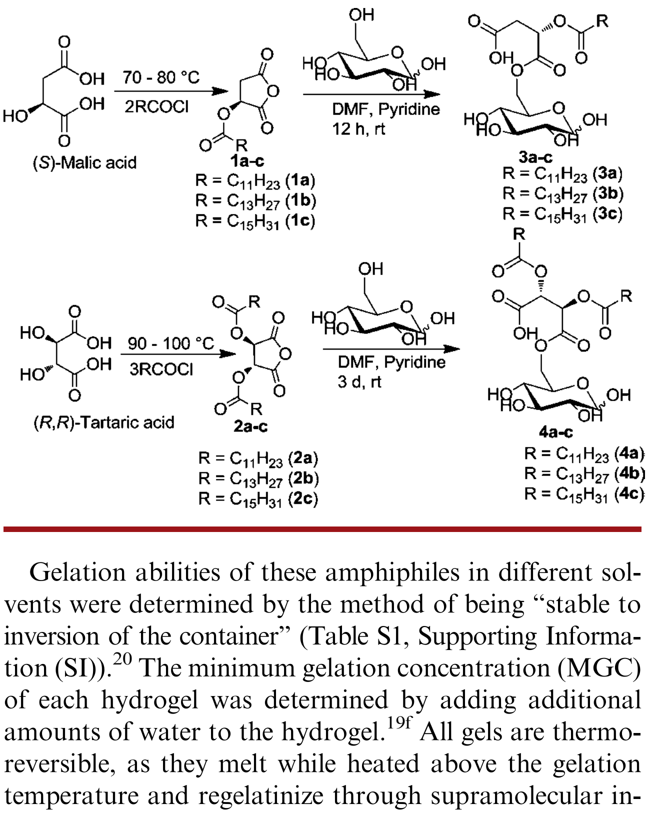
have been reported to efficiently gelatinize organic liquids. Although many examples of gelators for organic solvents have been reported in the literature, to the best of our knowledge, only a few methodical investigations addressed their gelation efficacy in water, so-called hydrogels largely based on renewable resources.[15] Hydrogels are among the most useful supramolecular systems with potential applications in photography, tissue engineering, cosmetics, and food processing, as vehicles for controlled drug delivery, and for template synthesis of nanoparticles and inorganic nanostructures and sensors.[16] A major challenge in this field is the elaboration of novel strategies by which structurally simple and eco-friendly gelators can be prepared in large quantities from cheap and abundant precursors.[17]

We recently found that hydroxycarboxylic acids such as malic and tartaric acid can be converted in one step and almost quantitatively into the corresponding *O*-acylated anhydrides by reaction with the corresponding fatty acid chlorides.[18a] These molecules are excellent and highly reactive electrophiles which easily and quantitatively undergo ring-opening reactions with nucleophiles from various renewable resources, such as L-ascorbic acid,[15a] polyols (e.g., glycerol) including sugar alcohols,[18b] and amino acids.[18c]

Here, we describe the syntheses, gelation behavior, and self-assembling properties of organogelators and hydrogelators based on D-glucose as starting material. To the best of our knowledge, there have been only few systematic studies to reveal and elucidate the influence of the hydrocarbon chain length on the self-assembly of synthetic amphiphiles; therefore, major attention has been devoted to that issue.[19a] Precise knowledge of this relationship would facilitate the reliable design of a gelator for a specific liquid with desired properties for various applications[19b−d] rather than their serendipitous discovery.[19b−e] We have synthesized a library of D-glucose based amphiphiles by systematic variation of the alkyl chains (C_{12} to C_{16}) of the *O*-acylated hydroxycarboxylic acid anhydrides (tartaric and malic acid anhydride) linked to the D-glucose moiety *via* an ester bond[19f] (Scheme 1).

Scheme 1. Synthesis of D-Glucose Based Low Molecular Weight Gelators



Gelation abilities of these amphiphiles in different solvents were determined by the method of being "stable to inversion of the container" (Table S1, Supporting Information (SI)).[20] The minimum gelation concentration (MGC) of each hydrogel was determined by adding additional amounts of water to the hydrogel.[19f] All gels are thermoreversible, as they melt while heated above the gelation temperature and regelatinize through supramolecular interactions upon subsequent cooling. Among the series of amphiphiles, **4a** can gelate some nonpolar solvents and water, whereas **3a**−**c**, **4b**, and **4c** can gelate in only a few of the tested solvents in addition to water. This implies that a balanced participation[19a,21] of H-bonding and van der Waals interaction is crucial to induce gelation in water or in a particular organic solvent. This can largely be regulated

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by systematic alteration of the H-bonding unit or tuning the hydrocarbon chains. Ambidextrous gelation properties of these amphiphiles might be useful for the development of hybrid materials in a variety of solvents and water.[22]

Robustness and embodiment of the gelation abilities in water can be illustrated by considering three parameters:[9a,19a,22] (*i*) minimum gelation concentration (MGC), (*ii*) thermal stability of the hydrogel (T_{gel}), and (*iii*) number of water molecules entrapped by one gelator molecule (N_g). All three parameters are strongly influenced by the length of the hydrocarbon chain in the lipophilic part of the molecule (Table 1). Thus the malic acid based amphiphile **3c** with a C_{16} hydrocarbon chain leads to a very stable hydrogel at rt (T_{gel} = 38 °C) with a minimum gelator concentration of 3.1% w/v (~950 water molecules are entrapped by one gelator molecule).

Table 1. Minimum Gelation Concentrations (MGCs) and T_{gel} Values of D-Glucose Based Amphiphiles in Water[a]

compound	MGC (w/v)	T_{gel}	N_g
3a	nongelator	–	–
3b	2.8%	20 °C[b]	~1000[b]
3c	3.1%	38 °C	~ 950
4a	7.3%	50 °C	~500
4b	4.6%	59 °C	~900
4c	2.5%	67 °C	~1750

[a] MGC = Minimum gelation concentration. T_{gel} = Thermal stability of the gel. N_g = Number of water molecules entrapped by one gelator molecule. [b] For + **3b** determined at +5 °C.

In contrast the corresponding amphiphile **3b** with a shorter hydrocarbon chain (C_{14}) produces a stable hydrogel only at lower temperature (T_{gel} = 20 °C) while **3a** with C_{12} gives no gel. Similarly among the series of tartaric acid based amphiphiles, **4c** displays robust gelation ability in water with the highest T_{gel} value whereas **4a** shows the least. This implies that one can regulate the structure and thermal stability of the hydrogel by tuning the length of the hydrocarbon chain for desired and specific applications.[17] The high and low melting points of the hydrogels might be attributed to structural differences in the self-complementary assembly, indicating more significant and adequate crystalline packing for amphiphiles with long fatty acid chains as compared to those with shorter ones.[19b,23] An increase in chain length enhances association among the fibers through van der Waals forces of attraction which drive the molecules to arrange in highly ordered, layered structures, hence contributing to the higher thermal stabilities of the hydrogels.

To achieve direct visualization of the morphology of the hydrogels, optical and scanning electron microscopic measurements have been performed on the xerogel obtained from a 1.1% (w/v) hydrogel of **4c** (Figure 1). The optical microscopic images revealed that the 3-D network structure of the hydrogel of **4c** consists of a vast fibrillar network with pores inside. The fibers inside the gelation network are 8–12 μm in length and 700–900 nm in diameter, which are then entangled to give a 3-D network structure that eventually induces gelation in water. SEM images have confirmed the size distribution of the fibers and morphology of the hydrogel of **4c**.

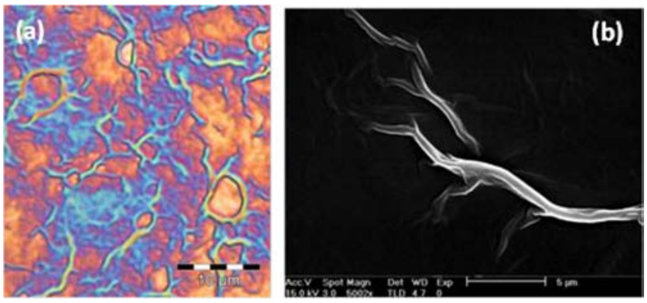

Figure 1. (a) Optical and (b) scanning electron microscopy image of the xerogel obtained from a 1.04% (w/v) hydrogel of **4c**.

Gelation experiments in water in the presence of variable amounts of DMSO show that the T_{gel} values decrease considerably with an increasing DMSO content in the gel sample, with a maximum value of T_{gel} for a gel containing only water (Table S2, Figure S3, SI). These results imply that the hydrogel of **4c** is destabilized in presence of DMSO. In the presence of water, DMSO can also contribute to H-bonding[15b,17] within the gel network, and an increase in this incorporation of DMSO apparently destabilizes the gel network in water as the DMSO concentration rises. This signifies that van der Waals forces of attraction across the hydrocarbon chains are probably the principal driving force for the gelation of **4c** in water.

In addition, a synergetic and significant contribution of intermolecular H-bonding during the gelation process was confirmed *via* ATR-IR spectroscopy (Figure S4, SI). The IR spectra reveal that in the DMSO solution of **4c** (10%, w/v), the band appearing at 1751 cm^{-1} can be assigned to the stretching vibrations of the carbonyl groups of all nonhydrogen bonded esters and the carboxylic acid group, while, in the xerogel of **4c** obtained from D_2O (10%, w/v), the stretching vibrations of a set of carbonyl groups are shifted to 1722 cm^{-1}. This observation strongly supports the existence of H-bonding between the carbonyl groups in the gel phase.

To gain more precise insight into the relative orientation of the molecules in the self-assembled state and the contribution of the different groups through selective supramolecular interactions into the gel network, temperature-dependent ^1H NMR spectroscopic measurements have been carried out (Figures S5–S6, SI). In the D_2O gel, the molecules are self-assembled in a highly organized rigid network; consequently, their signals are broadened and unresolved even at 95 °C. Therefore, a gel sample was prepared in a D_2O/DMSO-d_6 solvent mixture to obtain a relatively less rigid gel network. With a gradual increase in

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temperature from 30 to 90 °C the signals for the fatty acid protons were found to be slightly shifted downfield[1,5,15a,17,24] and became sharper as compared to the signals at 30 °C (Figure S6, SI). This indicates that a gradual increase in temperature leads to disordering of the self-assembled gel network into the isotopic form.[17] In addition, the broadening of the fatty acid proton signals in the gel phase also suggests the existence of van der Waals forces between the hydrocarbon chains inside the gel network.

To obtain information regarding supramolecular chirality in the gel network (rather than the inherent chirality of the individual gelator molecule), CD spectroscopic measurements were conducted (Figure S7, SI). The CD spectrum of self-assembled **4c** in water exhibits a negative Cotton effect thus implying that the dipole moments orient in an anticlockwise direction in the aggregate of the gel in water. In spite of the presence of enantiomerically pure D-glucose and (2*R*,3*R*)-tartaric acid in the core of the structure, **4c** does not exhibit any CD Cotton effect in methanol solution.[5,24] This implies that there is an intimate and intrinsic relationship between the chiral expression ability and the growth and stability of the 3-D gel network.

The above amphiphiles are good surface active agents which display foaming and emulsifying properties (HLB values, hydrophilic lipophilic balance). In the case of both the tartaric and malic acid based amphiphiles the foaming ability is much higher for shorter chains than those of the corresponding compounds with longer carbon chains, a result which might be attributed to the difference in solubility of the surfactants in water (Table 2).[25a]

Table 2. Surface Active Properties of **3a**–**4c**

compd[a]	foaming ability (mL)	foam stability (mL)	HLB values	CMC (mol/L)	γ_{CMC} (mN/m)
3a	680	675	>18	8.76×10^{-5}	21.5
3b	450	445	9	15.4×10^{-5}	21.6
3c	140	130	7	14.3×10^{-5}	26.6
4a	245	240	10	2.42×10^{-6}	20.5
4b	50	40	9	9.36×10^{-4}	29.6
4c	45	40	<3	–	–
SDS[b]	765	720	–	8.0×10^{-3}	22.1

[a] For foaming properties and CMCs, triethanolammonium salts were used. [b] SDS = Sodium dodecyl sulfate.

For a given hydrocarbon chain length the foaming ability of the malic acid based amphiphiles is much higher than that of the corresponding tartaric acid based amphiphiles. Among the series, **3a** possesses excellent foaming ability which is even higher than that of sodium dodecyl sulfate (SDS) and thus might be a useful alternative to SDS which causes untoward side effects.[25b,c] **3b** and **4a** possess moderate foaming abilities whereas **3c**, **4b**, and **4c** do not foam at all. Owing to their strong hydrophilic and lipophilic nature, respectively, amphiphiles **3a** and **4c** do not have any HLB values, whereas **3b**, **3c**, **4a**, and **4b** have HLB values in the range of 7–10 and hence might be useful for the preparation of oil in water emulsions in, e.g., the food industry or for cosmetics (Table 2).

CMC values of the amphiphiles were determined by the ring method[25d] based on surface tension measurements (Figure S10, SI). The CMC and γ_{CMC} (surface tension at CMC) values are shown in Table 2. In the case of the malic acid based amphiphiles there is no sharp increase in CMC with an increase of the hydrocarbon chain; however there is a low value of γ_{CMC} especially in the case of **3a** and **3b**. This implies that these amphiphiles have an inherent tendency to adsorb strongly at the air/water interface and thus reduce the tension thereat. The CMC value of tartaric acid based amphiphile **4a** is much lower than that for malic acid based amphiphiles **3a**–**c** which essentially implies that tartaric acid based amphiphile **4a** is a quasi-gemini surfactant; in the core of the molecule two hydrocarbon chains are connected with a spacer and hence facilitate the surfactant molecules to pack closely at the air/water interface due to the interactions between the hydrocarbon chains.[25e] Notably **4a** has a CMC value which is 3 orders of magnitude lower than that of the commercially available surfactant SDS and thus might be a useful alternative to SDS.

In summary, this publication describes the facile syntheses of a library of surface active compounds derived entirely from renewable resources, combination products of fatty acids, D-glucose, and hydroxycarboxylic acids. All molecules are accessible in just two simple steps and could thus be produced on an industrial scale. The compounds display a wide variety of attractive properties in being surfactants, emulsifiers, and inter alia excellent hydrogelators for numerous potential applications in the cosmetic and food industry.

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Supporting Information Available. Synthetic details, characterization data, NMR, FT-IR and CD spectra, DSC thermograms, and variable temp ^{1}H NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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