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A Novel Class of Organo- (Hydro-) Gelators Based on Ascorbic Acid

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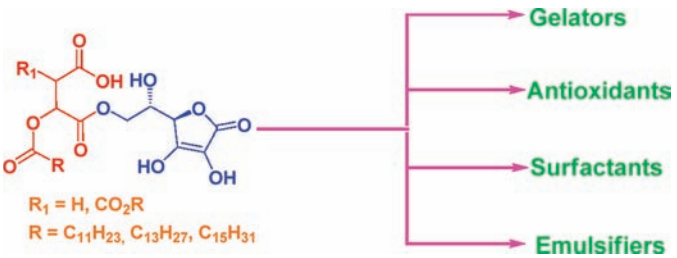
ABSTRACT



A library of novel, lipid-modified derivatives of ascorbic acid was shown to exhibit highly attractive properties as surfactants, emulsifiers, oil soluble antioxidants, and highly effective gelators in organic solvents and especially water. In these systems, intermolecular hydrogen bonding and van der Waals forces act synergistically to induce gelation as confirmed by spectroscopic studies. The morphology of the formed gel has been characterized by scanning electron microscopy.

Supramolecular gels are viscoelastic materials consisting of low molecular weight compounds which undergo spontaneous, thermoreversible self-assembly under nonequilibrium conditions into complex three-dimensional structures.[1] Multiple noncovalent interactions,[1,2] such as hydrogen bonding,[3] donor−acceptor, or hydrophobic interactions, between the organogel building blocks, give rise to the formation of fibers which subsequently entrain and immobilize the solvent molecules inside the interstices of a three-dimensional network.[4] Although many examples of gelators for organic solvents have been reported in the literature, only a few studies on gelators for water, so-called hydrogels, fully based on renewable resources, have been reported. Hydrogels are among the most useful supramolecular systems with potential applications[5] in

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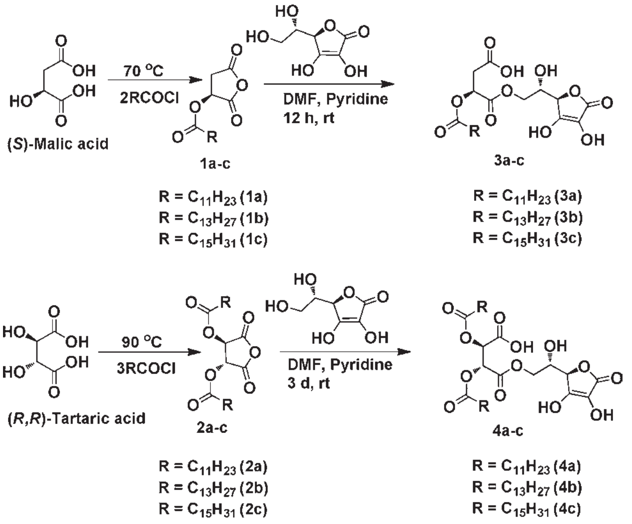
photography, tissue engineering, cosmetics, as vehicles for controlled drug delivery, template synthesis of nanoparticles and inorganic nanostructures, sensors, and food processing. A major challenge in this field is the elaboration of novel design strategies enabling the synthesis of structurally simple gelator molecules, easy to synthesize and available in large quantities from cheap starting materials for high volume applications.

We have focused our research efforts toward exploitation of one of the best known natural antioxidants, ascorbic acid (Vitamin C). It inhibits free radical initiated lipid peroxidation, a process presumably also implicated in a variety of chronic health problems such as cancer and cardiovascular diseases.[6] Vitamin C has been used *in vitro* only in aqueous solution as an antioxidant because of its hydrophilic nature. Hence, application of Vitamin C as an antioxidant in a lipophilic environment is rare.[7,8] The problem of solubility can be circumvented by converting hydrophilic Vitamin C into hydrophobic ester derivatives, which improves its solubility in lipophilic materials as well as retains its radical scavenging capacity in hydrophobic environments. However, problems associated with the chemical functionalization of Vitamin C exist which include low product yields due to nonregioselective reactions requiring laborious purifications by column chromatography.

We have recently found that hydroxycarboxylic acids like 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.[9] These molecules are excellent and highly reactive electrophiles which easily and quantitatively undergo ring-opening reactions with nucleophiles from various renewable resources, such as polyols (e.g., glycerol) including sugar alcohols,[10] and amino acids.[11]

We have now constructed a library of the corresponding Vitamin C derivatives, combination products of fatty acids and hydroxy carboxylic acids (tartaric acid and malic acid) linked to the primary hydroxy group of ascorbic acid *via* ester bonds (Scheme 1). Only the primary hydroxy group is esterified; all the other hydroxy groups are still available for the formation of hydrogen bonds, for complex formation or redox functions. The experimental details of the syntheses and the characterization of the amphiphiles are provided in the Supporting Information.

Scheme 1. Synthesis of Ascorbic Acid Derived Low Molecular Weight Gelators



The gelation ability of these compounds in different solvents was determined by the simple method of being "stable to inversion" of the container (Table 1).[12] A weighed amount of the corresponding ascorbic acid derived amphiphiles (50 mg) in 200 μL of an organic solvent or water was heated in a septum-capped test tube until the solid dissolved; the resultant mixture was then cooled to room temperature, and when the tube could be inverted without any flow, it was determined to be a "gel". A minimum gelation concentration (MGC) in water was determined by adding more water in 50 μL portions. Amphiphiles **3c**, **4b**, and **4c** showed excellent gelation abilities in a broad range of solvents. Solution to gel phase transition temperatures and minimum gelation concentrations in water are shown in Table S1 of the Supporting Information. In ascorbic acid amphiphiles derived from both *O*-acylated tartaric and malic acid anhydrides it was found that the gelation abilities and gel stabilities in water are highly influenced by the length of the hydrocarbon chains. **3c**, **4b**, and **4c** are very stable hydrogels at room temperature with minimum gelation concentrations of 0.9%, 4.5%, and 1.7% (w/v), respectively. In contrast tartaric and malic acid based amphiphiles with shorter chains (C_{12}) produce stable hydrogels only at low

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temperatures. These findings might be attributed to structural differences in the self-complementary assembly indicating more significant crystalline packing[13,14] for both tartaric and malic acid amphiphiles with long fatty acid chains as compared to shorter ones. Increasing the chain lengths for both tartaric and malic acid amphiphiles promotes more association among the fibers through van der Waals forces of attraction and drive the molecules to arrange in highly ordered layered structures. Ambidextrous gelation properties of these amphiphiles can be utilized to develop hybrid materials in a variety of solvents.

Table 1. Gelation Abilities of Ascorbic Acid Based Amphiphiles in Different Solvents[a]

compd	**4a**	**4b**	**4c**	**3a**	**3b**	**3c**
Water	G	G	G	TG	G	G
DMF	S	S	S	S	S	S
DMSO	S	S	S	S	S	S
ACN	S	G	G	S	S	AS
Methanol	S	S	S	S	S	S
$CHCl_3$	S	S	PG	S	S	PG
CCl_4	PG	G	G	G	TG[15]	PG
Benzene	S	G	PG	S	S	PG
Toluene	S	G	G	TG	S	PG

[a] G: gel. S: soluble. PG: partially gel. TG: transparent gel. AS: amorphous solid.

In order to obtain visual insights into the morphology of the hydrogels, SEM measurements of **4c** were performed. The SEM micrograph of a xerogel using 1.7% of **4c** in water is shown in Figure 1. The SEM image revealed that the hydrogel of **4c** could self-assemble into a three-dimensional network composed of numerous fibrillar aggregates that are 125−300 nm in diameter and several micrometers in length, which were entangled with each other to give a 3D network structure.

In order to investigate the driving force leading to the formation of a hydrogel, ATR-IR investigations were performed taking **4a** as an example (Supporting Information, Figures S29−S32). In a DMSO solution of **4a** the band appearing at 1747 cm^{-1} can be assigned to the stretching vibrations of the ester carbonyl groups and non-hydrogen bonded carboxylic acid group, while for the xerogel in D_2O the stretching vibrations of a set of carbonyl groups are shifted to 1713 cm^{-1}, strongly supporting the existence of hydrogen bonding between the carbonyl groups in the gel phase. This implies that the hydrogen bond formation is an important driving force for the aggregation of **4a** in water.

To gain even more insight into the driving force behind the self-assembly and the orientation of the molecules in the self-assembled state, temperature dependent ^1H NMR measurements of **4a** were carried out (Figures S27−S28, Supporting Information). In D_2O the gel molecules are organized in a highly rigid network and consequently their signals are broadened and unresolved even at 95 °C. Therefore, the gel sample was prepared in a D_2O/DMSO-d_6 solvent mixture (2.3:1 v/v). With a gradual increase in temperature from 30 to 90 °C in temperature dependent ^1H NMR experiments, the signals for the fatty acid protons were found to be slightly shifted downfield and became sharper as compared to the signals at 30 °C.

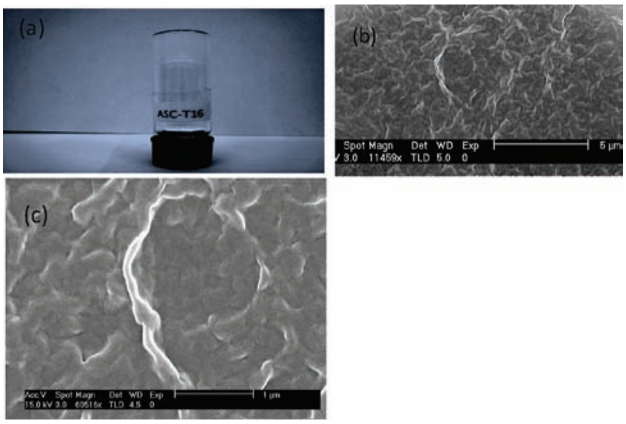

Figure 1. (a) Photographic image of the gel from **4c** in water; (b) SEM image of a xerogel of compound **4c** obtained from water. Scale bar, 5 μm. (c) SEM image of the xerogel of compound **4c** obtained from water. Scale bar, 1 μm.

This indicates that an increase of temperature leads to a disordering of the intermolecular aggregation into the isotopic form. In addition, the broadening of the fatty acid proton signals in the gel phase suggested the existence of van der Waals forces between the carbon chains inside the gel network. These results imply that intermolecular hydrogen bonding and van der Waals attraction force are very crucial and act synergistically to stabilize the self-assembled structure.

The reducing activities of ascorbic acid and the above amphiphiles have been determined by a known literature method[16] using the DPPH radical. The results are shown in Figure 2[17] and Table 2. The antioxidant efficiencies (EC_{50} values) of the above amphiphiles are comparable to those of ascorbic acid which implies that the lipid modification does not interfere with the radical scavenging properties. Although the hydroxy group at C-6 seems to have little inhibitory effect toward the reducing activity there is a slight difference in activities between ascorbic acid and these esters as has been

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(17) The intersections of each curve in Figure 2 are different because the concentration of the DPPH radical have been taken to be approximately 60−100 μM and the exact concentration has been calculated based on Lambert−Beers Law.

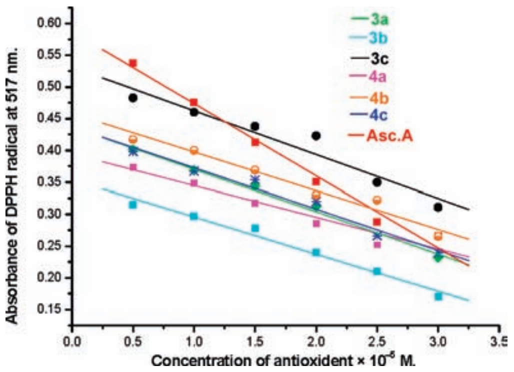

Figure 2. Typical calibration curves showing decolorization of DPPH-radical (at 517 nm) after addition of antioxidants at various concentrations.

Table 2. Antioxidant Efficiencies (EC_{50} Values) of the Compounds[a]

antioxidant	$EC_{50}(10^{-5}$ M)	n_{DPPH}
3a	3.28 ± 0.01	2
3b	3.03 ± 0.01	2
3c	3.86 ± 0.02	2
4a	3.33 ± 0.00	2
4b	3.84 ± 0.01	2
4c	3.38 ± 0.01	2
Asc.A	2.59 ± 0.01	2

[a] n_{DPPH} = the number of DPPH radicals reduced by one molecule of antioxidant. **Asc.A** = ascorbic acid. EC_{50} = concentration of antioxidant that causes 50% loss of the DPPH radical activity. Each value is the average ± S.D. of 6 measurements.

also observed[14,16e−16g] by other groups. This aspect warrants further studies. Due to the fatty acid residues, their solubilities in hydrophobic environments are clearly increased and hence these amphiphiles could be useful as stabilizers in food-related lipophilic media such as native oils.[18]

Last but not least, these amphiphiles are also interesting surfactants which display good foaming and emulsifying properties; the determination is described in the Supporting Information. As expected, the foaming and emulsifying properties of these amphiphiles are strongly influenced by the hydrocarbon chain length (Table 3). By increasing the chain length, their solubility in water is decreased which has an impact on their foaming abilities. The foaming ability of both malic and tartaric based amphiphiles with shorter chains (C_{12}) is much higher than that of the corresponding compounds with longer chains (C_{14} and C_{16}). Within this series of amphiphiles, **3a** is the best foamer due to its high HLB value (Hydrophilic-Lipophilic-Balance) that has been measured according to a literature[19] method, whereas **4c** showed the lowest foaming ability, also corresponding to its low HLB value. Amphiphiles **3b**, **3c**, **4a**, and **4b** possess HLB values in the range 8−13, and hence they may be useful for the preparation of O/W emulsions in e.g. the food industry.

Table 3. Foaming and Emulsion Properties of Ascorbic Acid Based Amphiphiles

compd	foam ability (mL[20]) of 0.1% solution	foam stability (mL) of 0.1% solution	HLB values
3a	719.1	717.6	>18
3b	528.4	520.9	12
3c	420.6	417.6	8−13
4a	700.0	695.6	9−10
4b	209.0	206.0	8−10
4c	58.7	52.9	2−5
SDS[a]	873.5	719.4	40

[a] **SDS** = sodium dodecyl sulfate.

In summary, we have constructed a library of ascorbic acid amphiphiles largely derived from renewable resources. Some of these display robust gelation abilities in a wide range of solvents, and the ambidextrous gelation properties of these amphiphiles may be useful for the development of hybrid materials in a variety of solvents. The thermal stabilities of the gelators in water are strongly affected by the length of the hydrocarbon chains of the lipophilic part of the molecule. This implies that one could regulate the structure and stability of a gel system by tuning the hydrocarbon chain length of the gelator molecules for desired applications. In addition to their supramolecular properties we have also determined their antioxidant, foaming, and emulsifying properties, which may find applications in the fields of food industry and cosmetics.

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

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