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Shun Yao, Robin Brahmi, François Portier, Jean-Luc Putaux, Jing Chen, et al.. Hierarchical Self-Assembly of Amphiphilic β -C-Glycosylbarbiturates into Multiresponsive Alginate-Like Supramolecular Hydrogel Fibers and Vesicle Hydrogel. *Chemistry - A European Journal*, 2021, 10.1002/chem.202102950 . hal-03377385

HAL Id: hal-03377385

<https://hal.science/hal-03377385>

Submitted on 14 Oct 2021

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Hierarchical Self-Assembly of Amphiphilic β -C-Glycosylbarbiturates into Multiresponsive Alginate-Like Supramolecular Hydrogel Fibers and Vesicle Hydrogel

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This paper is dedicated to the memory of our late colleague, Dr. Hugues Driguez, who recently passed away.

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Abstract: Ordered molecular self-assembly of glycoamphiphiles has been regarded as an attractive, practical and bottom-up approach to obtain stable, structurally well-defined, and functional mimics of natural polysaccharides. This study describes a versatile and rational design of carbohydrate-based hydrogelators through N,N'-substituted barbituric acid-mediated Knoevenagel condensation onto unprotected carbohydrates in water. Amphiphilic N-substituted β -C-maltosylbarbiturates self-assembled into pH- and calcium-triggered alginate-like supramolecular hydrogel fibers with a multistimuli responsiveness to temperature, pH and competitive metal chelating agent. In addition, amphiphilic N,N'-disubstituted β -C-maltosylbarbiturates formed vesicle gels in pure water that were scarcely observed for glyco-hydrogelators. Finally, barbituric acid worked as a multitasking group allowing chemoselective ligation onto reducing-end carbohydrates, structural diversity, stimuli-sensitiveness, and supramolecular interactions by hydrogen bonding.

Introduction

Naturally occurring polysaccharides are abundant and renewable materials produced by a wide range of living species from plants and animals to microorganisms. They play a role as energy sources (starch), as supports with numerous physical properties (cellulose, chitin), as rheo-fluidifying agents, for instance in synovial liquid, and as bioactive matrices by interacting with carbohydrate-binding proteins (glycosaminoglycans, polysialic acids).[1] The properties of polysaccharides are closely related to their rich and complex chemical nature and structural composition that were widely exploited in industrial applications such as medicine, cosmetics, foods, materials and many others. However, polysaccharide materials have some major disadvantages since their structures considerably vary depending on the source of raw materials and extraction processes resulting in ill-defined molecular weight,

polydispersity and non-reproducible batches. Thus, it makes them difficult to study and to fine-tune their biological or physicochemical properties.

To face the inherent complexity of natural biomacromolecules, scientists tried to develop simple and controllable models for a deeper understanding of their functionalities and further man-made applications. Roughly, polysaccharides can be regarded as polymeric scaffolds presenting multiple carbohydrate building blocks and chemical functions. Thus, many attempts have been made to mainly mimic specific biological activities of polysaccharides by using carbohydrate building blocks as pendant groups along a polymer backbone[2] or linked together through non-natural glycosidic linkages.[3] Only few reports focused on replicating the physicochemical properties of polysaccharides. In such context, we recently demonstrated that the multi-display of well-defined xyloglucan-oligomers, a hemicellulosic polysaccharide establishing a non-covalent network with cellulose in plant cell wall, grafted onto a polymeric backbone allowed strong interactions with cellulose nanocrystals.[4] Although this strategy has been successfully achieved, the synthesis of glycopolymers still requires a multi-step process and it is also challenging to precisely control the degree of grafting. Building polysaccharide mimics from the bottom-up self-assembly of well-defined glycoamphiphiles emerges as an appealing approach.[5] Owing to numerous advantages, such as easy synthesis and well-defined molecular structures, glycoamphiphiles bearing programmed molecular-scale information could be transferred to the surrounding environment via hierarchical self-assembly into superstructures with a nanoscale precision. For more than ten years, our group has been developing carbohydrate-based amphiphilic block copolymers that self-assemble into micellar drug carrier in aqueous media[6] or into high-resolution nanostructured thin-films.[7]

In this study, we designed glyco-hydrogelators that are low molecular weight glycoamphiphiles that self-assembled into hierarchical networks entrapping water to form supramolecular hydrogels through non-covalent interactions.[8] The idea was to mimic the stimuli-triggering and responsiveness of conventional polysaccharide hydrogels such as alginate that is an anionic unbranched polysaccharide extracted in large amounts from marine brown algae. It consists of a linear copolymer backbone containing consecutive blocks of α -L-galuronic (G-blocks) and β -D-mannuronic (M-blocks) linked by β -(1,4) glycosidic bonds. Alginate forms a hydrogel in the presence of divalent cations such as Ca^{2+} or trivalent cations such as Fe^{3+} or at pH close to the apparent pK_a of carboxylic acids, c.a., 3.[9] These gels are industrially used in the field of beverage and food, and in biomedical applications including drug delivery, tissue engineering, wound healing and so forth. However, difficulties associated with purification of alginate from natural sources with precise sequences of G- and M- blocks and with a narrow polydispersity have impeded a perfect control of gelation properties, thus encouraging us to design alginate mimetics.

In this context, we describe here a simple way to obtain stimuli-responsive glyco-hydrogelators based on amphiphilic β -C-glycosylbarbiturates, capable of self-assembling either into fibrous networks or, unprecedentedly, into interconnected vesicles resulting in supramolecular hydrogels. On the one hand, the hydrogelation of the single-tailed glycoamphiphiles was triggered upon lowering the pH or adding calcium ions, similarly to alginates. The hydrogels exhibited a macroscopic gel-sol transition in response to temperature, pH and ethylenediaminetetraacetic acid (EDTA) addition. On the other hand, the double-tailed glycoamphiphiles formed thermoreversible multilamellar vesicle gels in pure water.

Results and Discussion

Even if the first glyco-hydrogelator has been described thirty-six years ago by Pfannemüller and Welte,[10] it is still challenging to rationally design effective hydrogelators.[11] However after carefully studying reported molecular structures, some trends emerged: i) a hydrophilic carbohydrate to ensure steric stabilizing of superstructures in water and directional hydroxyl cooperative hydrogen-bonding between fibers; ii) a hydrophobic segment (mainly alkyl or aryl group) as the driving force for aggregation; iii) a complementary H-donor and acceptor groups (mainly amide or urea function), protected from the competition with water molecules, for directing intermolecular self-assembly; iv) the whole self-assembly process being finely controlled by a subtle hydrophilic/hydrophobic balance (HLB).[12]

For practical synthesis reasons, the conjugation of carbohydrates to hydrophobic segments takes place at the reducing end position leading to linear glycoamphiphiles.[13] However, the reducing-end modification of carbohydrates still entails laborious and time-consuming protection-deprotection multisteps, which incites the glycochemist community to develop various protecting-group-free strategies.[14] We recently reported a convenient direct reducing-end modification of unprotected carbohydrates through N,N'-disubstituted barbituric-mediated Knoevenagel condensation in water.[15] Compared to other strategies, we were able to readily design a series of homo- and hetero-clickable sodium salt of β -C-glycosylbarbiturates. The remarkable structural and functional diversity offered by the barbituric acid chemical toolbox prompted us to produce a new modular architecture of amphiphilic β -C-glycosylbarbiturates, taking into account our previous design guidelines. Molecular-scale information programmed in our potential glycoamphiphile gelators are constituted of a hydrophobic alkyl chain linked to a hydrophilic carbohydrate through a monosubstituted cyclic urea exhibiting both acceptor and donor H-bonds (Figure 1a).[16]

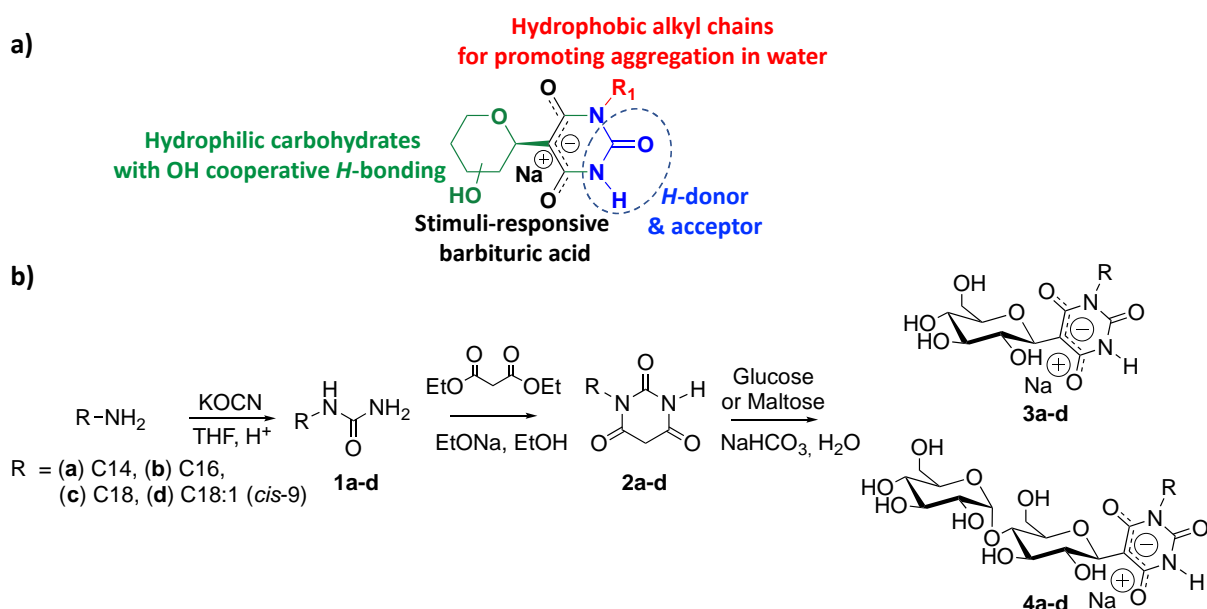


Figure 1. (a) Rational chemical design of stimuli-responsive sodium salt of amphiphilic β -C-glycosylbarbiturates with molecular information promoting hydrogelation. (b) Synthetic pathway for obtaining sodium salt of amphiphilic β -C-glycosylbarbiturates (3a-d and 4a-d) as potential glyco-hydrogelators.

In addition, it was assumed that barbituric acid could act as an alginate-constituting carboxylic acid and therefore would respond in a similar way to external stimuli such as pH and metal cations.

To determine the serendipity to achieve a proper HLB for exhibiting hydrogelation, we screened a series of four glucose-based (3a-d) and four maltose-based (4a-d) β -C-glycosylbarbiturates containing various saturated alkyl chains (C14 in 3a and 4a, C16 in 3b and 4b, C18 in 3c and 4c) or one unsaturated oleyl chain (C18:1 (cis-9) in 3d and 4d) (Figure 1b). Glucose and maltose were selected based on the accessibility and economy of these hydrophilic carbohydrate blocks. The chemical library was facilitated by the modular nature of the synthesis, which involved the Knoevenagel condensation of N-monosubstituted barbituric acids with unprotected glucose or maltose in water with satisfactory yields (from 49 to 78 %). The key chemical platform of N-monosubstituted barbituric acids (2a-d) was readily obtained from the cyclization of N-monosubstituted ureas (1a-d) with diethylmalonate in the presence of sodium ethoxide. N-monosubstituted ureas (1a-d) were easily synthesized, according to a modified procedure,[17] by nucleophilic addition of the corresponding alkylamines to potassium isocyanate in THF with an equimolar of aqueous hydrochloric acid (1M HCl). Noteworthy, the purification in the two first step (Figure 1b) was performed by a simple filtration (yields higher than 80% for each step), highlighting the convenient synthetic pathway of this new class of glycoamphiphiles.

To investigate the hierarchical self-assembling properties of amphiphilic β -C-glycosylbarbiturates into supramolecular hydrogels, tube-inversion experiments were performed, that involved cooling to induce gelation (self-assembly) after dissolution into aqueous solution via heating. However, for glucose-based samples 3a-d, no dissolution was observed even after heating while for maltose-based samples 4a-d, a total dissolution occurred at room temperature.

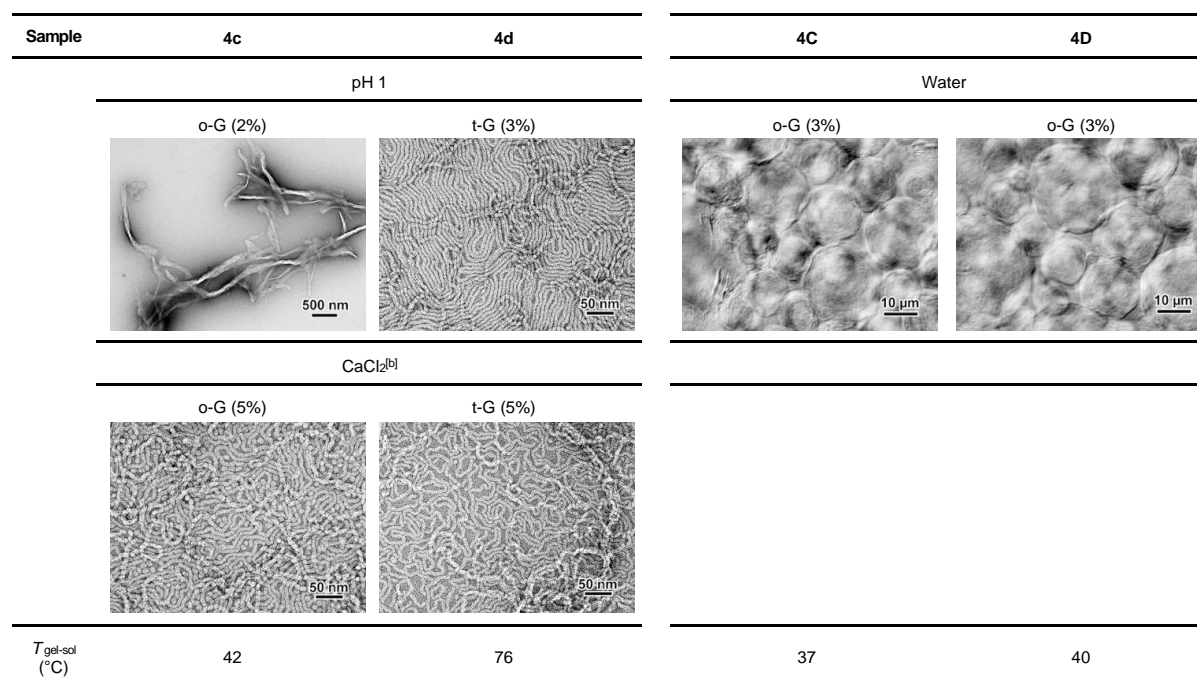


Figure 2. Characteristics and microscopy images of supramolecular hydrogels for 4c-d and 4C-D. The numbers in brackets refer to the minimal gelation weight concentration (MGC). [a] G: Stable gel to tube inversion. o: opaque. t: transparent. [b] $[CaCl_2]/[sample] = 0,5$

The shift from a monosaccharide to a disaccharide drastically changed their solubility in water. Like for alginates, we restarted gelation tests by adding soluble divalent metal ions or by lowering the pH in order to quench the negative charge allowing the self-assembly of glyco-amphiphiles to take place. Upon such conditions, hydrogelation was observed only for 4c and 4d and some characteristics were summarized in the Figure 2. As previously, 4a and 4b were fully dissolved whether in acidic conditions or in presence of calcium chloride. So, a few glyco-hydrogelators were identified consisting of a hydrophilic disaccharide maltose coupled to a hydrophobic aliphatic chain of C18 4c or C18:1 (cis-9) 4d that self-assembled in a strong acidic medium (H-hydrogel, $\text{pH} \leq 1$) or at neutral pH upon adding CaCl_2 (Ca-hydrogel) to produce an opaque and transparent self-supporting gel, respectively. This difference of macroscopic aspect between 4c and 4d hydrogels is mainly due to a better water-solubility of 4d owing to the unsaturated chain.[18] The pH- and calcium-triggered hydrogels of our β -C-glycosylbarbiturates are consistent with other carboxylic acid-containing hydrogelators,[19] indicating that barbituric acid behaves like a classical carboxylic acid. Indeed, the protonation of barbituric acid shields repulsive negative charges within the aggregates of glyco-hydrogelators and initiates self-assembly through weak non-covalent interactions such as hydrogen bonding, van der Waals and hydrophobic interactions. And for Ca-hydrogels, the gelation at neutral condition occurred during solubilization by heating, owing to the screening of the negatively charged barbiturate ring. Surprisingly, hydrogelation occurred only in strong acidic conditions, by far below the expected pK_a value of about 4.5 for 5-monosubstituted barbituric acids.[20] An explanation could arise from the tautomer form adopted by barbituric acid in acidic conditions, since it could exist as either the ketone (KH), the enol (EH), or as a mixture of both tautomers (Figure 3d).[21]

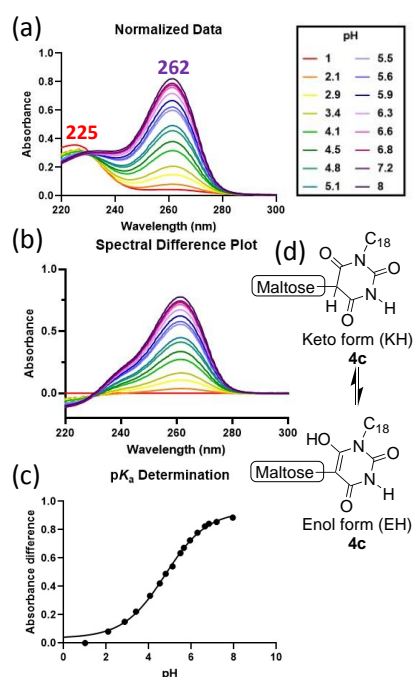


Figure 3. Spectral data analysis and pK_a determination of 4c. (a) UV spectrum of glycosylbarbiturate 4c in different aqueous buffer solutions ranging from pH 1 to 8. (b) Plot of the spectral difference between different solutions of 4c. (c) Plot of the sum of the absolute absorbance difference values at 262 and 225 nm vs pH to determine the pK_a . (d) Tautomer forms of glycosylbarbiturate 4c.

To better understand the tautomer form predominantly present in acidic hydrogelation conditions, we recorded the UV spectra in the range of 220-400 nm of the glycosylbarbiturate 4c by varying the pH and determined the apparent pK_a by using a similar data analysis as described by Martínez and Dardonville[22] (Figures 3a-c; See the Supporting information). We found an apparent pK_a value of 4.78 which is in the expected range (Figure 3c). But more importantly, at pH 1, 4c is under KH form with a maximum absorption at 237 nm, whereas, for instance, at pH 4, a mixture of KH and EH forms are still coexisting with a second λ_{max} at 262 nm.[23] On the basis of UV spectroscopy, we postulate that the KH form is needed for exhibiting hydrogelation, probably because the β -diketone contributes to supramolecular binding.

Next, we noted that H-hydrogels were thermoreversible, as attested by alternating heating (solution) and cooling (gel) cycles (Figure 4). We determined the temperature at which the gel converted into a solution, also referred as the gel-to-sol transition temperature ($T_{gel-sol}$), that is a physical signature of the thermal stability of the supramolecular hydrogel.[24] $T_{gel-sol}$ values of H-hydrogels for 4c and 4d were found at 42 and 76°C, respectively, at corresponding MGCs, and were determined by the “inverting vial” method (Figure 4, See supporting information). In contrast, thermoreversibility of Ca-hydrogels were not observed -at least below the boiling point of water- likely because the Ca^{2+} complexes that tie fibers together have a higher coordination energy with barbiturate groups compared to the energy associated with H-bonding, like already observed for carboxylate functions.[25] However, the addition of EDTA, a chelator of metal ions, returned Ca-hydrogels to the liquid state (Figure 4). Similarly, gel-sol reversibility can be achieved by adding NaOH to H-hydrogels, which highlights the pH-reversibility of our systems due to protonation/deprotonation of the barbituric acid (Figure 4).

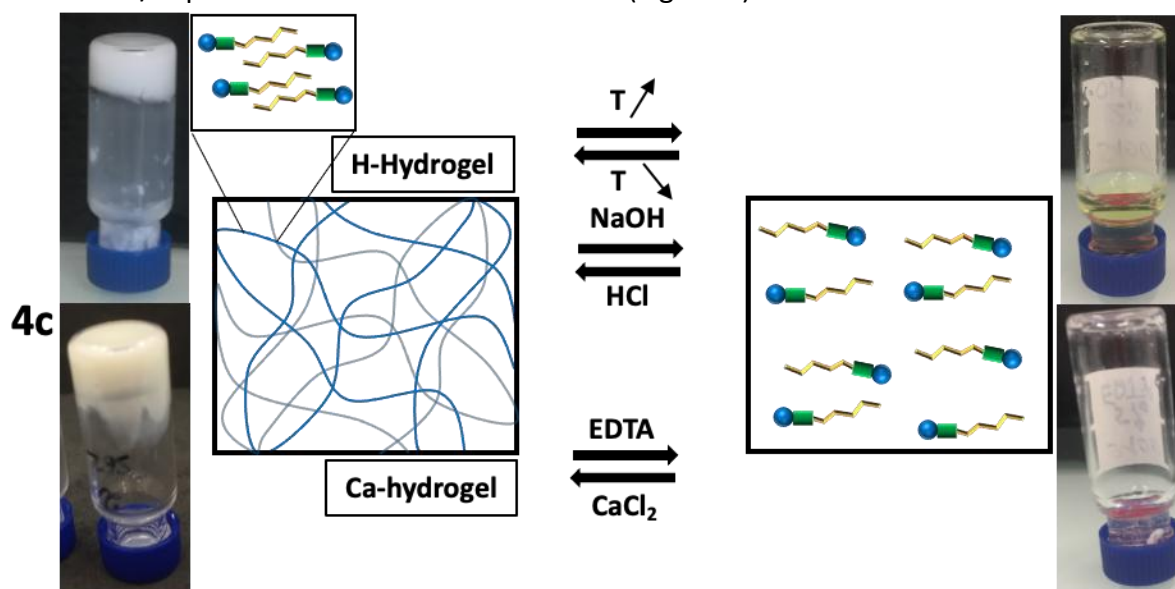
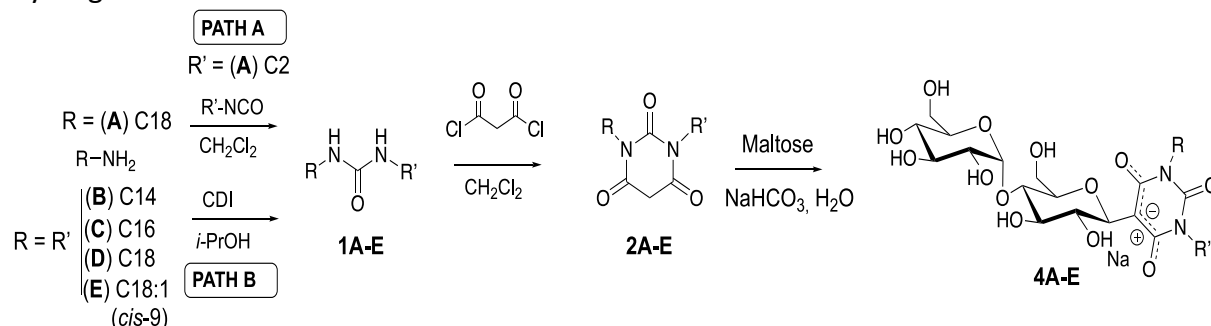


Figure 4. Schematic representation and optical photos of stimuli-responsiveness of the H- and Ca-hydrogels made from 4c. (The blue, green and yellow colors indicate maltose, barbiturate and C18 aliphatic chain, respectively)

To further establish the mode of interaction between our glyco-hydrogelators, we blocked the H-bond donor of the free amine by N-ethylation to afford 4A according to the synthesis route described in Scheme 1, path A. The nucleophilic attack by octadecylamine on ethylisocyanate resulted in an asymmetrical alkylurea intermediate 1A that was cyclized into

the corresponding barbituric acid derivative 2A with malonylchloride. The Knoevenagel condensation between 2A and the reducing-end position of maltose yielded the glyco-amphiphile 4A. Gelation tests for 4A did not lead to hydrogelation highlighting the important contribution of urea function as H-donor and acceptor site to obtain supramolecular hydrogels.



Scheme 1. Synthetic routes for obtaining sodium salt of amphiphilic N,N'-dialkyl β-C-maltosylbarbiturates (4A-E).

However, in order to see if disubstitution of the barbituric acid with two long alkyl chains could enhance hydrophobic interactions to compensate the loss of H-donor and acceptor sites, amphiphilic N,N'-disubstituted β-C-glycosylbarbiturates with C14 (4B), C16 (4C), C18 (4D) or C18:1 (*cis*-9) (4E) aliphatic chain were synthesized (Scheme 1, path B). Briefly, the symmetrical alkylureas 1B-E were obtained from self-condensation of alkylamines using a phosgene-free synthesis by using carbonyldiimidazole (CDI).[15] The cyclization with malonyl chloride produced the corresponding barbituric acid derivatives 2B-E that were finally coupled onto maltose to yield amphiphilic N,N'-dialkyl β-C-maltosylbarbiturates 4B-E.

For gelation tests, while 4B and 4E were found to be unsuccessful whatever the conditions and led to viscous solutions, 4C and 4D showed hydrogelation (V-hydrogels) at 3 wt.% in water at neutral pH. Two cycles of heating-cooling were needed to observe gelation because of the low solubility of 4C and 4D in water. These results indicate that if H-donor/acceptor interaction is an important parameter for promoting hydrogelation, it could be avoided by increasing other types of interactions such as hydrophobic ones. Moreover, decreasing pH for protonation of barbituric acid was not requested which opens up opportunities in terms of biological applications.

Transmission electronic microscopy (TEM) was used to reveal structural features of the self-assembled H- and Ca-hydrogels from 4c and 4d and V-hydrogels from 4C and 4D (Figure 1). Since the gels could not be directly observed by TEM, small fragments were taken, redispersed in water, and homogenized by vortexing or mild sonication to obtain non-viscous solutions or smaller gel microfragments. The H-hydrogel from 4d and Ca-hydrogels from 4c and 4d, both saturated and monounsaturated glyco-hydrogelators self-assembled into 6–7 nm-wide and several micrometer-long tortuous wormlike cylinders (Figures S32-34) that physically entangled into a network that forms the hydrogel matrix. The supramolecular organization in the H-hydrogel from 4c is clearly different. The molecules self-assembled into flat ribbons with a length ranging from 30 to 90 nm that piled up to form thicker and longer bundles (Figure S31). At higher magnification, the twist of this bundles allowed visualizing the edge-on ribbons (Figure S31c) formed by 4 nm-wide single lamellae placed side by side. The size is consistent with the model of bilayer structures of interdigitated octadecyl chains (Figure 4), since the molecular length of 4c was determined about 3.2 nm.[26] The wormlike-

to-ribbon transition morphology of 4c observed from Ca-hydrogel to H-Hydrogel could be explained by the decrease of the spontaneous curvature of the micellar surface owing to charge shielding resulting in a decrease of repulsive forces between the negatively charged barbiturate head groups. The smaller dimensions and density network of ribbons is in line with the low $T_{\text{gel-sol}}$ value.

The observation of diluted V hydrogels from 4C and 4D by TEM revealed several micrometer-large electron opaque particles. Therefore, the gels were directly observed by optical microscopy, with or without dilution in water. The gel contained polydisperse and densely packed spherical particles with a diameter ranging from 15 to 150 μm (Figure 2, Figures S35a,c and S36a,c). The images from the dilute gel suggest that the particles might be giant multilamellar vesicles (Figures S35b,d and S36b,d). Indeed, smaller particles ($< 1 \mu\text{m}$) observed by TEM appear as deflated vesicles (Figures S35e and S36e). The fiber-to-vesicle transition morphology could be rationalized by the simple model of packing parameters which relies on the geometric shape of the amphiphile.[27] The cone-like single-tailed glycoamphiphiles tend to form wormlike cylinders, while the cylinder-shaped double-tailed glycoamphiphiles rather form bilayers resulting in vesicles (Figure 5).

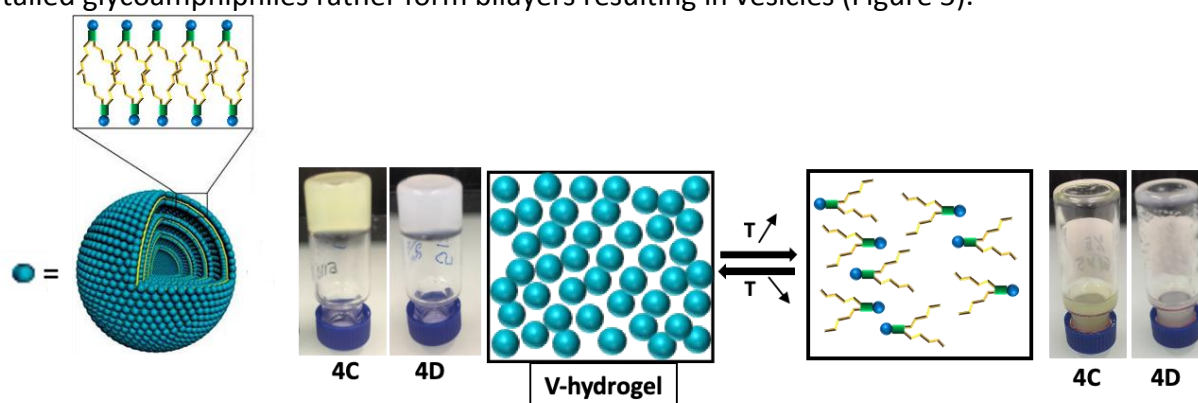


Figure 5. Schematic representation and photographs of the thermo-reversible gel-to-sol transition of V-hydrogels 4C and 4D.

By virtue of the hydroxyl group moieties of the carbohydrate head, the 4C and 4D vesicles eventually percolate, because of hydrogen-bonding-promoted intervesicular attraction, forming a continuous 3D network of connected vesicles. Moreover, owing to the nature of weak interconnected bonds, the vesicle gels exhibited a thermoreversible property with a $T_{\text{gel-sol}}$ of 37 and 40 $^{\circ}\text{C}$, for 4C and 4D, respectively (Figures 2 and 5). Only one example of vesicular glyco-hydrogel system was reported in the literature in 1999 by Bhattacharya's group,[28] and also consisted of double-tailed disaccharide amphiphiles. Typically, vesicle gels are mainly observed for surfactants such as phospholipids.[29] Vesicle gels have attracted much attention because they combine the advantages of both supramolecular gels and vesicles,[30] making them useful for drug delivery applications. And taking into account the important structural and functional role of glycolipid assemblies, such as sphingosine, cerebroside or ganglioside,[31] in disease-associated cell membrane disorders, our system could serve as biomimetic cell membranes.

Conclusion

We have synthesized a novel class of glyco-hydrogelator capable of hierarchical self-assembly into interconnected superstructures that hold water molecules to form hydrogels. The molecular architecture of carbohydrate-based gelators was designed through barbituric acid-mediated Knoevenagel condensation onto unprotected carbohydrates. First,

amphiphilic N-alkyl β -C-glycosylbarbiturates self-assembled into supramolecular hydrogels characterized by entanglements of wormlike cylinders and triggered via lowering the pH or adding Ca^{2+} ions highlighting the successful bioinspired approach for bottom-up nanofabrication of alginate mimetics. On the one hand, we showed that barbituric acid was a convenient and modular chemical toolbox since it allows the incorporation of aliphatic groups, stimuli-responsiveness, and contains a cyclic urea mandatory for promoting supramolecular hydrogels. On the other hand, amphiphilic N,N'-dialkyl β -C-glycosylbarbiturates induced the self-assembly into percolating multilamellar vesicle network, leading to a thermoreversible hydrogelation.

The simplicity in the preparation and design of β -C-glycoamphiphiles is an important point in favor of their applications as matrices[32] with both supramolecular order and functions related to biorelevant carbohydrates.

Acknowledgements

We are grateful for financial support from CNRS, Université Grenoble Alpes, LabEx ARCANÉ and CBH-EUR-GS (ANR-17-EURE-0003), the Glyco@Alps program (ANR-15-IDEX-02), Institut Carnot PolyNat (No. 16-CARN-025-01), National Natural Science Foundation of China (51803227), S&T Innovation 2025 Major Special Program of Ningbo (2019B10063), CAS President's International Fellowship for Visiting Scientists (2019VBA0016). and the NanoBio-ICMG Platform (UAR 2607, Grenoble) for granting access to the electron microscopy, NMR and mass spectrometry facilities. S.Y. thanks the China Scholarship Council (CSC) for his scholarship support (201908320428).

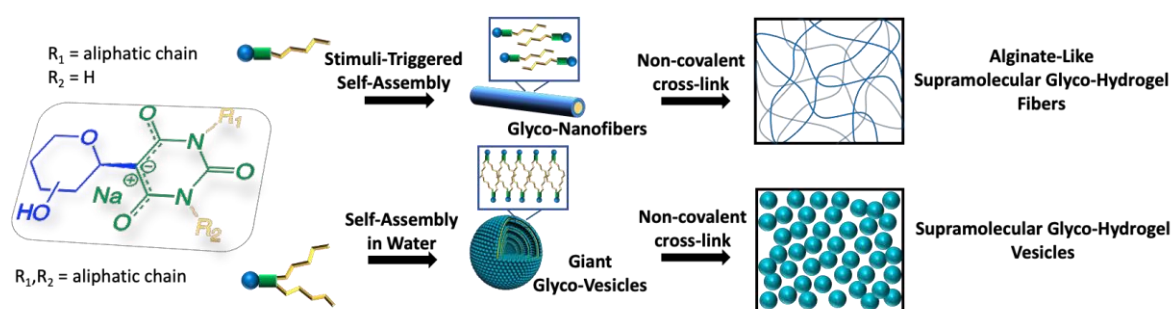
Keywords: Carbohydrate chemistry • glycoamphiphile • self-assembly • supramolecular hydrogels • biomimetic materials

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Barbituric acid-mediated Knoevenagel condensation on unprotected carbohydrates enabled the molecular design of amphiphilic β -C-glycosyl barbiturates as hydrogelators. The single-tailed glycoamphiphiles self-assembled into alginate-like multistimuli-triggered and responsive supramolecular hydrogel fibers. While, the double-tailed glycoamphiphiles led to vesicle hydrogels. Barbituric acid proves to be an efficient and versatile chemical toolbox for the access and design of glycoconjugates.