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Novel deoxycholic acid alkylamide-phenylurea-derived organogelators

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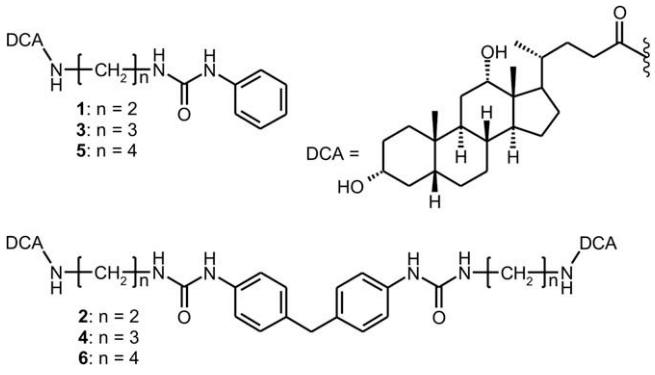
ABSTRACT

Three monomeric and three dimeric deoxycholic acid (DCA) alkylamido-phenylurea derivatives are designed based on known gelators and are synthesized and characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI-TOF mass spectrometry, and elemental analyses. Among them, a monomeric derivative forms supramolecular gels in $CHCl_3$ and chlorobenzene, whereas a dimeric derivative gels THF and higher 1-alkanols containing 7–10 carbons. The morphologies of their xerogels are studied by scanning electron microscopy (SEM). No signature of macroscopic chirality of the gels is visible.

Bile acids and their derivatives are potential carriers for liver specific drugs and they can be used as cholesterol-lowering agents.[1] They have also been used for the treatment of bile acid deficiency and liver diseases such as primary biliary cirrhosis.[2] Interest in low molecular weight gelators has grown in recent years.[3] One such group are bile acid derivatives, which are efficient gelators in aqueous media[4] and organic solvents.[5] We have earlier demonstrated that bile acid amidoalcohols are effective organogelators in chlorinated and aromatic organic solvents.[6] Also urea derivatives are known as hydrogelators[7] and organogelators.[8] Urea groups are also good binding sites for anions in receptor design.[9] Our synthetic design is based on the above-mentioned facts that both bile acid amidoalcohols and urea derivatives are known gelators. In continuation of our research with bile acid-based gelators,[10] we now present syntheses and the characterization of six deoxycholic acid alkylamido-phenylurea derivatives, two of them being effective gelators in organic solvents.



The synthesis of **1**–**6** proceeds via the reaction of methyl deoxycholate with an α,ω-diaminoalkane to give the deoxycholic acid ω-aminoalkylamide. This was allowed to react with phenyl isocyanate or methylene 4,4′-diphenyl diisocyanate to form the desired product.[11] Structural characterization of compounds **1**–**6** was based on their one-dimensional ^{1}H, ^{13}C, and ^{13}C DEPT-135 as well as two-dimensional PFG DQF ^{1}H–^{1}H COSY, PFG ^{1}H–^{13}C HMQC, and PFG ^{1}H–^{13}C HMBC spectra and by comparison with previous data,[6] elemental analyses and ESI-TOF mass spectra.[11]

Gelation studies were performed in 16 organic solvents (Table 1) at concentrations of 2% and 1% (w/v), and if in the latter case a gel or a viscose solution was formed, also in 0.5% solution. The contents of the test-tube was heated at the boiling point until all

Table 1
Gelation properties of compounds **1**–**6**

Solvent	1	2	3	4	5	6
$CHCl_3$	S+	I	G (10)	I	I	I
Chlorobenzene	P	I	G (5)	PS	I	I
Toluene	PS	I	P	I	I	I
p-Xylene	PS	I	P	I	I	I
Ethyl acetate	S	I	PS	I	I	I
Acetone	S+	I	S	I	I	I
THF	S+	P	S+	PS	I	G (10)
Ethanol	S+	S+	S+	S+	S	S
1-Propanol	S+	S+	S+	S+	S	S
1-Butanol	S+	S	S+	S+	S	S
1-Pentanol	S+	S	S+	S+	S	S
1-Hexanol	S+	S	S+	S+	S	S
1-Heptanol	S+	S	S+	S+	S	G (20)
1-Octanol	S+	S	S+	S	S	G (20)
1-Nonanol	S+	S	S+	S	PS	G (20)
1-Decanol	S+	S	S+	S	PS	G (20)

G = gel formed when cooled to room temperature. Minimum gelation concentration (mg/ml) in parentheses. S+ = soluble at rt without warming, S = dissolved at bp, PS = partly soluble at the bp, I = insoluble at the boiling point, P = precipitated upon cooling.

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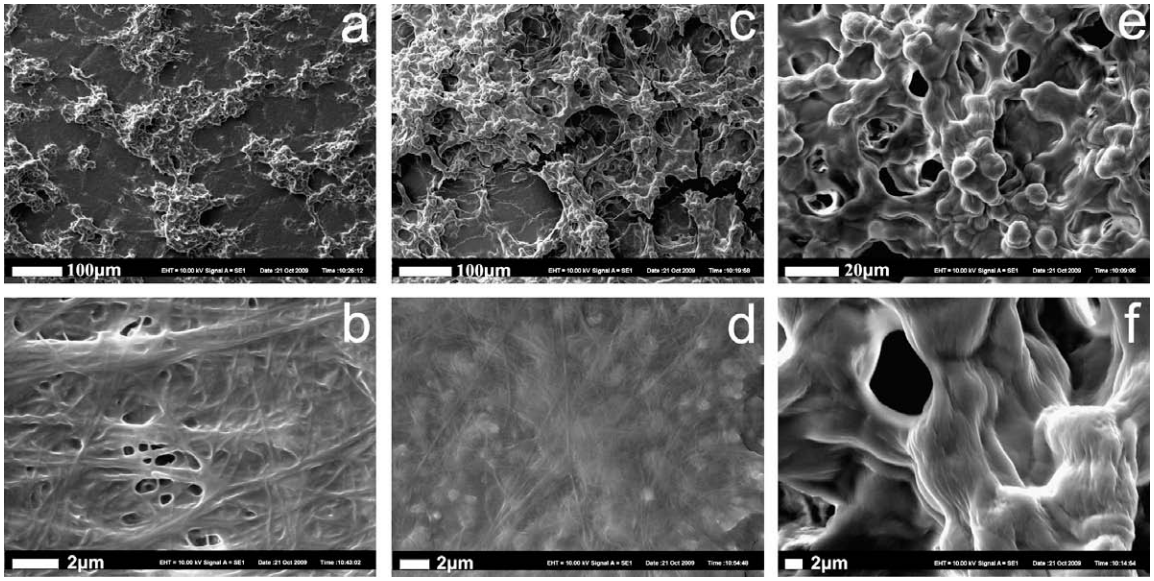

Figure 1. SEM images of xerogels: (a and b) **6** in 1-heptanol; (c and d) **6** in 1-octanol; (e and f) **6** in 1-nonanol.

the solid material had dissolved (if soluble), and then cooled in an ultrasonic bath. The gel formed immediately upon cooling or within half an hour. If no flow was observed when the test-tube was turned upside down, the contents were considered to be a gel.

The formation of gels is based on self-assembly of organic molecules driven by intermolecular interactions.[12] In our compounds the hydrogen bonds between the urea, amide, and hydroxy groups are the strongest driving forces in gel formation.[13] Also, weaker π–π interactions may have some influence.[14] A monomeric derivative, **3** formed supramolecular gels in $CHCl_3$ and chlorobenzene, whereas dimeric derivative **6** formed a gel in THF and higher 1-alkanols containing 7–10 carbons (1-heptanol, 1-octanol, 1-nonanol, and 1-decanol, respectively) (Table 1). According to these results, it seems that the long aliphatic chain in alcohols also has an important role in gel formation. The other derivatives did not form gels in any of the 16 solvents studied. Their solubility in alcohols is probably too good for gel formation in the case of monomeric derivatives **1** and **3**, whereas **5**, although more sparingly soluble, did not form a gel regardless. We also expected that dimeric **2** and **4** would form gels in some alcohols as a result of their solubility, but not even thickening of the solution was observed in the concentration range studied. The dimeric derivatives, as well as monomeric **5**, were sparingly soluble in the other solvents, except alcohols.

The alkyl spacer (varying from ethyl to butyl) between the amide and urea groups in **1**–**6** affects their solubilities in the solvents tested, and it seems to follow the order: propyl > ethyl > butyl. It is also evident that monomeric derivatives have better solubility than their dimeric counterparts.

The morphologies of the xerogels were studied by scanning electron microscopy (SEM) using a Zeiss EVO 50 scanning electron microscope. The gels were first dried at room temperature and then in a vacuum desiccator. The samples were coated with a thin layer of gold before imaging. The SEM images revealed that the xerogels of **6** from 1-heptanol and 1-octanol contained fibrous aggregates (Fig. 1b and d). The xerogel of **6** from 1-nonanol (Fig. 1f) did not show such a clear fibrous structure but mere bulkier formulations with large hollows inside. Although bile acids themselves are chiral and pure optical isomers, no signature of macroscopic chirality of the gels was visible. A close resemblance in the packing pattern in the gel state, xerogel, and bulk solid observed recently by us[10] can open a way to design gels suitable for different applications such as drug delivery, stereospecific synthesis, etc.[15]

In conclusion, we have designed and synthesized six deoxycholic acid alkylamido-phenylurea derivatives. Two of these derivatives showed gelation ability in organic solvents: monomeric derivative **3** in chlorinated solvents, and dimeric derivative **6** in THF and higher 1-alkanols containing 7–10 carbons. No signature of macroscopic chirality of the gels was visible. It was also found that the length of the alkyl chain between the amide and urea groups affects the solubility of the derivative. Our plan is to extend this research to other common bile acids and study whether some drug molecules are incorporated in these gels for drug delivery and other applications.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.101.

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