CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Systematic Modulation of the Supramolecular Gelation Properties of Bile Acid Alkyl Amides

Authors: Riikka Kuosmanen, Rakesh Puttreddy, Elina Sievänen, and Kari Rissanen

To be cited as: *Chem. Eur. J.* 10.1002/chem.201803151

Link to VoR: http://dx.doi.org/10.1002/chem.201803151

Supported by
ACES

WILEY-VCH

10.1002/chem.201803151

WILEY-VCH

FULL PAPER

Systematic Modulation of the Supramolecular Gelation Properties of Bile Acid Alkyl Amides

Riikka Kuosmanen,[a] Rakesh Puttreddy,[a] Kari Rissanen*[a] and Elina Sievänen*[a]

Abstract: The self-assembly properties of nine bile acid alkyl amide-based low-molecular weight gelators (LMWGs) are studied in detail. Based on the results the number of hydroxyl groups attached to the steroidal backbone plays a major role in the gelation, although the nature of the aliphatic side chain modulates the gelation abilities as well. Of the 50 gel systems studied, 35 are based on lithocholic acid and 15 on cholic acid derivatives. The deoxycholic acid derivatives did not form any gels. The gelation commences primarily in aromatic solvents and the gels manifest typical fibrous or spherical morphologies. The ^{13}C CPMAS NMR spectra measured from the crystalline materials and the corresponding wet organogels are analogous, suggesting that the chemical environments *viz.* the intermolecular interactions found in the organogels and in the crystalline state are similar. The single crystal X-ray structures of all nine bile acid amide derivatives studied revealed very similar molecular conformations in the solid state and gave insights into the possible intermolecular interactions in the gel state.

Introduction

Supramolecular gels formed by low molecular weight gelators (LMWGs) have been under intensive research in the past decades.[1–3] The properties of these soft systems differ from those of pure solids or liquids leading to emergence of applications in numerous fields, such as sensing,[4] biomedicine,[5] or materials technology.[6] Some of the recent examples include the use of supramolecular ionogels in non-covalent antibacterial coatings[7], in environmental remediation[8], and as radical scavengers[9]. Supramolecular gels manifest a network consisting of fibers or other nano- or microstructures, which immobilizes the bulk solvent by weak interactions, such as hydrogen bonding, π-π interactions, metal ion coordination, or van der Waals forces.[1,2] Some gel materials exhibit crystalline character, and the organization of the gelator in the crystalline state of the gel fiber can provide a concrete way of linking aspects of these two extremes. This lays the foundation for trying to understand how changes in the molecular structure affect the properties of the formed gels.[10-22]

Bile acids are end products of cholesterol metabolism formed in the liver enhancing the digestion and absorption of lipids and lipid-soluble vitamins. They are of pharmacological interest, being potential carriers and enhancers of absorption of drugs as well as major regulators of cholesterol homeostasis.[23–24] Bile acids possess a unique structure with a convex hydrophobic β-side, a concave hydrophilic α-side, and a polar side chain.[25] Because the molecule is polar on one side and apolar on the other, it is facially amphiphilic and its aggregates in water differ from those of classical surfactants.[26] Since the difference in the steric crowding enables derivatization of each hydroxyl group attached to the steroidal backbone individually, the water/lipid-solubility of the molecules can be easily tailored. More convertibility is achieved by modifying the side chain of bile acids.[27–28]

Several bile acid amide derivatives containing a functional group at the end of the aliphatic side chain have been reported and their properties studied by us.[29–36] Many of them have shown to be effective gelators, and one even formed stimuli-responsive metallogels.[34] Recently, we have focused on the bile acid derivatives that have no functional group at the end of the aliphatic side chain. The aim has been to determine the role of the functional group in self-assembly properties. Within the group of bile acid ethyl amides, the lithocholic acid derivative was shown to form hydrogels in addition to organogels.[37]

In the current study, the self-assembly and gelation properties of nine bile acid alkyl amides were studied in detail. Careful control of the crystallization under equal conditions resulted in good quality single crystals of all nine amides. The subsequent single crystal X-ray studies showed that the N···H, O···H, and H···H interactions were the most important intermolecular interactions affecting organization of the molecules in the solid state. Of the 50 gel systems formed, 35 consisted of lithocholic acid (**LCA**) derivatives and 15 of cholic acid (**CA**) derivatives, whereas deoxycholic acid (**DCA**) derivatives did not form any gels. Even though the length and branching of the aliphatic side chain clearly have an effect on the gelation abilities of the compounds, the number of hydroxyl groups attached to the steroidal backbone plays a major role in the gelation. The ^{13}C CPMAS NMR spectra measured from both the crystalline material and the corresponding wet gels are analogous, suggesting that the chemical environments *viz.* the intermolecular interactions found in the gel and in the crystalline state are similar.

Results and Discussion

Synthesis

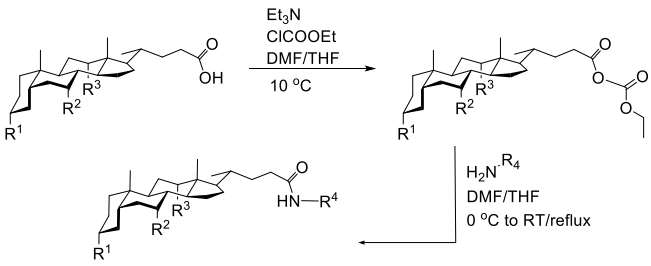
LCA, **DCA**, and **CA** amides **LCA1**−**CA9** were synthesized by following straightforward and facile literature methods (Scheme

[a] M.Sc. Riikka Kuosmanen, Dr. Rakesh Puttreddy, Prof. Kari Rissanen, Dr. Elina Sievänen
University of Jyvaskyla Department of Chemistry, Nanoscience Center, P.O. Box 35, 40014 Jyvaskyla, FINLAND
E-mail: kari.t.rissanen@jyu.fi, elina.i.sievanen@jyu.fi

Electronic Supporting Information for this article is given via a link at the end of the document.

10.1002/chem.201803151

1).[29–30,32–34,37–38] All compounds were purified by simple recrystallizations with yields varying between 32 % and 73 % (See Electronic Supporting Information for more details).



LCA1 R^1=OH, R^2=H, R^3=H, R^4=$(CH_2)_2CH_3$
DCA2 R^1=OH, R^2=H, R^3=OH, R^4=$(CH_2)_2CH_3$
CA3 R^1=OH, R^2=OH, R^3=OH, R^4=$(CH_2)_2CH_3$
LCA4 R^1=OH, R^2=H, R^3=H, R^4=$(CH_2)_3CH_3$
DCA5 R^1=OH, R^2=H, R^3=OH, R^4=$(CH_2)_3CH_3$
CA6 R^1=OH, R^2=OH, R^3=OH, R^4=$(CH_2)_3CH_3$
LCA7 R^1=OH, R^2=H, R^3=H, R^4=$(CH_2)_2C(CH_3)_2$
DCA8 R^1=OH, R^2=H, R^3=OH, R^4=$(CH_2)_2C(CH_3)_2$
CA9 R^1=OH, R^2=OH, R^3=OH, R^4=$(CH_2)_2C(CH_3)_2$

Scheme 1. The synthetic route leading to compounds **LCA1**–**CA9**.

Single Crystal X-ray Analysis

Single crystals of compounds **LCA1**–**CA9** suitable for X-ray diffraction analysis were obtained by slow evaporation of either acetonitrile, DMF, or ethyl acetate solutions. The compounds create a pseudo isomorphous and isostructural series, crystallizing in the monoclinic space group $P2_1$ without solvent molecules (Figures 1 and 2). This differs markedly from the behavior of bile acid derivatives with shorter alkyl (ethyl) chains, where solvent molecules have a key role in stabilizing the crystal lattice.[37] This suggests that for the compounds **LCA1**–**CA9** with longer alkyl side chains the intermolecular bile acid-to-bile acid interactions are preferred over the bile acid-solvent interactions. The hydroxyl and amide groups are fully utilized in forming the intermolecular O–H···O and N–H···O hydrogen bonds to give a typical ordered 1-D bilayered structure (Figure S7).[39–41] The Hirshfeld surface analysis[42–45] for crystal structures of compounds **LCA1**–**CA9** indicates that these bilayers form a compact 3-D crystal lattice by high percentage of H···H interactions (Table S6 and Figures S9-S17).

Gelation Properties

The gelation abilities of compounds **LCA1**–**CA9** were tested in 36 solvents and of compounds **LCA1**–**CA6** additionally in 12 aqueous solutions. The results obtained are presented in Electronic Supporting Information (Tables S1-S3), while only selected gelation experiments are shown in Table 1. A total of 50 gel systems were formed, of which 35 by **LCA** and 15 by **CA** derivatives, respectively. In accordance with our previous results, **DCA** derivatives did not form any gels. Gel formation is mostly fa-

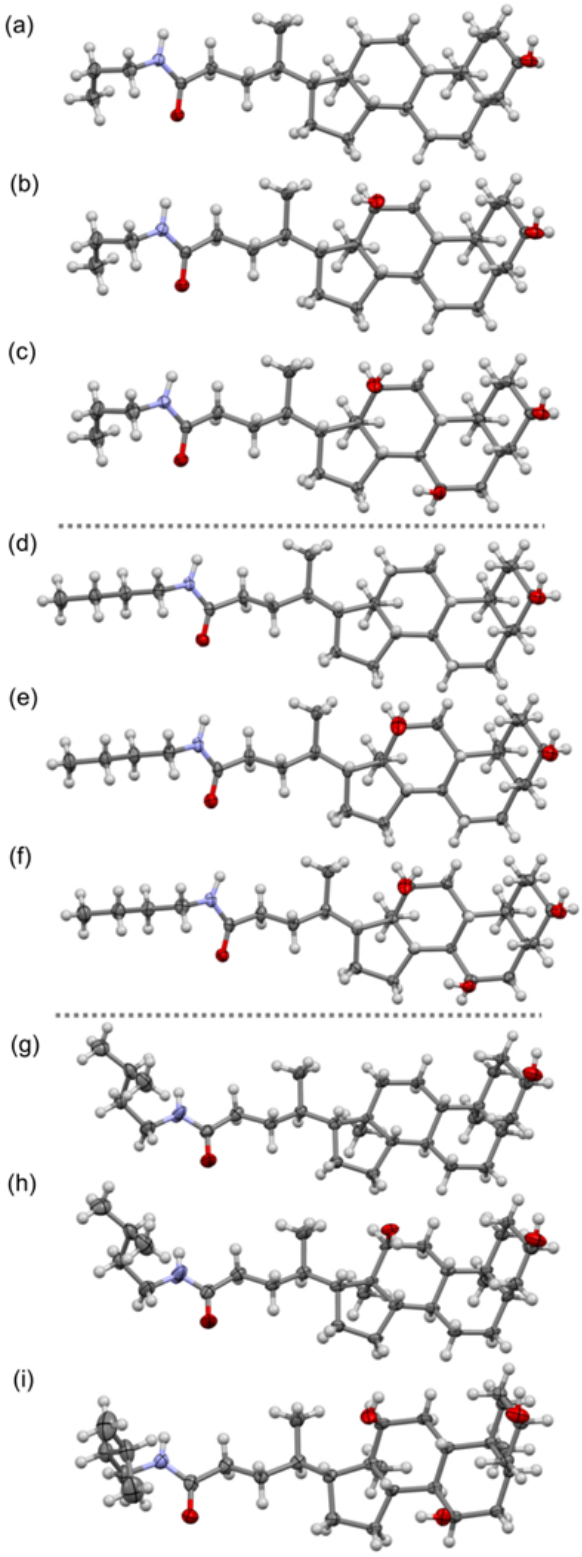


Figure 1. The X-ray crystal structures of (a) *N*-propyllithocholamide, **LCA1**, (b) *N*-propyldeoxycholamide, **DCA2**, (c) *N*-propylcholamide, **CA3**, (d) *N*-butyllithocholamide, **LCA4**, (e) *N*-butyldeoxycholamide, **DCA5**, (f) *N*-butylcholamide, **CA6**, (g) *N-iso*-pentyllithocholamide, **LCA7**, (h) *N-iso*-pentyldeoxycholamide, **DCA8**, and (i) *N-iso*-pentylcholamide, **CA9**, with thermal ellipsoids at 50% probability level.

10.1002/chem.201803151

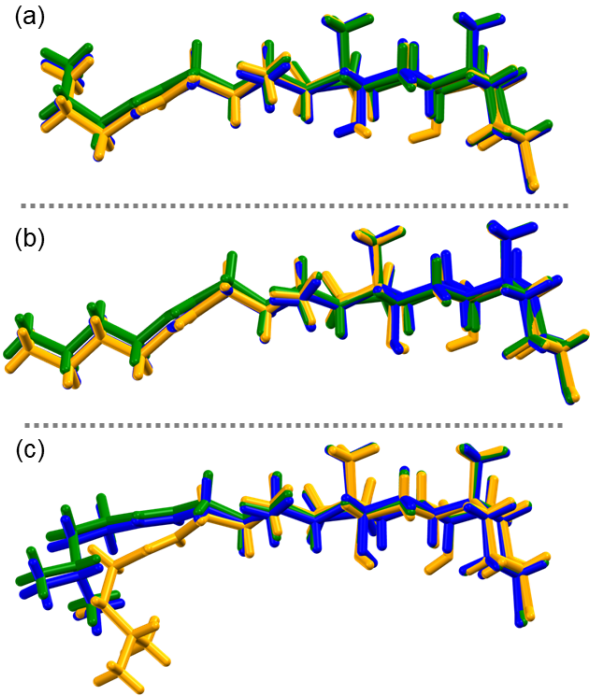


Figure 2. The overlay of the X-ray crystal structures of (a) **LCA1**, **DCA2**, and **CA3**, (b) **LCA4**, **DCA5**, and **CA6**, and (c) **LCA7**, **DCA8**, and **CA9** shown in capped stick model. Color codes: green (**LCA1**, **LCA4**, **LCA7**), blue (**DCA2**, **DCA5**, **DCA8**), and gold (**CA3**, **CA6**, **CA9**).

Table 1. Gelation test results at 1 % (w/v) for compounds **1**–**9**.

Solvent	LCA1	CA3	LCA4	CA6	LCA7	CA9
Benzene	NG	PG	**G**	NG	**G**, PG	**G**
Toluene	NG	**G-**	**G**	NG	**G-**	**G**
Ethylbenzene	NG	NG	PG	NG	**G**,**G-**, PG	**G**
o-Xylene	PG	NG	**G-**	**G-**	**G-**	**G**
m-Xylene	NG	NG	**G**	NG	**G**	**G**
p-Xylene	**G**	NG	**G**	NG	**G**	**G-**
tert-Butylbenzene	NG	NG	NG	NG	**G-**	PG
Cumene	**G-**,**G**	NG	**G**	NG	**G**	**G-**, PG
Chlorobenzene	**G**	NG	**G-**	NG	**G-**	NG
Anisole	**G**, PG	**G**	**G**	**G-** **G**	PG, **G-**	**G**
1,4-Dioxane	**G-**	**G-**	**G**	NG	**G-**, PG	PG
Acetonitrile	NG	NG	NG	NG	**G-**, PG	NG
Carbontetrachloride	**G-**, PG	NG	PG	NG	NG	NG
Ethyl acetate	**G-**, PG	NG	NG	NG	NG	NG

G = gel with appr. 0−5 % free solvent, **G-** = gel with appr. 5−20 % free solvent, PG = gel with appr. 50 % free solvent, NG = no gel.

vored in aromatic solvents, which is commonly observed for bile acid derivatives.[30–33,35–37] Furthermore, the gels of the lithocholic acid derivatives **LCA1**, **LCA4**, and **LCA7** as well as those of the cholic acid derivatives **CA3**, **CA6**, and **CA9** were thixotropic by nature similar to the gels formed by the ethyl amide derivatives reported previously by us.[37]

Because the formation of the bilayered structures, involving the functional groups in the head (hydroxyl groups) and tail (carboxylic acid groups or their derivatives) of the steroidal backbone, is typical for bile acid derivatives in the solid state,[39–41] it is reasonable to assume that similar structures exist also in the semi-solid or gel-states. In the case of **CA** and its derivatives the inter-bilayered interactions are reinforced by hydrogen bonds between the hydroxyl groups at positions 7α and 12α (Table S6). Thus the interstices between the bilayers formed up by the lipophilic β-faces of the steroidal backbones create suitable environments for the entrapment of aromatic solvent molecules. The **LCA** derivatives lack hydroxyl groups on the steroidal α-face, and are thus relatively lipophilic both on α- and β-sides. This property favors the entrapment of the aromatic solvent molecules. These structural features account for the tendency of **CA** and **LCA** derivatives to form supramolecular gels particularly in aromatic solvents. The **DCA** derivatives, which bear only one hydroxyl group on the α-side of the steroidal skeleton, manifest a different polarity profile. In addition, their mutual orientation is altered (Figures S21b and S22c), which prevents the formation of favorable space for entrapment of solvent molecules and thus disfavors supramolecular gel formation.

Morphology

The bile acid derivatives typically form gels consisting of differently organized fibres or of spherical assemblies. [30–33,35–37] The derivatives **LCA1**, **LCA4**, and **LCA7** formed gels with flat fibres in chlorobenzene (Figures 3a-c). The width of the fibres in the case of compounds **LCA1** and **LCA4** was approximately 600−800 nm and the length approximately 40−50 μm. Compound **LCA7** formed clearly thicker (up to 1.6 μm) and longer (200 μm) fibres. When the gelator concentration was increased from 1 % to 2 % (w/v), the fibres formed fan-shaped bundles. Similar fan-shaped bundles were observed previously within the 1 % hydrogels of **LCA** ethyl amide.[37] Interestingly, compounds **LCA1** and **LCA7** formed hollow nanotubes in ethyl acetate, as can be seen in Figure S3. The nanotubes of compound **LCA1** were approximately 390 μm long and 30 μm in diameter, whereas the flat fibres co-existing with the tubes were approximately 60 μm long and 950 nm wide, respectively. The nanotubes were clearly shorter and thinner in the case of compound **LCA7,** for which the length varied between 12 μm and 32 μm and the width between 700 nm and 3.3 μm.

The non-gel-forming amides **DCA2, DCA5**, and **DCA8** showed clearly crystalline nature. Compound **DCA2** formed a crystal with wood-like surface (Figure 3d), whereas rods with frayed ends were seen in the case of compound **DCA5** (Figure 3e). Compound **DCA8** possessed larger entities, which consisted of individual rods (Figure 3f). The largest assembly was approximately 19 μm long and 9 μm wide. The single rods were non-uniform in size; their lengths varied from 250 nm to 1 μm, whereas they were approximately 230 nm wide. Together with the

entities consisting of rods extremely small spherical assemblies (1.8-3.3 µm in diameter) were observed in the case of compound **DCA8**.

The amides **CA3**, **CA6**, and **CA9**, for one, formed spherical assemblies, which coexisted with fibres. The assemblies of the propyl amide derivative **CA3** were spherical both in 1 % and 2 % chlorobenzene gels (Figure 3g). The 1 % gel consisted of spheres of 1.1−1.45 µm in diameter (Figure S1c), whereas in the 2 % gel the spheres were more versatile in size. The 1 % chlorobenzene gel of the butyl amide derivative **CA6** contained some crystalline material (Figure S1d). The crystals were rectangular in shape, and their sizes varied greatly; thickness varying between 21−67 µm and length between 40−230 µm, respectively. In the 2 % gel some of the crystals had further assembled in spherical structures (Figure 3h). The 1 % chlorobenzene gel of the *iso*-pentyl derivative **CA9** (Figure S4c) also consisted of spherical assemblies, whose diameters were considerably larger (120 µm) than those detected in the gel formed by compound **CA3** and the surface had a folded structure. The 2 % gel of compound **CA9** possessed an extensively folded surface (Figure 3i).

Based on the SEM images an obvious morphological difference between the gel-forming **LCA** and **CA** derivatives and the non-gel-forming **DCA** derivatives can be observed. The gel-forming derivatives possess fibrous and spherical structures, whereas the non-gel-forming derivatives form clearly crystalline assemblies.

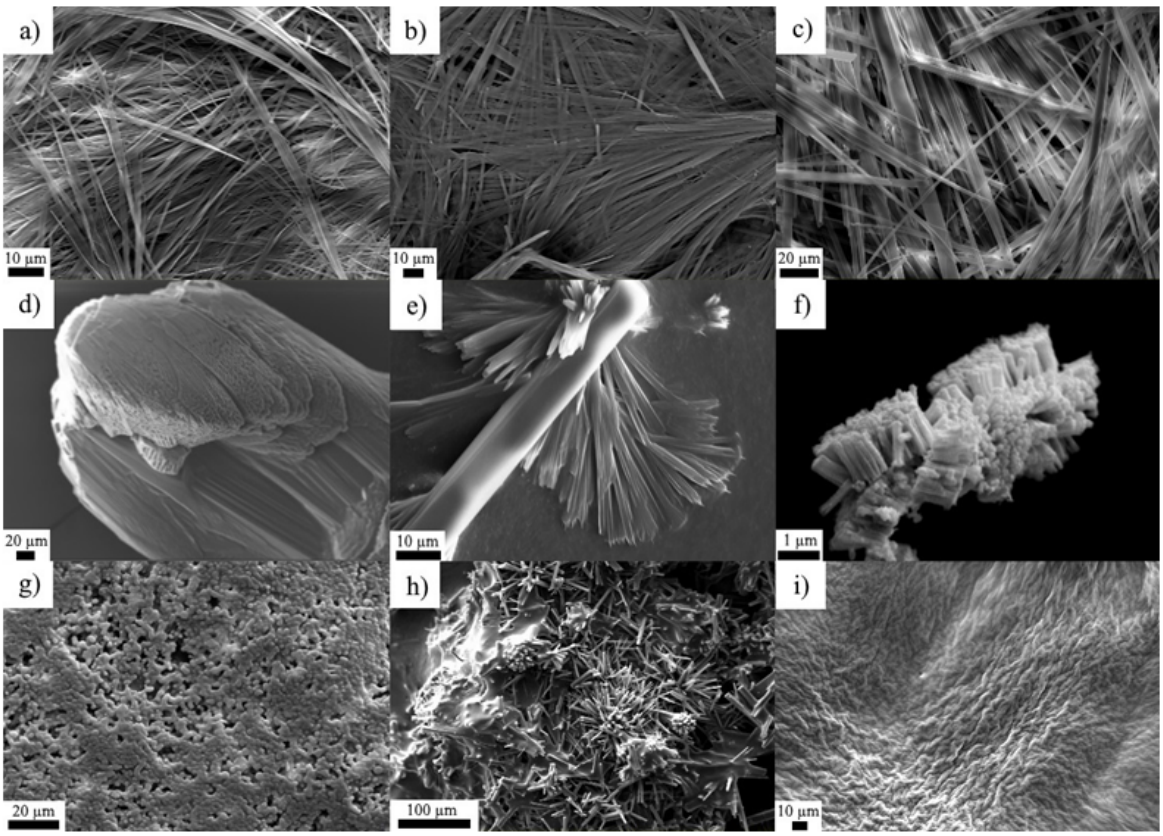


Figure 3. a) 2 % (w/v) chlorobenzene gel of compound **LCA1**, b) 2 % (w/v) chlorobenzene gel of compound **LCA4**, c) 2 % (w/v) chlorobenzene gel of compound **LCA7**, d) 2 % (w/v) chlorobenzene solution of compound **DCA2**, e) 2 % (w/v) chlorobenzene solution of compound **DCA5**, f) 2 % (w/v) chlorobenzene solution of compound **DCA8**, g) 2 % (w/v) chlorobenzene gel of compound **CA3**, h) 2 % (w/v) chlorobenzene gel of compound **CA6**, and i) 2 % (w/v) chlorobenzene gel of compound **CA9**.

^{13}C CPMAS NMR

For the ^{13}C CPMAS NMR measurements, 2 % (w/v) gel samples of compounds **LCA1**, **CA3**, **LCA4**, **CA6**, and **CA9** in chlorobenzene were prepared. Despite numerous efforts, for compound **LCA7** a reasonable S/N ratio was not reached by using a concentration of 2 % (w/v), which is why the concentration was increased to 4 % (w/v). The hot solution containing the compound in question was quickly pipetted into a rotor. The crystalline samples of compounds **LCA1**, **CA3**, **LCA4**, **CA6**, and **CA9** were prepared by recrystallizing the compounds in acetonitrile, and that of **LCA7** in DMF to maintain consistency with the single crystal X-ray analyses. The crystalline samples were dried under vacuum before the measurements. The gel samples were spun at a rate of 4 kHz and the crystalline ones at 10 kHz. The possibility of melting of the gel due to rotation was taken into

account by using a slower spinning speed. Furthermore, the phase of the sample was ascertained to be a gel by visual inspection immediately after the measurement.

As can be seen from Figure 4, the ^{13}C CPMAS NMR spectra of the derivatives **LCA1**, **LCA4**, and **LCA7** measured from the crystalline materials corresponding to the X-ray crystal structures (Figure 1 and Figures 4a, c, and e) and from the chlorobenzene gels (Figures 4b, d, and f) are similar to each other. The same applies for the other gel-forming series, the derivatives **CA3**, **CA6**, and **CA9** (Figures S23-S25) as well. This suggests that the chemical environments and intermolecular interactions in the solid state and in the gel are alike.

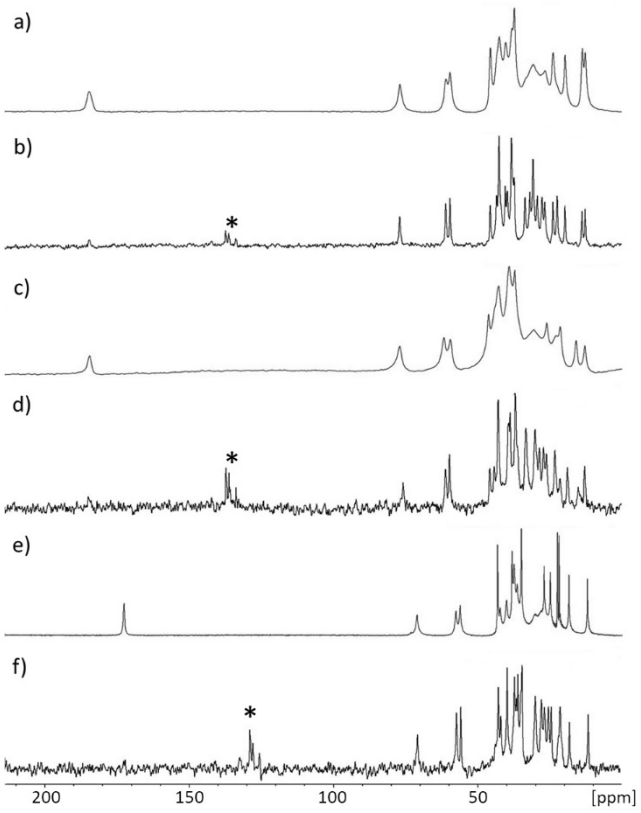


Figure 4. ^{13}C CPMAS NMR spectra of compounds **LCA1**, **LCA4**, and **LCA7**: **LCA1** recrystallized from acetonitrile (a), 2% (w/v) chlorobenzene gel of **LCA1** (b), **LCA4** recrystallized from acetonitrile (c), 2% (w/v) chlorobenzene gel of **LCA4** (d), **LCA7** recrystallized from DMF (e), and 4% (w/v) chlorobenzene gel of **LCA7** (f). In the gel samples, carbon signals from the chlorobenzene solvent are marked with an asterisk.

Conclusions

As a continuation of our systematic studies on the effect of the side chain modification on the gel-forming properties of bile acid derivatives, a detailed study on self-assembly properties of nine bile acid alkyl amides is reported. Based on the results the number of hydroxyl groups attached to the steroidal backbone seems to play a major role in gelation, although the nature of the aliphatic side chain has an impact on the gelation abilities as well. Of the 50 gel systems formed, 35 consisted of **LCA** and 15 of **CA** derivatives, whereas **DCA** derivatives did not form any gels. The intermediate polarity profile on the α-side of the **DCA** derivatives seems to prevent favourable interactions for supramolecular gel formation. The gels of **LCA** and **CA** derivatives were formed mostly in aromatic solvents exhibiting typical fibrous or spherical morphologies. The ^{13}C CPMAS NMR spectra measured from the crystalline materials corresponding to the X-ray crystal structures and from the chlorobenzene gels of **LCA** and **CA** derivatives are similar to each other indicating similar chemical environments and intermolecular interactions in the crystalline state and in the gels. When used with caution the correlation between single crystal X-ray crystallography and solid-state NMR may provide additional insight for inspecting the structure of the supramolecular gels.

Experimental Section

Details of the syntheses, compound characterizations, and gelation property studies are given in the Electronic Supporting Information.

Acknowledgements

Ellen and Artturi Nyyssönen Foundation (R.K.), the Academy of Finland (R.P., grant no. 298817), and the University of Jyväskylä are acknowledged for financial support. The authors are grateful to Lab. Tech. H. Salo for SEM studies, Lab. Eng. E. Haapaniemi for liquid state NMR spectroscopy, and Spec. Lab. Tech. J. Lind for mass spectrometry. B.Sc. Sonja Into, B.Sc. Sasu Jaakkola, Mr. Karri Björklund, and Mr. Aleksi Tiusanen are thanked for their contributions to the synthetic work.

Keywords: bile acid amides • X-ray crystallography • supramolecular gels • intermolecular interactions • CPMAS NMR

Literature

[1] P. Terech, R.G. Weiss, *Chem. Rev.*, **1997,** *97*, 3133–3160.
[2] R.G. Weiss, P. Terech (Eds.), Molecular Gels: Materials with Self-Assembled Fibrillar Networks, Springer, Dordrecht, **2006**.
[3] J.W. Steed, *Chem. Commun.*, **2011**, *47*, 1379–1383.
[4] J.R. Hiscock, F. Piana, M.R. Sambrook, N.J. Wells, A.J. Clark, J.C. Vincent, et al., *Chem. Commun.*, **2013,** *49*, 9119–9121.
[5] S.M.N. Simões, F. Veiga, J.J. Torres-Labandeira, A.C.F. Ribeiro, A. Concheiro, C. Alvarez-Lorenzo, *Macromol. Biosci.*, **2013,** *13*, 723-734.
[6] A. Ajayaghosh, V.K. Praveen, *Acc. Chem. Res.*, **2007**, *40*, 644–656.
[7] C. Rizzo, R. Arrigo, N. T. Dintcheva, G. Gallo, F. Giannici, R. Noto, A. Sutera, P. Vitale, F. D'Anna, *Chem. Eur. J.*, **2017,** *23*, 16297-16311.

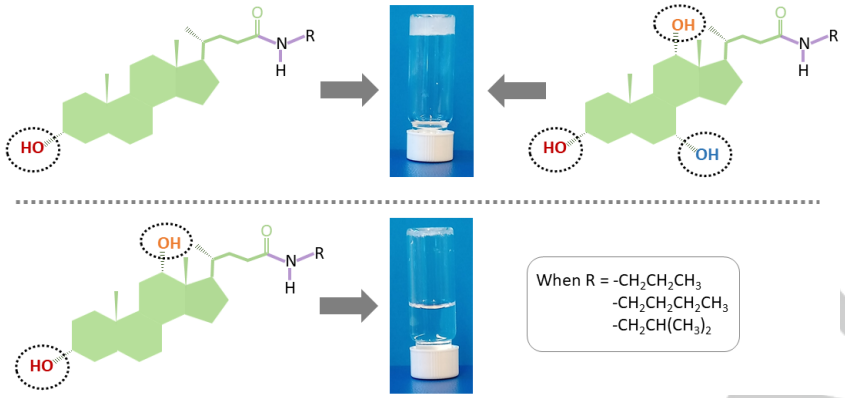
[8] S. Marullo, C. Rizzo, N. T. Dintcheva, F. Giannici, F. D'Anna, *J. Colloid Interface Sci.*, **2018,** *517*, 182-193.
[9] C. Rizzo, F. Arcudi, L. Dordevic, N. T. Dintcheva, R. Noto, F. D'Anna, M. Prato, *ACS Nano*, **2018,** *12*, 1296-1305.
[10] E. Ostuni, P. Kamaras, R.G. Weiss, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1324–1326,.
[11] D.J. Abdallah, S.A. Sirchio, R.G. Weiss, *Langmuir*, **2000,** *16*, 7558–7561.
[12] D.R. Trivedi, A. Ballabh, P. Dastidar, B. Ganguly, *Chem. Eur. J.*, **2004,** *10*, 5311–5322.
[13] M. George, G. Tan, V.T. John, R.G. Weiss, *Chemistry*, **2005,** *11*, 3243–3254.
[14] D.R. Trivedi, P. Dastidar, *Chem. Mater.*, **2006,** *18*, 1470–1478.
[15] A. Ballabh, D.R. Trivedi, P. Dastidar, *Chem. Mater.* **2006,** *18*, 3795–3800.
[16] D.R. Trivedi, P. Dastidar, *Cryst. Growth Des.*, **2006**, *6*, 2114–2121.
[17] M.-O.M. Piepenbrock, G.O. Lloyd, N. Clarke, J.W. Steed, *Chem. Commun.*, **2008,** 2644–2646.
[18] A. Ballabh, T.K. Adalder, P. Dastidar, *Cryst. Growth Des.* **2008,** *8*, 4144–4149.
[19] P. Sahoo, N.N. Adarsh, G.E. Chacko, S.R. Raghavan, V.G. Puranik, P. Dastidar, *Langmuir*, **2009,** *25*, 8742–8750.
[20] U.K. Das, D.R. Trivedi, N.N. Adarsh, P. Dastidar, *J. Org. Chem.*, **2009,** *74*, 7111–7121.
[21] J. Chen, J.W. Kampf, A.J. McNeil, *Langmuir*, **2010,** *26*, 13076–13080.
[22] J. Gao, S. Wu, T.J. Emge, M.A. Rogers, *CrystEngComm*, **2013,** *15*, 4507–4515.
[23] A. Enhsen, W. Kramer, G. Wess, *Drug Discov. Today*, **1998**, *3*, 409–418.
[24] E. Sievänen, *Molecules*, **2007**, *12*, 1859–1889.
[25] D.M. Small, in *The Bile Acids Chemistry, Physiology, and Metabolism*, P.P. Nair, D. Kritchevsky, Eds., Plenum Press New York, **1971**, 249–356.
[26] S. Mukhopadhyay, U. Maitra, *Curr. Sci.*, **2004,** *87*, 1666–1683.
[27] A.P. Davis, *Molecules*, **2007**, *12*, 2106–2122.
[28] Nonappa, U. Maitra, *Org. Biomol. Chem.*, **2008**, *6*, 657–669.
[29] V. Noponen, S. Bhat, E. Sievänen, E. Kolehmainen, *Mater. Sci. Eng. C*, **2008,** *28*, 1144–1148.
[30] V. Noponen, M. Lahtinen, A. Valkonen, H. Salo, E. Kolehmainen, E. Sievänen, *Soft Matter*, **2010,** *6*, 3789–3796.
[31] M. Löfman, J. Koivukorpi, V. Noponen, H. Salo, E. Sievänen, *J. Colloid Interface Sci.*, **2011,** *360*, 633–44.
[32] V. Noponen, H. Belt, M. Lahtinen, A. Valkonen, H. Salo, J. Ulrichová, A. Galandáková, E. Sievänen, *Steroids*, **2012,** *77*, 193–203.
[33] V. Noponen, A. Valkonen, M. Lahtinen, H. Salo, E. Sievänen, *Supramol. Chem.*, **2013,** *25*, 133–145.
[34] V. Noponen, K. Toikkanen, E. Kalenius, R. Kuosmanen, H. Salo, E. Sievänen, *Steroids*, **2015,** *97*, 54–61.
[35] M. Löfman, M. Lahtinen, M. Pettersson, E. Sievänen, *Coll. Surf. A*, **2015**, *474*, 18–28.
[36] M. Löfman, M. Lahtinen, K. Rissanen, E. Sievänen, *J. Colloid Interface Sci.*, **2015,** *438*, 77–86.
[37] R. Kuosmanen, R. Puttreddy, R.-M. Willman, I. Äijäläinen, A. Galandáková, J. Ulrichová, H. Salo, K. Rissanen, E. Sievänen, *Steroids*, **2016,** *108*, 7–16.
[38] S. Bergström, A. Norman, *Acta Chem. Scand.*, **1953,** *7*, 1126–1127.
[39] Y. Hishikawa, R. Watanabe, K. Sada, M. Miyata, *Chirality*, **1998,** *10*, 600–618.
[40] K. Nakano, K. Sada, Y. Kurozumi, M. Miyata, *Chem. Eur. J.*, **2001,** *7*, 209–220.
[41] N. Yoswathananont, K. Sada, K. Nakano, K. Aburaya, M. Shigesato, Y. Hishikawa, K. Tani, N. Tohnai, M. Miyata, *Eur. J. Org. Chem.*, **2005,** 5330–5338.
[42] M. A. Spackman, D. Jayatilaka, *CrystEngComm*, **2009**, *11*, 19–32.
[43] M. A. Spackman, J. J. McKinnon, *CrystEngComm*, **2002,** *4*, 378–392.
[44] J. J. McKinnon, D. Jayatilaka, M. A. Spackman, *Chem. Commun.*, **2007**, 3814–3816
[45] J. J. McKinnon, M. A. Spackman, A. S. Mitchell, *Acta Crystallogr. Sect. B*, **2004**, *60*, 627–668.

10.1002/chem.201803151

WILEY-VCH

Entry for the Table of Contents

FULL PAPER



Riikka Kuosmanen, Rakesh Puttreddy, Kari Rissanen, and Elina Sievänen**

Page No. – Page No.

Systematic Modulation of the Supramolecular Gelation Properties of Bile Acid Alkyl Amides

A detailed study on the self-assembly properties of nine bile acid acid alkyl amide-based low-molecular weight gelators resulted in 50 gel systems, 35 of which were based on lithocholic acid and 15 on cholic acid derivatives. Deoxycholic acid derivatives, however, did not form any gels. Gelation commenced primarily in aromatic solvents and the gels manifested typical fibrous or spherical morphologies. The ^{13}C CPMAS NMR spectra measured from the crystalline materials and the corresponding organogels were analogous, suggesting that the chemical environments and consequently the intermolecular interactions in the organogels and in the crystalline state are similar. The single crystal X-ray structures of all nine bile acid amide derivatives revealed similar molecular conformations in the solid state giving insights into the possible intermolecular interactions in the gel state.