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Supramolecular gels based on bile acid salts

Nataliya F. Goldshleger,[a] Anatolii S. Lobach,[a] Vladimir E. Baulin,[b, c] Aslan Yu. Tsivadze [c]

[a] Institute of Problems of Chemical Physics, Russian Academy of Sciences
prosp. Akademika Semenova 1, 142432 Chernogolovka, Moscow Region, Russian Federation
[b] Institute of Physiologically Active Compounds, Russian Academy of Sciences
Severnyi pr. 1, 142432 Chernogolovka, Moscow Region, Russian Federation
[c] A.N.Frumkin Institute of Physical Chemistry and Electrochemistry, Russian Academy of Sciences
Leninsky prosp. 31, 119991 Moscow, Russian Federation

The results of studies of the formation and properties of supramolecular hydrogels based on salts of bile acids, biological surfactants, are summarized. The attention is focused on the properties of sodium deoxycholate, in particular, its capacity for efficient solubilization and delivery of hydrophobic drugs, binding of metal ions and formation of fluorescent hydrogels. The features of formation of hydrogels with the participation of crown-substituted phthalocyanines and sodium deoxycholate are discussed, including the aggregation state and the fluorescent properties of the active component.
The bibliography includes 184 references.

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I. Introduction

Supramolecular chemistry is a young field of chemistry. Its investigation objects are molecules, often structurally or functionally similar to biological ones, that are self-assembled *via* intermolecular interactions to form supramolecular assemblies. The term 'supramolecular chemistry' (chemistry beyond the molecule) and its key concepts were introduced in 1978 by Jean Marie Lehn.[1]

Gels attract a lot of attention, because they are abundant in Nature and because gel-forming compositions are used for industrial and household purposes. The similarity of properties of synthetic gels and living tissues, such as reversible sorption of large amount of water, biocompatibility and the ability to retain and transfer an active component and to release it upon external stimulus, leads to broad applications of gels and promotes further investigations of gelation (see, for example Refs 2 – 7). Gels refer to smart materials, *i.e.*, materials that are sensitive to

N.F.Goldshleger. PhD in Chemistry, Senior Researcher at the IPCP RAS.
Telephone: + 7(496)522 – 7222, e-mail: nfgold@icp.ac.ru
Current research interests: fullerene chemistry, supramolecular chemistry, surfactants, crown-substituted phthalocyanines, solubilization, supramolecular gels.
A.S.Lobach. PhD in Chemistry, Senior Researcher at the same Institute.
Telephone: + 7(496)522 – 1424, e-mail: lobach@icp.ac.ru
Current research interests: chemistry of carbon nanomaterials, fullerenes, nanotubes, graphene sheets, hybrid and composite materials, supramolecular gels, aerogels.
V.E.Baulin. Doctor of Chemical Sciences, Leading Researcher at the IPAC RAS, Chief Researcher at the IPCE RAS.
Telephone: + 7(495)724 – 5360,
e-mail: mager1988@gmail.com
Current research interests: organic chemistry, inorganic chemistry, coordination chemistry, supramolecular chemistry, complex formation.
A.Yu.Tsivadze. Academician, Doctor of Chemical Sciences, Professor, Head of Laboratory and Scientific Adviser at the IPCE RAS.
Telephone: + 7(495)952 – 0462, e-mail: tsiv@phyche.ac.ru
Current research interests: metal coordination compounds, chemistry of crown-substituted phthalocyanines and porphyrins, materials for electrochemical energy generation and molecular electronics.

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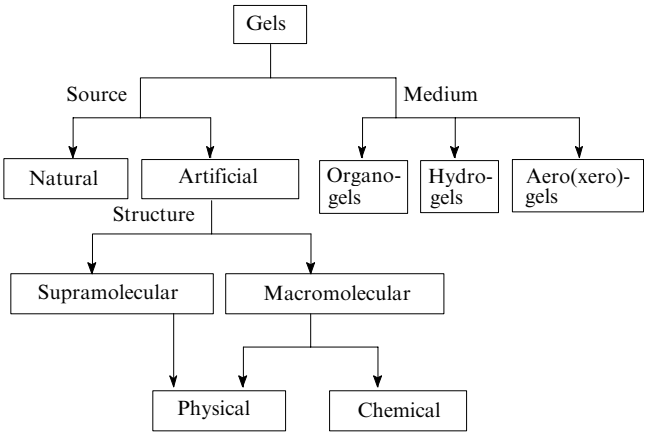


Figure 1. Classification of gels.

changes in the environment and modify their properties in response to external stimuli.[8] Hydrogels based on hydrophilic (natural and synthetic) polymers formed *via* covalent bonding or non-covalent interactions are referred to as 'chemical' or 'physical' hydrogels, respectively. Gelation is not limited to polymers acting as the gelators, but can also involve modern materials, *e.g.*, carbon nanotubes, graphene and graphene oxide.[9–12] The classification of gels is shown in Fig. 1.

One of the approaches to fabrication of smart materials is the supramolecular approach consisting in the use of intermolecular interactions — hydrogen bonds, including CH–π bonds, ion–ion, ion–dipole, van der Waals, hydrophobic and coordination interactions, π–π stacking and so on — to arrange molecules into complex structural entities that can functionally model biological objects. The energy of intermolecular interactions is much lower than the energy of covalent bonds in organic molecules and can seldom reach a value of about 100 kJ mol^{-1} (for example, in the case of CH–π hydrogen bonds, the bond energy is 0.84–10.5 kJ mol^{-1}).[13] On the one hand, the large number of non-covalent interactions enhances the stability of supramolecular assemblies. On the other hand, weak non-covalent interactions provide for the reversibility of association (or self-organization) of molecules and for the possibility to control the equilibrium by varying external conditions (pH, nature of the solvent, temperature, ionic strength, ligand–receptor interaction, *etc.*). Currently, there is no unified approach for predicting the gelation properties of molecules on the basis of their structure.

The review of Goldshleger *et al.*[14] considers the role of non-covalent interactions in redox transformations in water of electroactive components (fullerene and its derivatives, metal phthalocyanine complexes) encapsulated in an artificial lipid matrix. Reversible reduction reactions, in particular,

$$C_{60} + e \rightleftharpoons C_{60}^{-\bullet} \quad (1)$$

are implemented in films of, for example, tetraoctyl- (TOA^+) and didodecyldimethylammonium (DDA^+) bromides.[14,15] A study of the molecular and crystal structure of the $[C_{60}^{-\bullet}][TOA^+]$ and $[H_2Pc^{-\bullet}][TOA^+]C_6H_4Cl_2$ salts (H_2Pc is phthalocyanine) demonstrated the presence of a large number of short C–H···π-contacts,[16,17] which confirmed the assumption of formation of a microheterogeneous environment around fullerene or phthalocyanine molecules in the films of hydrophobic ammonium cations — artificial cationic surfactants — and the crucial role of this environment in the reversible reduction of, for example, fullerene in aqueous solutions. These studies have drawn our attention to solubilization of phthalocyanines, including crown-substituted ones,[18] and to gelation involving these compounds in the presence of surfactants in aqueous media.

In recent years, the interest in the self-organization of small molecules has markedly enhanced. Supramolecular gels based on small molecules have a number of advantages. Apart from amphiphilicity of molecules and participation of non-covalent interactions in the gelation (like in biological structures), they are characterized by accessibility, high purity, known chemical structure, biocompatibility of the initial components and easy gelation.[19–24] The gels that combine polymers and low-molecular-mass gelators and are promising for the manufacture of high-tech materials are considered in a review of Cornwell and Smith.[25]

Molecular gels are prepared from compounds the molecules of which are able to form numerous hydrogen bonds. Examples of such compounds are amino acids and their derivatives,[26,27] sugars[28] and peptides.[29,30]

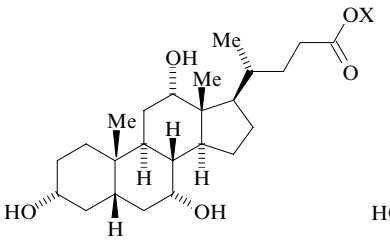
Steroid derivatives have been thoroughly studied from this point of view: bile (cholic) acids and their salts, most often, sodium deoxycholate (SDC), function as components of low-molecular-mass gels.[31–34] Salts of bile acids are physiologically essential compounds. Human bile contains so-called pair bile acids: glycocholic, glycodeoxycholic, glycochenodeoxycholic, taurocholic, taurodeoxycholic and taurochenodeoxycholic acids — conjugates of cholic, deoxycholic and chenodeoxycholic acids with glycine and taurine (the structures of bile acids and the corresponding Na salts are presented below). They are synthesized in liver from cholesterol, thus regulating simultaneously its degradation rate, and participate in digestion of food by solubilizing food lipids, fatty acids, fat-soluble vitamins and so on.[35] The presence of numerous reviews and monographs devoted to bile acids and bile salts (see, for example, Refs 33, 36–40) attest to high importance of these studies.

The present review deals with the properties of bile salts (BS), first of all, sodium deoxycholate, the formation of biocompatible hydrogels, the ability of gels to accumulate active substances (guest molecules) and release them upon external stimulus. The review mainly covers recent publications devoted to bile salts. Particular attention is paid to the ability of macrocyclic compounds for example, crown-substituted phthalocyanines, to be solubilized by bile salts in aqueous media and to act as active components of SDC-based hydrogels.

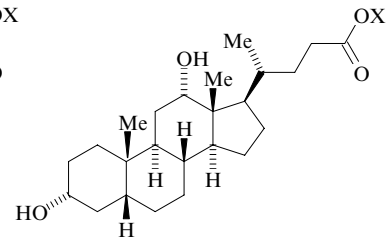
II. Formation of supramolecular hydrogels and methods used for their investigation

Supramolecular gels based on small molecules (molecular mass < 3000 Da) are materials that immobilize numerous solvent molecules, including water molecules, in their network structure. When the content of water is below 97%, the hydrogel state, rheological properties and response to external stimuli are similar to those for polymer gels.[41] Surfactant-based microheterogeneous systems are colloid solutions that can also be considered as 'weak' gels because of their organization (see a review[42] and references cited therein). They are characterized by rather high concentra-

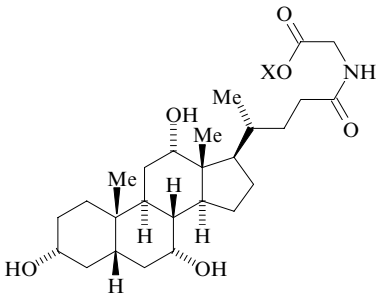
Structures of bile acids



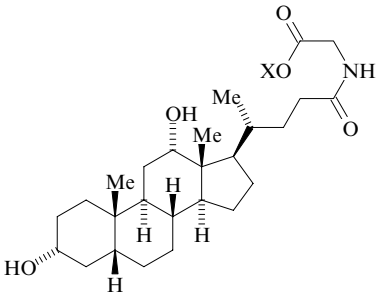
X = H (cholic acid, CA);
X = Na (sodium cholate, SC)



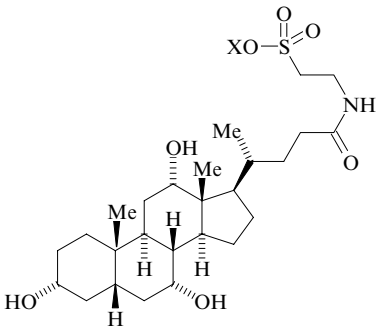
X = H (deoxycholic acid, DCA);
X = Na (sodium deoxycholate, SDC)



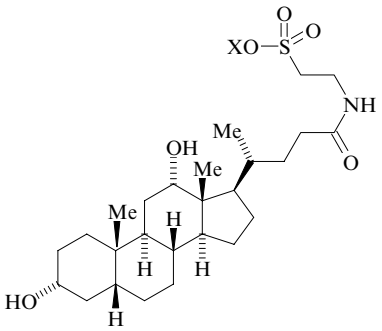
X = H (glycocholic acid, GCA);
X = Na (sodium glycocholate, SGC)



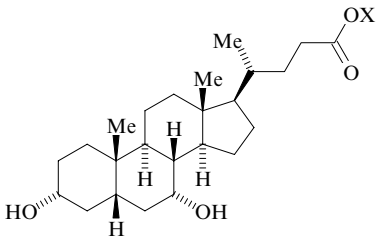
X = H (glycodeoxycholic acid, GDCA);
X = Na (sodium glycodeoxycholate SGDC)



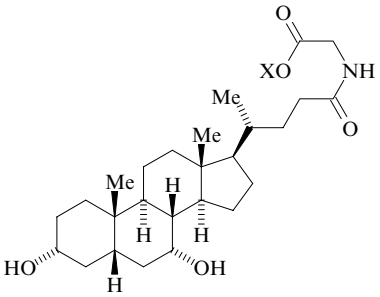
X = H (taurocholic acid, TCA);
X = Na (sodium taurocholate STC)



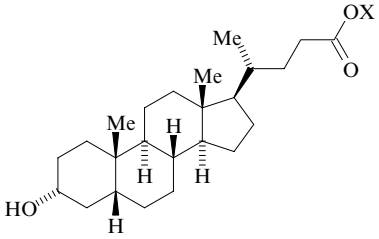
X = H (taurodeoxycholic acid, TDCA);
X = Na (sodium taurodeoxycholate, STDC)



X = H (chenodeoxycholic acid, CDCA);
X = Na (sodium chenodeoxycholate, SCDC)



X = H (glycochenodeoxycholic acid, GCDCA);
X = Na (sodium glycochenodeoxycholate, SGCDC)



X = H (lithocholic acid, LCA);
X = Na (sodium lithocholate, SLC)

tions of the gelator and sensitivity to additives, in particular, salts. The introduction of a chromophore or molecular receptor into the gelator molecule ensures the gel variability under the action of irradiation or chemicals.

II.1. Preparation of supramolecular hydrogels

Low-molecular-mass gels consist of small gelator molecules, which are self-assembled to nano- and micro-sized structures. Gel is a two-component colloid dispersion with a continuous macroscopic-size structure. The structure remains stable on the experimental time scale and possesses definite rheological properties (see Ref. 3 and references cited therein). The hydrogel formation takes place under conditions of equilibrium between dissolution and precipitation of the gelator in the aqueous medium. In terms of the degree of molecular ordering, the gel is an intermediate, most often, metastable state. The thermal reversibility of solution – gel transitions and the equilibria that accompany them govern both the size of aggregated particles and the binding of particles in the gel network. Three organization levels of the gel structure are distinguished: primary (molecular level), secondary (nanolevel, 10 – 1000 nm particle size) and tertiary (macrolevel, 1 – 1000 μm) ones. The tertiary structure determines the final stage of the process — gelation or phase separation with precipitation.[3,8]

If the gelator contains a carboxyl or amino group, a change in the pH is the most popular type of stimulus used to regulate the degree of ionization of the compound in water and to control the solution – gel and gel – solution transitions. For example, the process of gelation involving bile salts is affected by pH of the solution. A temperature change and ultrasonication are the physical methods of treatment of supramolecular assemblies stimulating the gelation.[43,44] A gel can also be formed upon irradiation.[45] In the case of two-component systems, the gelation is determined by the natures of the gelator and solvent molecules.[46] A review is devoted to the benefits and shortcomings of the gelation process in multicomponent systems.[47]

Gels respond to external physical and chemical stimuli. Many gels are thixotropic, *i.e.*, their state varies from an elastic solid to an easy-flowing liquid, depending on the applied load and the time of its action. After removal of the load, the gel shape and mechanical strength are usually restored. The effect of chemicals, including acids, bases, redox-active compounds, *etc.* on molecular gels has been analyzed in a review.[48]

II.2. Methods of investigation of supramolecular hydrogels

Visualization. A simple indication of the formation of a hydrogel is invariability of the shape upon turning the reaction vessel upside down.[49]

Rheology. The macroscopic (rheological and thermodynamic) properties of the gels are studied by means of rheometry and differential scanning calorimetry (DSC). Differential scanning calorimetry is used to determine the gelation temperature (T_{gel}), which corresponds to disruption of intermolecular contacts or complete rearrangement of the hydrogel on heating of the sample. One more important parameter is the heat of phase transition. Rheology provides information about the type of the gel network (tertiary structure), which is responsible for gel formation.

Microscopy. Various types of microscopy can be used to study the morphology of the supramolecular hydrogel matrix, namely, the nano- and microstructures forming the matrix. Atomic force microscopy (AFM) provides an image of a hydrogel sample, including *in situ*, *i.e.*, without dehydration.[50, 51] Transmission and scanning electron microscopy (TEM and SEM, respectively) can be used to study, with a nanometre resolution, characteristic features of the sample and morphology of aggregates that form the hydrogel. The low-temperature procedures for sample examination (cryo-TEM) developed in biology eliminate many experimental difficulties and can be used to study the hydrogel in its natural state. As an example, Fig. 2 presents the SEM image of the sodium deoxycholate – NaCl – amino acid hydrogel; Figures *a* and *b* show the effect of component concentrations on the gel morphology.[34]

Small-angle X-ray (and neutron) scattering. Small-angle neutron scattering (SANS) and small-angle X-ray scattering (SAXS), which are similar to TEM in the resolution, provide averaged information about the supramolecular hydrogel matrix without changing its physical state. Small-angle scattering is a potent method used to determine the size and shape of nanoparticles suspended in the solution.[52, 53] In some cases, for example, in the presence of a crystalline phase, X-ray crystallography is used.

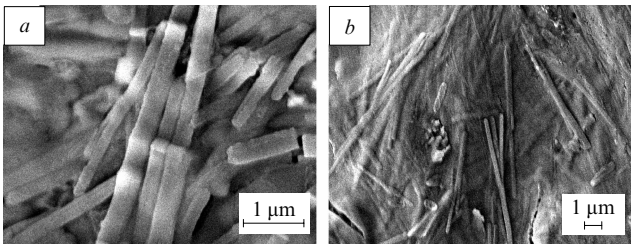


Figure 2. SEM images of the nanorods formed upon self-assembly in the systems: 50 mmol litre^{-1} SDC – 30 mmol litre^{-1} alanine – 100 mmol litre^{-1} NaCl (*a*) and 50 mmol litre^{-1} SDC – 50 mmol litre^{-1} alanine – 100 mmol litre^{-1} NaCl (*b*).[34]

Spectroscopy. Many gels exhibit characteristic absorption and luminescence properties sensitive to changes in the physical state.[54] Optical (UV/Vis electronic spectroscopy, IR spectroscopy and fluorescence) and magnetic (NMR spectroscopy) methods provide information about the molecular organization of a hydrogel, including intermolecular interactions in its primary and secondary structures. These methods are also demanded in the studies of supramolecular hydrogels with an encapsulated active component.[55] Detailed considerations of methods used to study small-molecule gels can be found in the literature.[3, 56]

III. Bile acids and bile salts: structural features and surfactant properties

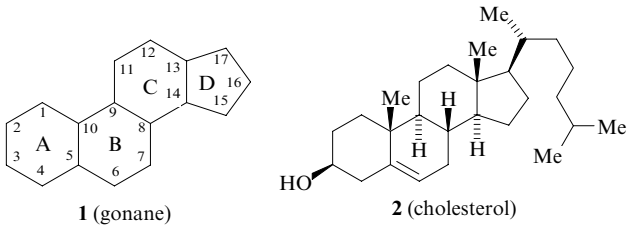
III.1. Characteristics of bile salts

Bile salts are natural anionic surfactants with strongly pronounced features. An important characteristics of BS is the ability to form micelles in aqueous solutions. The vitally important biologcal functions of BS are observed at concentrations above the critical micelle concentration (CMC), which depends on the structure of molecules, pH and ionic strength of the solution, temperature and so on. These factors affect the micellar parameters of different BS in different ways.

Traditional surfactants, *e.g.*, sodium dodecyl sulfate (SDS), are molecules with well-defined hydrophilic and lipophilic groups — relatively small polar head and long (alkyl or alkylaromatic) flexible tail. They possess high values of the hydrophilic-lipophilic balance (HLB);† this is related to their structure, which is responsible for the packing of molecules into spherical micelles (Fig. 3).[57]

Bile acid molecules have a rigid, slightly bent sterane backbone. The steroid structure is based on the gonane core (cyclopentaneperhydrophenanthrene, **1**) consisting of three non-linearly fused cyclohexane moieties (A, B and C) and one cyclopentane moiety (D).

Structures 1, 2



1 (gonane) **2** (cholesterol)

In the cholesterol molecule (**2**), the rings are in the *trans*-configuration and the C(5) and C(6) atoms of ring B are connected by a double bond. The cholesterol molecule contains a hydroxyl group in position 3 and an alkyl chain in position 17. Unlike cholesterol, in bile acid molecules, rings A and B are *cis*-fused. The orientations of the OH group at the C(3) atom in bile acid and cholesterol molecules correspond to the α and β sides, respectively.

† The HLBs for all known surfactants in Griffin's scale range from 1 to 40. Ten is the approximate border between the lipophilic and hydrophilic surfactants. The HLB of the most hydrophilic surfactant, sodium dodecyl sulfate, is 40.

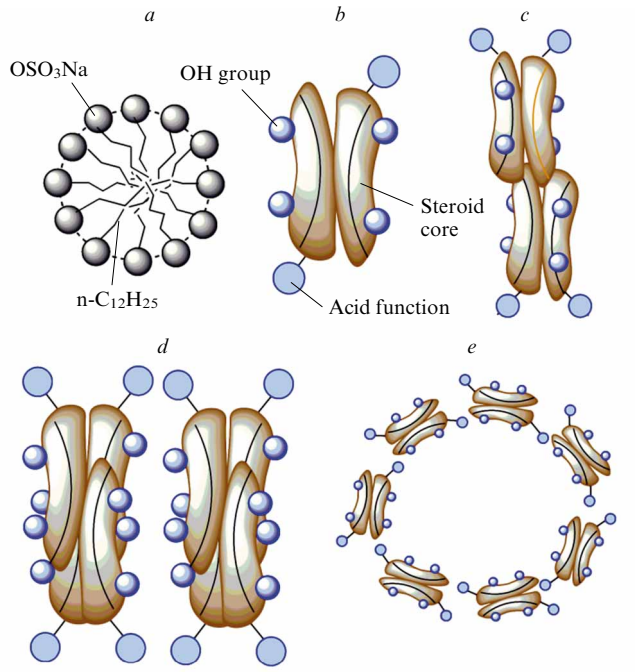


Figure 3. Schematic view of the sodium dodecyl sulfate micelle (*a*) and sodium deoxycholate (micelle) aggregates: primary (*b*, *c*) and secondary (*d*, *e*; helical, top view) structures.[32]

The hydrophilic α-side of the BS‡ core bears the hydroxyl groups and a carboxyl group attached to the core by a short alkyl spacer (for SDC and SC) or a sulfo group in the case of conjugation with taurine *via* a peptide bond (TSDC and STC). The number, positions and stereochemistry of the hydroxyl groups in human BS molecules differ, but all of the salts, similarly to the cholesterol molecule, contain a hydroxyl group in position 3. The hydrophobic β-side bears methyl groups.

Figure 4 shows the spatial structure of the cholic acid molecule (see Ref. 58 and references cited therein). The hydroxyl group at the C(3) atom and the side-chain carboxyl group correspond to the head and the tail of the molecule. The distance between them (the length of the cholic acid molecule) is 20 – 21 Å, while the distance between the α- and β-sides (core thickness) is about 3.5 – 4.0 Å. The hydroxyl groups in positions 7 and 12 are located on the left and right sides of the molecule, respectively. The hydroxyl group at C(3) is closer to the OH group in position 7 than to that in position 12. The methyl groups and the side chain are mainly located on the right side. Owing to asymmetry and multiple non-covalent interactions, including hydrogen bonds, between the OH groups of different molecules, crystalline bile salts, like proteins, form hierarchical structures — primary, secondary and tertiary ones and the host – guest type assemblies. The chiral selectivity of BS is important for the molecular host – guest recognition. The difference between the enthalpies of binding of enantiomers by SC micelles corresponds to the chiral

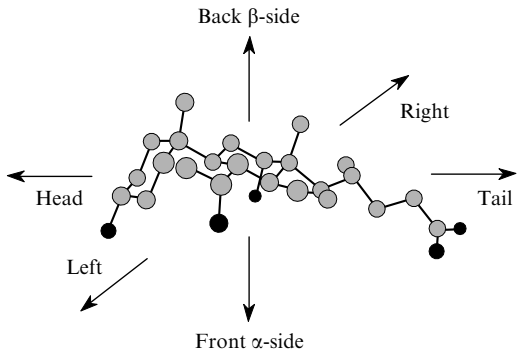


Figure 4. Spatial structure of the cholic acid molecule with three indicated directions: head – tail, left – right, front (concave) α-side – back (convex) β-side.[58]

selectivity. For example, in the case of racemic (*R,S*)-1,1′-bi(2-naphthol), this difference is ~1 kJ mol^{-1}.[59]

The hydrophilic and hydrophobic parts of BS molecules are rather weakly discriminated.[32, 34, 60, 61] The notion of 'planar diphilicity' was introduced to describe the amphiphilic properties of these compounds. Owing to their amphiphilic nature, bile salts are considered in terms of views, notions and approaches developed for micelle-forming surfactants. The BS molecules have HLB values of 14 – 16 (*e.g.*, for SDC it is 16), which is close to the lower HLB limit for micelle-forming surfactants.[62] As a result of their diphilic nature, BS are self-assembled in aqueous solutions to give micelles, the structures of which differ from those of micelles formed by traditional surfactants (see Fig. 3 *b* – *d*). The micellization of BS depends on the hydrophobic effect (hydrophobic surface minimization) and hydrogen bonds, which are determined by the number, position and orientation of hydroxyl groups. The backbone rigidity and positions of OH groups dictate the direction of hydrogen bonds. The number of hydroxyl groups influences the hydrophobic properties of molecules and, hence, the CMC values. For example, cholic acid micelles (three OH groups) are formed at the concentration of 15 mmol litre^{-1}; in the case of deoxycholic, chenodeoxycholic or ursodeoxycholic acids (two OH groups), they are formed at 5 – 10 mmol litre^{-1}, while for lithocholic acid (one OH group), this concentration is as low as 2 – 3 mmol litre^{-1}.[63, 64] The CMC values for salts with two hydroxyls in the molecule (SDC and TSDC) are lower than those for trihydroxy acid salts (SC and STC); this confirms higher hydrophobicity of dihydroxy acid salts.[65] For equal numbers of OH groups in the BS molecule, the critical micelle concentrations are lower for taurine conjugates than for salts containing a carboxylate ion; this may be due to differences in the bulk characteristics of polar groups. The presence of a hydrophobic substituent affects the CMC values of BS derivatives. For example, for the photoactive cholic acid salts§ the CMC in water decreases by 2 – 3 orders of magnitude compared to the value for the compound devoid of such substituent.[64]

‡ The hydrophilic face or only the hydrophilic 'edge' depending on the orientation and positions of hydroxyl groups.

§ The substituent is in the β(3) position, which increases the hydrophobicity of the molecule.

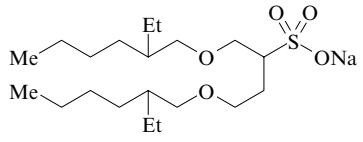
Some BS characteristics resemble the behaviour of classic surfactants, while other properties are more similar to the properties of, in particular, low-molecular-mass gelators. The differences between the traditional surfactants and bile salts are that the self-assembly of amphiphilic BS molecules in aqueous medium affords supramolecular structures of different size ranging from small (micelles) to large (nanofibres, nanotubes and nanoribbons). For example, lithocholic acid molecules are self-assembled as nanotubes and helical nanoribbons.[66] The ionic strength and pH have an influence on the formation of particular sorts of particles. Small-angle X-ray scattering was invoked to characterize the morphological details of fresh and aged systems — to detect the transition from nanoribbons to nanotubes during aging.

The formation of hydrogels based on BS has been known since rather long ago.[67–71] The number of OH groups in the BS molecules determines their hydrophobicity and, hence, the tendency for gelation. The sodium lithocholate gel is formed in water even at pH 12.0.[66] Gelation of sodium deoxycholate takes place in the vicinity of physiological pH; and no gelation occurs for sodium cholate.[72]

III.2. Sodium deoxycholate

Sodium deoxycholate — a biocompatible, biodegradable and non-toxic compound — occupies a special place among bile salts, because its molecules can spontaneously form gels in water. Metal or anionic surfactant ions, for example, sodium bis(2-ethylhexyl)succinate (Na-AOT, **3**) are involved in the formation of BS-based supramolecular aggregates.[73, 74]

Structure 3



3 (Na-AOT)

In the case of a traditional micelle-forming synthetic surfactant, sodium dodecyl sulfate, a cooperative transition takes place at the CMC, that is, micelles of virtually equal size are formed from free molecules. Unlike SDS, in the case of SDC, the average micelle size increases monotonically with increasing its overall concentration. This behaviour of SDC molecules results in pronounced differences in the micellar parameters, in particular, CMC, determined with the use of invasive and non-invasive methods¶ or with the use of one and the same method by different research teams (see, for example, papers[32, 63, 75] and references cited therein). Furthermore, because of the small size of micelles, the analytical purity of the salts is of great importance for determination of micellar parameters.

Sodium deoxychlolate micelles are characterized by smaller aggregation numbers (N_{agg}) and greater polydispersity than SDS micelles. The average N_{agg} value is 2–5 molecules up to SDC concentration of ~50 mmol litre^{-1}. When [SDC] > 0.1 mol litre^{-1}, N_{agg} can be as high as 20.[76] The hydrodynamic radii (R_h) of sodium deoxycholate micelles calculated by the Stokes–Einstein equation from NMR diffusometry data lie in the range of 0.75–2.5 nm for the sodium deoxycholate concentration range of 10–100 mmol litre^{-1} (Ref. 75). An increase in the ionic strength (addition of NaCl) decreases the CMC of sodium deoxycholate: when the NaCl concentration is 0.1 mol litre^{-1}, the critical micelle concentration of SDC is 1.18 mmol litre^{-1} (Ref. 77). For SDC, the micelle formation and the change in the micelle shape (CMC_1 and CMC_2) occur in a buffer solution at salt concentrations of 10 and 50 mmol litre^{-1}, respectively. Some parameters of SDC and SDS micelles are given in Table 1.

Table 1. Critical micelle concentrations, hydrodynamic radii and aggregation numbers for sodium deoxycholate and sodium dodecyl sulfate micelles at 298 K.

Surfactant	CMC /mmol litre^{-1}		R_h /nm	N_{agg}	Ref.
	–	NaCl (0.1 M)			
SDC	2.4 [a]	–	~0.7 [b]	2–5 [c]	76, 78, 79
	2.34 [d]	–		11 [e]	77, 78
	2.04 [a]	1.18		9 [e]	77, 80
	4.1			15 [f]	81, 82
SDS	7.75 [g]	1.2	1.7	60–70	83–86

Note. CMC determination methods: [a] from fluorescence of pyrene in aqueous solution; [d] from surface tension; [g] from electrical conductivity. R_h and N_{agg} determination methods [b] quasielastic light scattering, aqueous solution (308 K, pH 8.3, [SDC] = 0.1 mol litre^{-1}): ~0.7 and 2 nm (mean standard deviation: ±0.04 nm) for [NaCl] = 0 and 0.2 mol litre^{-1}, respectively; [c] calculation; [f] small-angle neutron scattering, [SDC] = 0.1 mol litre^{-1}; [e] at 308.2 K.

For the reasons mentioned above, accurate determination of CMC (and differentiation of CMC_1 and CMC_2) appears to be quite a difficult task. Lopez *et al.*[87] found two CMC values in a low-concentration region of SDC. The smaller of the two values, which corresponded to the formation of small primary micelles, was pH- and temperature-independent. The second (greater) value corresponding to the formation of larger aggregates and, in some cases, gelation, was markedly affected by pH and temperature.

III.3. Models of bile salt aggregates in aqueous solution

Several models for self-organization of bile salts in solutions have been proposed. The first one is a two-stage model including micelle formation and change in the micelle shape, which implies the presence of CMC_1 and CMC_2 (see above).[88–90] The first stage comprises the formation of small aggregates near the CMC (for SDC, see Fig. 3 *b*,*c*) *via* the interaction of hydrophobic parts of different molecules. Hence, the hydrophilic parts of the molecules are exposed to the aqueous phase. Apart from organizing the hydrophilic (polar) surface, the hydroxyl and carboxyl groups of BS molecules are involved in the formation of intermolecular hydrogen bonds and thus contribute to micellization of bile salts, together with non-specific hydrophobic interactions. According to this model, further growth of micelles with increasing BS concentration and involvement of hydrogen bonding between the OH groups of micelles in the supramolecular organization give rise to

¶ The non-invasive approach implies the absence of direct intervention into the process being studied. Another group of methods is based on the introduction of additional components into the solutions and their solubilization in surfactant micelles. An example is the determination of CMC of a salt based on pyrene fluorescence in aqueous solution as a function of concentration.

elongated micelles. When the salt concentration is < 30 mmol litre^{-1}, the contribution of hydrogen bonding to the formation of elongated micelles is small.[91] The participation of hydrogen bonds in the formation and stabilization of micelles is a specific feature of BS not inherent in classic surfactants.[92]

The role of hydrophobic interactions and hydrogen bonds in BS micellization is an actively discussed issue (see, for example, Ref. 32 and references cited therein). According to calculations, SDC micelles are formed through hydrophobic interactions, whereas in the case of SC, micelles are formed through both types of interaction.[76,91] The core rigidity can lead to incomplete separation of hydrophilic and hydrophobic domains in the micelles: some hydrophobic parts may be in contact with water, whereas hydrophilic parts may get inside the micelle. According to NMR spectroscopy, in the case of STC and TSDC, at least two structures of dimeric fragments of micelles can exist for each salt (Fig. 5; the characters stand for: A, antiparallel; B, back; F, face and P, parallel).[93]

The major contribution to the shape of STC micelles is made by ABB and PBB structures, whereas for TSDC micelles, these are ABF and PBF structures. This is attributable to the fact that the TSDC molecule is devoid of the OH group in position 7. As a result, the facial side of the TSDC molecule, which is less hydrophilic than that of STC, can contact with the hydrophobic surface of another TSDC molecule *via* hydrophobic interactions. All this attests to an intricate character of processes in micellar solutions of bile salts and, apparently, to different properties of the binding sites of different salts.

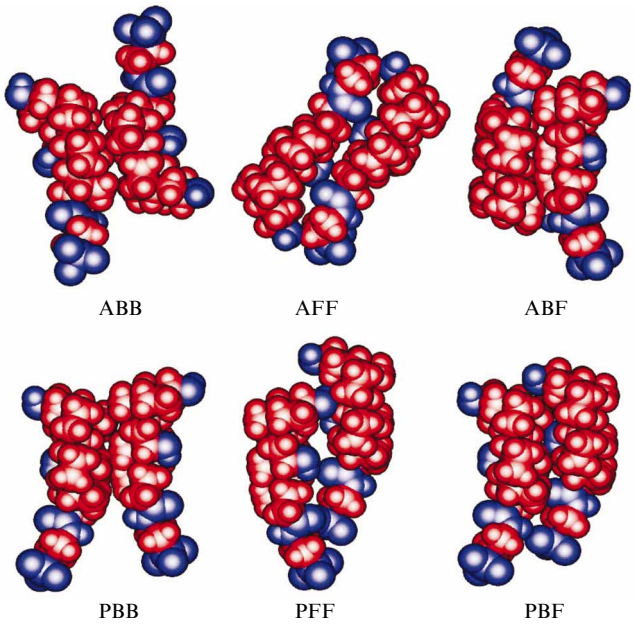


Figure 5. Possible dimeric structures of tauro-conjugated bile salts: ABB (antiparallel back-to-back with hydrophobic sides); AFF (antiparallel face-to-face with hydrophilic sides); ABF (antiparallel back-to-face with hydrophobic and hydrophilic sides); PBB (parallel back-to-back with hydrophobic sides); PFF (parallel face-to-face with hydrophilic sides); PBF (parallel back-to-face with hydrophobic and hydrophilic sides); with the assumption of some flexibility of dimeric fragments.[93]

The molecular and crystal structures of rubidium and sodium deoxycholates have been studied.[94–96] It was found that the salt anions in the crystal form a helix. The inner area of the helix is filled with cations surrounded by water molecules, as in the case of reverse micelles. The ion – ion and ion – dipole interactions, together with a hydrogen bond network, stabilize this helix.

Analysis of the supramolecular assemblies of bile acids and their derivatives by various physicochemical methods (including, in some cases, X-ray crystallography) demonstrated that they have a common hierarchical structure.[58,97] The molecules are arranged along the crystallographic axis to form helical ribbons. The latter form sheets through hydrogen bonding, and the sheets are combined in both parallel and antiparallel fashion through van der Waals forces. This gives rise to a free chiral space (cavities) for the inclusion of guest molecules. Figure 6 shows the formation of a helical ribbon in relation to deoxycholic acid.

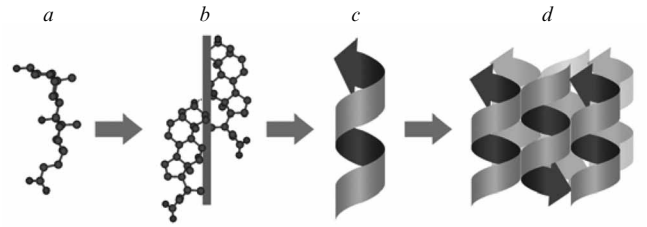


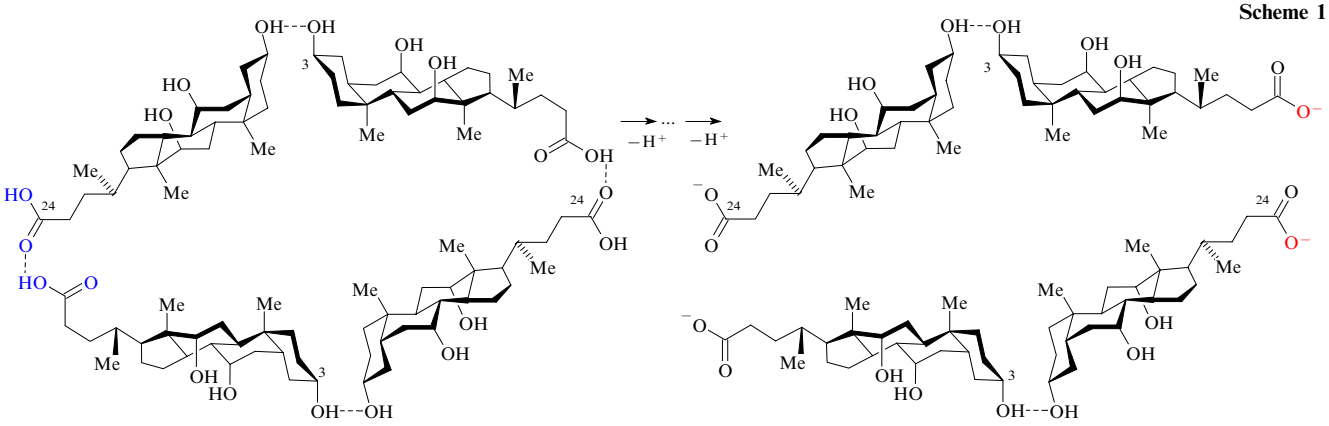
Figure 6. Schematic view of the formation of hierarchical assemblies of deoxycholic acid: chiral molecule (*a*), bimolecular assembly (*b*), right-handed helix along the 2_1 crystallographic axis (*c*), helix bundles as a chiral crystal with space group $P2_12_12_1$ (*d*).[58,97]

The DCA molecules are linked to each other through positions 3 and 12. This gives rise to a bimolecular assembly with rightward rotation and is followed by the formation of a right-handed 2_1-helix. The antiparallel association of the helices through carboxyl groups gives rise to a crystal (space group $P2_12_12_1$) composed of antiparallel bilayers.

Cholic acid tetramers are the major building blocks in the hierarchical CA crystallization process (Scheme 1).[98] The tetramers are self-assembled into stacks, with the hydrophobic and hydrophilic sides of CA molecules facing inwards and outwards, respectively, with subsequent formation of sheets. According to Wang *et al.*,[98] structures of this type can also be formed for SC upon stepwise deprotonation of cholic acid. This would allow the hydrophobic part of the molecule to avoid the contact with aqueous environment, while stacking of mixed SC and CA tetramers giving octamers and so on would yield rod-like micelles.

The model of the helical micelle in solution, which has some limitations,[32] is constructed by analogy with the bile salt structures in the crystal. The effect of the salt and electrolyte (NaCl) concentrations and temperature on the shape, N_{agg} value and average R_h values of SDC micelles was studied by SAXS and EPR spectroscopy.[95] The results were processed in terms of the helical model of SDC micellar aggregates, which implies the formation of a helical ribbon in solution, similar to that present in the SDC crystal structure. The radius of the helix (9 – 12 Å) is consistent with the values of 10 and 10.5 Å found in the SDC crystal and nanofibres, respectively. An increase in the ionic strength of the solution (increase in the NaCl concentration)

Scheme 1

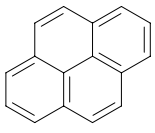


and decrease in the temperature promote the growth of SDC micelles along the helix axis.[95]

An aggregation model — the formation of monodisperse ellipsoid type BS aggregates — was used in a SANS experiment.[99] In the absence of a buffer solution at SC and SDC concentrations of 0.1 mol litre^{-1} ($\gg$ CMC), *i.e.*, when elongated micelles were formed, the spectrum exhibited the correlation peaks at Q = 0.12 and 0.1 Å^{-1} for SC and SDC, respectively. The dimensions of the rod-like SDC micelle were ~31.7 and 8 Å (longer and shorter axes of an elongated ellipsoid, respectively) and the hydrodynamic radius was 16.3 Å.

A widely used procedure for determination of the micellar parameters of BS (CMC, aggregation numbers, degree of counter-ion binding), in particular, SDC, includes investigation of the effect of salt concentration on the emission spectra of pyrene (**4**) (guest molecule).[81] Since the intensity ratio of the first and third vibronic peaks (I_1/I_3) in the emission spectrum of pyrene depends on the polarity of the environment (see Ref. 100 and references cited therein), fluorescence is also a reliable test for the change in the microenvironment (polarity) upon pyrene solubilization in aqueous solutions of SDC. The obtained I_1/I_3 ratios for pyrene in solutions of single bile salts (SC, SDC, STC, TSDC) and their equimolar binary or ternary mixtures indicated that the microenvironment of BS micelle-solubilized pyrene molecules is almost non-polar and resembles a hydrocarbon solvent.[65] The CMC and micellization equilibrium constants (K_{eq}) for SC and SDC ($\ln K_{eq} = 19.9 \pm 1.4$ and 28 ± 3, respectively) attested that micellization was more preferable for SDC than for SC.[101] As the salt concentration increased, micelles grew in one direction corresponding to the ellipsoid longer axis, as has already been noted. Other parameters (shorter axes) remained almost invariable. Charge characteristics showed not only the difference between BS and traditional surfactant micelles, but also specific features of SC or SDC micelles. The cavity accessible for the insertion of guest molecules, in particular, pyrene, proved to be less hydrophobic in SC micelles than in SDC micelles.[100, 101] This behaviour of BS confirms their aggregation mechanism involving hydrophobic interactions.[88]

Structure 4



4 (pyrene)

A molecular dynamics study of six bile salts (SC, SGC, STC, SDC, GSDC and TSDC) has been reported.[102] All calculations were performed for an aqueous solution at 37 °C containing salts in 10 mmol litre^{-1} concentrations in NaCl (120 mmol litre^{-1}), that is, for physiological conditions. The calculated radius of inertia of a micelle was ~1 nm, and the N_{agg} values were in the 5–8 nm range. By dynamic light scattering, the TSDC micelle size was determined for concentrations of 100, 50 and 25 mmol litre^{-1} in an aqueous NaCl solution. Although even with these salt concentrations, the scattered light signal was weak, it occurred in the region corresponding to particle radius of 2 nm, according to the modelling data. As noted above, according to calculations, BS micelles were stabilized by hydrophobic interactions between the lipophilic faces of the molecule. As a result, the core of the micelle resisted the inclusion of water molecules, while BS molecules inside the cluster (micelle) had high mobility. These specific features of BS micelles are responsible for their ability to solubilize hydrophobic compounds *in vivo*.

In mixtures containing water and BS (and some other components if necessary), it is possible to observe several types of supramolecular self-assembly; increase in the salt concentration, temperature change, addition of electrolytes, *etc.*, result in solid substances with large amounts of trapped water, fibres, lyotropic liquid crystals and/or gels.

IV. Hydrogels based on sodium deoxycholate: structure and properties

The mechanism of gelation in aqueous solutions of SDC has been analyzed.[103] It is based on the formation of a three-dimensional network of helical polymer-like SDC aggregates — organized microdomains, the size of which (aggregation number) increases during the process. The curve for SDC aggregation number *vs.* time has an induction period, which disappears upon the introduction of a minor amount of the hydrogel into the solution. During the induction period (first stage), aggregates of the minimum (critical) length needed for the onset of gelation are probably formed. The second stage includes two simultaneous processes: the aggregate growth and their interaction with one another, giving rise to SDC hydrogel in aqueous solution. Thus, three levels of organization of the supramolecular gel can be

observed during gelation: the primary (molecular) level, the secondary (nano) level with the formation of extended fibre-like structures and the tertiary structure of the gel, resulting from interaction of separate nanostructures. When the SDC concentration is 49.3 mmol litre^{-1} and the temperature is 313 K, the R_h values are 397, 1098 and 1310 nm at pH 7.32, 7.13 and 7.00, respectively, *i.e.*, at lower pH, protonated SDC aggregates of a larger size are formed.[96]

As in the case of micellar solutions of SDC, stationary and time-resolved fluorescence spectroscopy with pyrene as the fluorescent probe was used to study the gelation in aqueous solutions of SDC at nearly neutral pH.[100] From comparison of the intensity ratio of pyrene emission peaks in various media (the I_1/I_3 values for water, cyclohexane and SDC-containing gel are 1.96, 0.61 and 0.70, respectively), it follows that solubilized pyrene resides in a non-polar (hydrocarbon) microenvironment. The invariability of this ratio and the characteristic fluorescence decay time (τ_1) indicate that pyrene is located only in SDC aggregates and that no changes took place during the hydrogel formation. The microenvironment of pyrene molecules encapsulated in the SDC gel shields them from water and oxygen; hence, no quenching of the pyrene (guest) fluorescence upon excitation in the aqueous medium is observed. Hence, one deals with formation of a fluorescence-active hydrogel involving SDC.

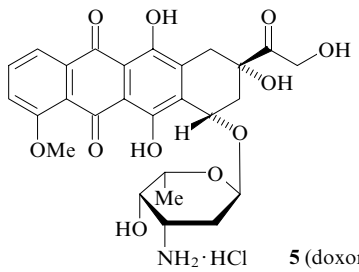
The mechanical strength and viscoelastic properties of the SDC hydrogel are insufficiently high. The introduction of organic or inorganic modifying agents into an SDC hydrogel yields hybrid (composite) hydrogels, which have much higher mechanical and viscous properties.

IV.1. The system sodium deoxycholate – sodium chloride

The self-assembly of SDC in an aqueous solution of NaCl (pH 7) affords a hydrogel with pH-dependent structure,[104] which is in line with the results obtained previously.[69] According to AFM data, SDC hydrogels are formed as three-dimensional networks of worm-like nanofibres and nanofibre bundles (Fig. 7). The diameter of the nanofibres found from the linear profile of the AFM image of the hydrogel is 65 ± 20 nm. The pK_a value of the deoxycholate molecule is about 6.6 – 6.8. The hydrogel formation at pH 7 indicates that hydrogen bonds play an important role in SDC gelation. Using low-coherence dynamic light scattering (LC DLC), the microrheology of the gels was studied in the presence of polystyrene nanoparticles encapsulated in the gel as light-scattering objects. The gel was shown to possess viscoelastic properties. The size of the cavities in the nanofibre network was $\sim$180 nm.

The properties of the SDC hydrogel as a drug delivery vehicle were studied for doxorubicin hydrochloride (DOX, **5**) as the active component.[104]

Structure 5



5 (doxorubicin hydrochloride)

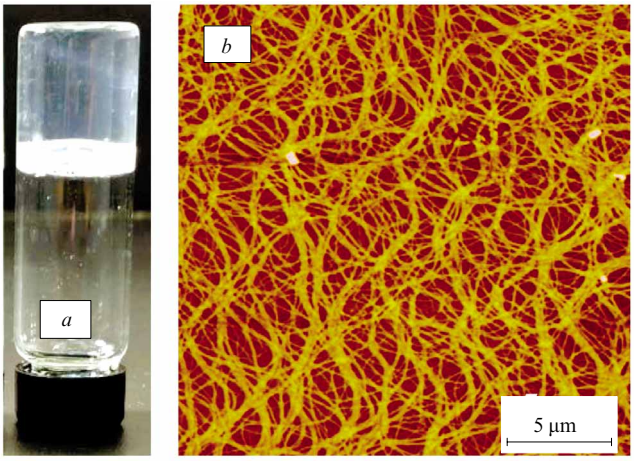


Figure 7. Photographic image of the SDC hydrogel formed at pH 7 (*a*) and AFM image of the surface of dried SDC hydrogel (*b*).[104]

This drug is an anthracycline antibiotic used in the cancer chemotherapy, but characterized by rather low bioavailability.[82] When an aqueous solution of DOX (0.172 mmol litre^{-1}) is applied on the SDC – NaCl hydrogel surface, the gel swells (Figs 8 – 10). The hydrogel swelling ratio depends on the pH (see Fig. 8) and is calculated as

$$(H_t - H_0)/H_0 \qquad (2)$$

where H_0 is the height of the gel before application of the DOX solution and H_t is the height of the swelling gel at a particular point of time. The swollen gel is stable and fluoresces upon UV excitation (see Fig. 8 *c*), which confirms the incorporation of the antitumour agent. The release of DOX from the gel to the aqueous phase is also pH-dependent and rather slow (see Fig. 10).[104]

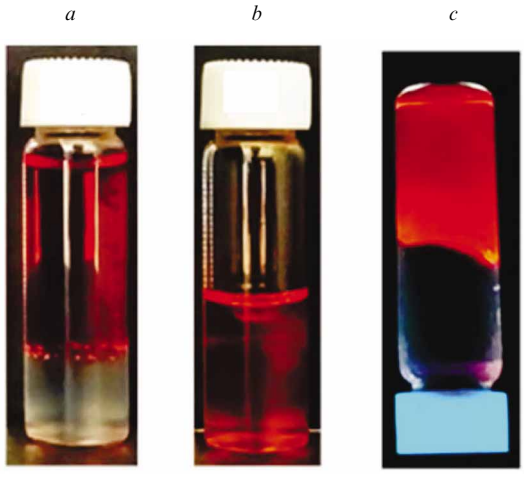


Figure 8. Photographic images of the SDC hydrogel with a DOX solution applied on the gel surface at pH 7 (*a*) or encapsulated into the gel (*b*) and fluorescence of the DOX-containing hydrogel on exposure to UV light after removal of the excess solution from the surface (*c*).[104]

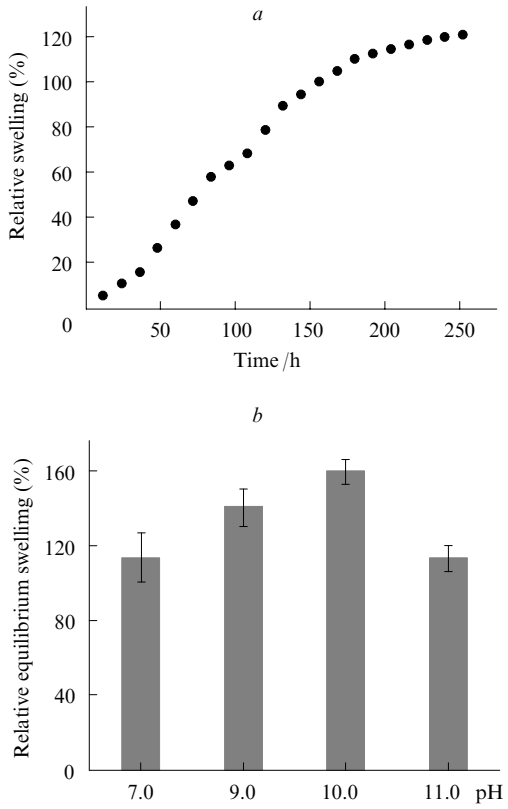


Figure 9. Kinetics of hydrogel swelling upon encapsulation of DOX (room temperature, pH 7) (*a*) and equilibrium swelling of SDC hydrogel *vs.* pH of the solution (*b*).[104]

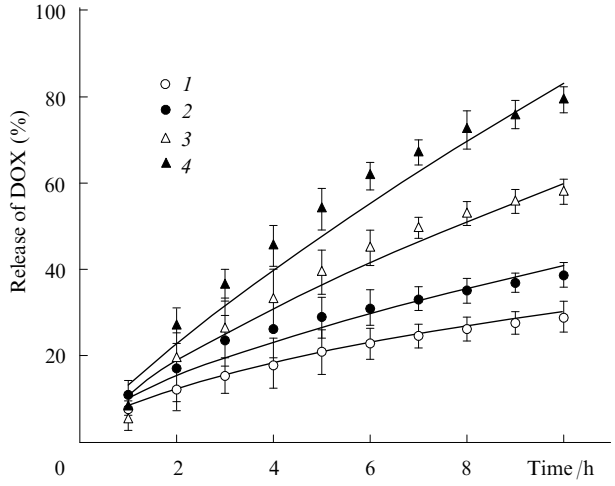


Figure 10. Release of DOX from SDC hydrogel into an aqueous solution at different pH: 7 (*1*), 9 (*2*), 10 (*3*) and 11 (*4*).[104]

IV.2. The systems sodium deoxycholate – sodium halide – amino acid

The phase behaviour and the effect of various types of external stimuli have been studied for supramolecular hydrogels obtained by mixing sodium deoxycholate and amino acids with different isoelectric points (Table 2) in an aqueous medium.[34]

Table 2. Amino acids and their isoelectric points.[105]

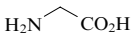
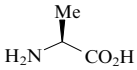
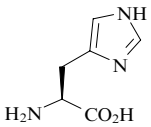
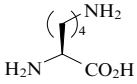
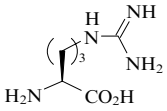
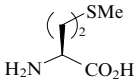
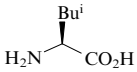
Amino acid	Abbreviation	Formula	pH
Glycine	Gly		6.00
L-Alanine	Ala		6.10
L-Histidine	His		7.60
L-Lysine	Lys		9.74
L-Arginine	Arg		10.70
L-Methionine	Met		5.74
L-Leucine	Leu		6.00

Figure 11 depicts the macroscopic transformations gel – solution – gel for SDC upon the variation of temperature, pH and addition of amino acids and inorganic salts.[34] For example, the SDC hydrogel was formed at room temperature and pH 4.0. [At low pH values given in Fig. 11 *a*,*b*, poorly soluble deoxycholic acid is likely to appear in the sample; the acid has $pK_a = 6.58$, CMC = 0.21 mass % ($\sim$5 mmol litre^{-1}) and water solubility of 0.24 g litre^{-1} at 15 °C; it precipitates from aqueous solution at pH < 5.0.] On heating to 80 °C, the gel dissolved, but cooling the system down to 20 °C induced a reversible solution – gel transition (see Fig. 11 *a*,*b*). The colour of the gel did not change upon the introduction of 10 mmol litre^{-1} arginine (see Fig. 11 *c*), but completely disappeared when the amino acid concentration in the solution was increased to 50 mmol litre^{-1} (see Fig. 11 *d*). Furthermore, the hydrogel colour changed with increasing pH from 4.0 to 6.86 (see Fig. 11 *e*). As pH was increased to 9.18, the gel – solution transition took place (see Fig. 11 *f*). The colourless hydrogel of 50 mmol litre^{-1} SDC – 10 mmol litre^{-1} arginine at pH 6.86 changed colour upon the addition of 100 mmol litre^{-1} NaCl (see Fig. 11 *f*), but no changes took place when the same amount of sodium chloride was added to a transparent solution at pH 9.18 (see Fig. 11 *g*,*h*).

A change in the pH influences the gel formation kinetics, mechanical strength and chemical transformations of various types.[34, 106] As the pH of the solution decreases, the gel strength increases, because neutralization of the carboxylate group (and transformation of some SDC molecules into deoxycholic acid) leads to strengthening of hydrogen bonds and weakening of electrostatic repulsion between the SDC polar groups. The introduction of amino acids and sodium halides has an opposite effect on the gel. In the presence of NaCl or (to a lesser extent) NaBr, supramolecular systems

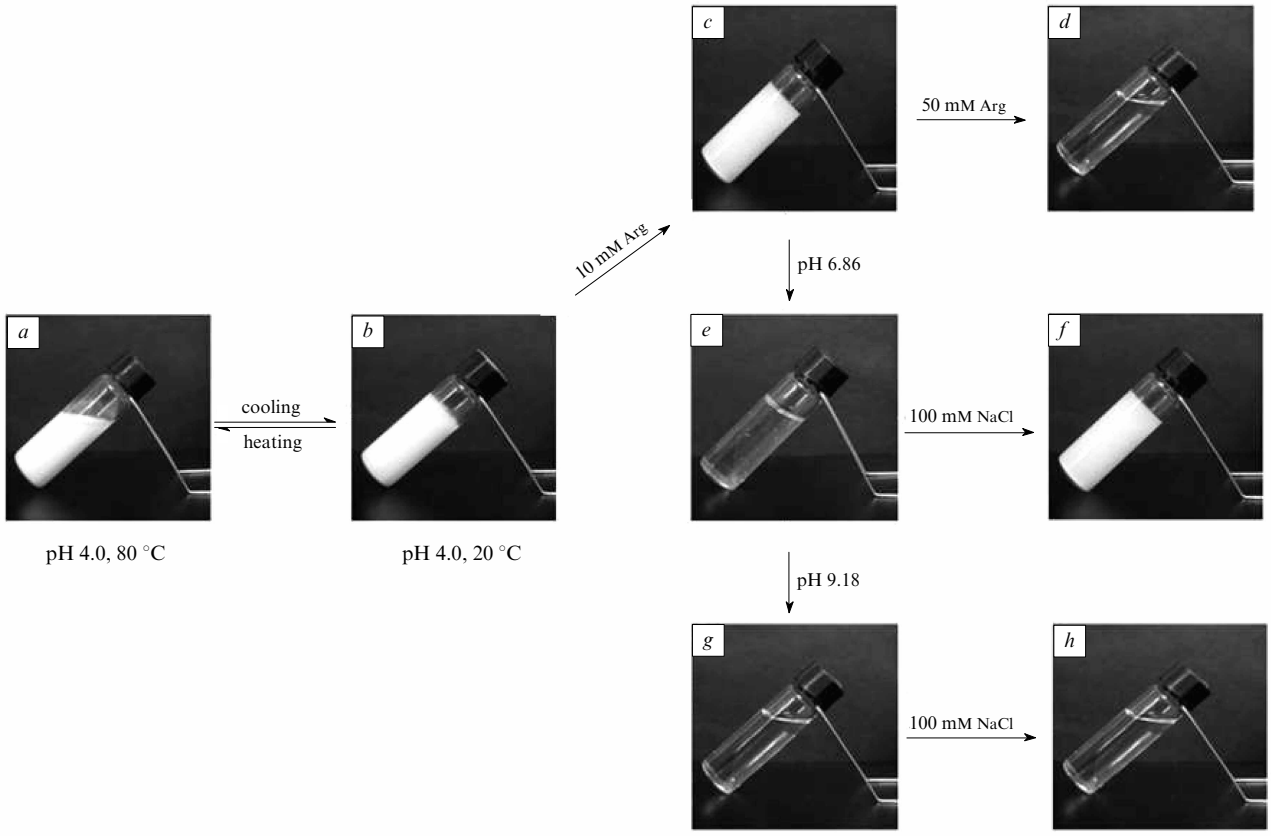


Figure 11. Transformation of supramolecular systems based on SDC in aqueous solution upon the introduction of amino acid and NaCl (see text).[34]

based on SDC are highly prone to gelation and form gels with high mechanical strength at room temperature. The amino acids Gly and Ala facilitate the gelation, while Lys and Arg loosen the gel by increasing the pH and thus promoting hydrogen bond cleavage.[34, 107]

Figure 12 shows the schematic view of strengthening and destruction of the network of SDC-based low-molecular-mass gel. The formation of supramolecular hydrogels is a complicated process determined by the synergism of non-covalent interactions of various types. The sodium ion can play a dual role in SDC gelation. The introduction of the sodium ion decreases the electrostatic repulsion of likely charged polar groups. In addition, the formation of weak coordination bonds between the sodium ion and carboxylate groups of SDC promotes binding of polar CO_2^- groups (according to hydrogen bonding type), thus ordering the arrangement of SDC molecules, which may be favourable for growth of SDC micelles predominantly in one direction to give fibre-like aggregates. This type of supramolecular assembly of SDC in solution was mentioned above in analysis of the TEM, SAXS and SANS data. In relation to amphiphilic dipeptides with aromatic substituents, it was shown (see Ref. 108 and references cited therein) that salts exert a strong influence on the molecular self-assembly in water.

The interaction between SDC and amino acid molecules is determined by at least four factors: electrostatic interaction between the CO_2^- groups of the deoxycholate anion and NH_3^+ groups of amino acid; hydrophobic interaction between the lipophilic groups of SDC (or amino acid and SDC); steric effect manifested upon the contact with the amino acid molecule and rigid steroid SDC molecule; and hydrogen bonding between the deoxycholate OH groups

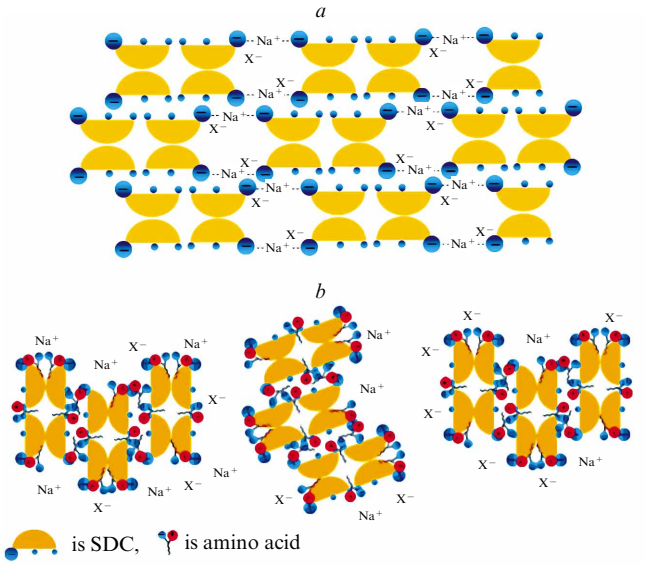


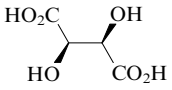
Figure 12. Structure of the SDC–NaX hydrogel (X = Cl, Br) (*a*) and destruction by amino acids (*b*).[107]

and amino acid CO_2^- groups.† Other possible contacts are intramolecular hydrogen bonds between the OH and CO_2^- groups of the deoxycholate anion, intermolecular interaction between the deoxycholate CO_2^- groups and amino acid OH (NH_2) groups, between water and SDC or amino acid molecules and so on.[107] In addition, water clusters in the gel are different in the case of hydrophobic and hydrophilic amino acids containing non-polar and polar side groups, respectively. In the former case, their structure is strengthened and the probability of hydrogen bonding increases, whereas in the latter case, water clusters are destroyed.[109,110] According to the hydropathy index,‡ Arg (−4.5) is more hydrophilic than Lys (−3.5). The introduction of hydrophilic amino acids destroys the water cluster structure and, hence, the SDC-containing gel. The hydrophobic interaction between the hydrophobic groups of Arg and SDC is also weak compared with that for Lys and SDC. These effects may promote the destruction of the SDC gel. The introduction of the amino acid into the gel together with an active component, for example, methylene blue, allows one to monitor the release of the dye.[34] The supramolecular SDC gels possess thixotropic properties, which are important for medical applications.[111]

IV.3. The system sodium deoxycholate – organic acids (including amino acids)

Transparent and turbid gels are formed upon the addition of organic acids, in particular, L-tartaric acid (**6**) (isoelectric point at pH 2), to an aqueous solution of SDC.[112]

Structure 6



6 (L-tartaric acid)

Figure 13 shows the SEM images of the freeze-dried sodium deoxycholate hydrogel obtained in the presence of L-tartaric acid in various concentrations. The gel microstructures representing densely packed nanofibres were detected in all solutions and reached a size of several micrometres. The mechanical strength of hydrogels depended on the pH of the solution. With increasing concentration of components, the density of nanofibres in the sample increased (see Fig. 13 *a*–*c*). When the SDC concentration was 100 mmol litre^{-1} (pH 8.1), SDC gelation took place in the presence of 20 mmol litre^{-1} L-tartaric acid to give a transparent gel. The pH value was neutral (~7.0). The concentration of the acid affected hydrogen bonding between SDC molecules and thus promoted their packing. At high acid concentration, the fibres became short and tough (see Fig. 13 *d*). Hydrogels were destroyed with the formation of a precipitate — poorly soluble

† In the pH range from 4.0 to 9.0, almost all amino acids mainly exist as zwitter-ions with the protonated amino group and dissociated carboxyl group. At physiological pH (7.1–7.4), amino acids (except histidine) do not possess measurable buffer capacity, which appears only at pH values in the vicinity of their p*K* (*i.e.*, pH 1.7–3.2 and 8.6–10.8).

‡ The hydropathy index of amino acids is the number characterizing hydrophobic or hydrophilic properties of the amino acid side chain. The higher this value, the more hydrophobic the amino acid.

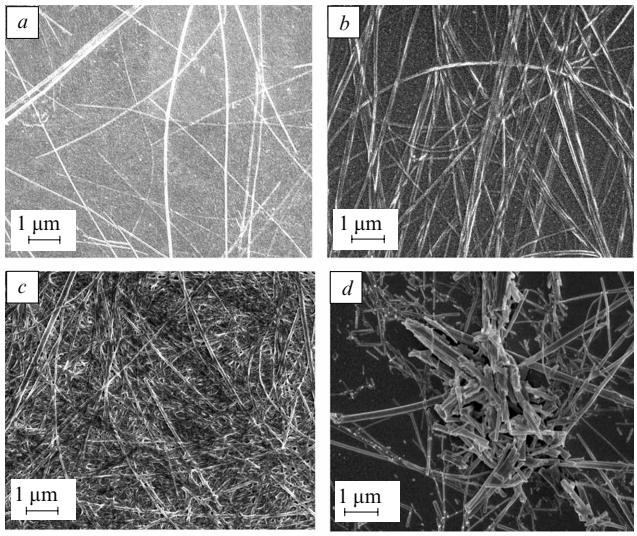
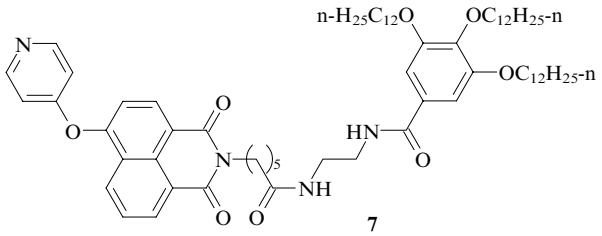


Figure 13. SEM images of nanofibres formed in the system SDC (*n* mmol litre^{-1}) – L-tartaric acid (*m* mmol litre^{-1}) 24 h after mixing: $n = 10$, $m = 1$ (*a*); $n = 100$, $m = 10$ (*b*), $n = 100$, $m = 25$ (*c*); $n = 100$, $m = 30$ (*d*).[112]

deoxycholic acid, most of which was not subsequently involved in the gelation. The IR absorption bands of the hydrogel formed from SDC (100 mmol litre^{-1}) in the presence of various amounts of L-tartaric acid at 1712, 1600 and 1382 cm^{-1} attest to the presence of carboxyl and carboxylate groups and point to the existence of O–H···O hydrogen bonds between the SDC and deoxycholic acid molecules (or SDC and L-tartaric acid molecules). Hydrogels formed from SDC and aspartic, malic, citric and terephthalic acid were also studied.[112]

Cao *et al.*[113] discussed the control of chirality of supramolecular aggregates in organogels based on an achiral gelator, 1,8-naphthalimide **7** derivative, by addition of tartaric acid in polar media.

Structure 7



7

Without affecting the fluorescence activity, tartaric acid changes the layered structure of the gel, thus opening up a simple way to the construction of optically active gels. The formation of SDC-based gel in the presence of organic acids, in particular, L-tartaric acid, includes the formation of sheets involving both components.[112]

Enhanced attention to SDC aggregation in the presence of amino acids is caused by biocompatibility and biodegradability of both components and the influence of amino acids on the mechanical properties of low-molecular-mass gels based on a steroid SDC molecule (see above) — the discovered strengthening or loosening of the gel *in vitro*. The surfactant properties of individual salts, sodium cholate (1–20 mmol kg^{-1}) and sodium deoxycholate

Table 3. Critical micelle concentrations or critical aggregation concentration (CAC) for sodium cholate and deoxycholate in pure water and in aqueous amino acid solution (0.1 mol kg^{-1}) at $T = 298.15$ K and a pressure of 0.1 MPa.[115]

System	CMC /mmol kg^{-1}	
	SC	SDC
Water	14.3 (13.8)	5.6 (5.4)
His	13.8 (13.6)	5.2 (5.0)
Gly	13.6 (13.4)	4.6 (4.4)
Met	13.2 (13.2)	3.9 (3.8)
Leu	12.5 (12.8)	3.5 (3.4)

Note. The data were obtained by UV spectrophotometry (with pyrene as the fluorescent probe) and by the surface tension method (in parentheses).

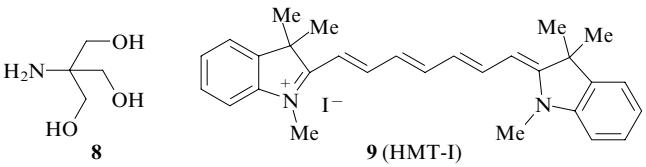
(0.5–10 mmol kg^{-1}), in aqueous solutions of glycine, leucine, methionine and histidine (0.1 mmol kg^{-1}) in the temperature range of 293.15–318.15 K were investigated by measuring the electrical conductivity and by fluorescence spectroscopy (most sensitive to surfactant micellization).[114] The thermodynamic parameters of micellization of bile acid salts were calculated, including the standard Gibbs energy ($\Delta_{mic}G^{\circ}$), the standard enthalpy ($\Delta_{mic}H^{\circ}$) and the standard entropy ($\Delta_{mic}S^{\circ}$). The micellization of bile salts is stepwise also in aqueous amino acid solutions. The CMC values for sodium cholate and deoxycholate decrease in the presence of amino acids in comparison with those in pure water, *i.e.*, amino acids decrease the BS hydrophilicity according to the series His > Gly > Met > Leu (Table 3), *i.e.*, leucine is the most hydrophobic. The addition of amino acids to solutions of SDC containing pyrene as the guest molecule leads to lower critical aggregation concentrations of SDC, lower micropolarity and higher N_{agg}. This also attests to more hydrophobic environment for pyrene solubilized in SDC–amino acid micelles as compared with the environment in SDC micelles. The amino acids Arg and His affect the micellar parameters to a lesser extent than Lys.[116]

As the water molecules are replaced by amino acid molecules, the characteristic size of the hydration shell around the surfactant ionic groups may decrease. Shielding of the negatively charged CO_2^- groups of the deoxycholate anion decreases their repulsion.[117] In addition, as has already been noted, water clusters around the hydrophobic part of the surfactant monomer are destroyed in the presence of amino acid, which also increases the hydrophobicity of salts. Leucine solubilized in micellar solutions of BS stabilizes micelles to a higher extent, which results in the lowest CMC values for the presence of leucine in the series of amino acids. This effect is more pronounced for SDC than for sodium cholate, because the former contains less OH groups.[114] The putative order of formation of primary and secondary SDC aggregates and their binding to amino acids are shown in Fig. 14.

IV.4. The systems sodium deoxycholate – miscellaneous modification agents

The increase in the mechanical strength of the SDC hydrogel can be achieved and the spectral characteristics of fluorescent organic nanoparticles encapsulated in the gel can be changed also by adding another modifying additive: tris(hydroxymethyl)aminomethane (TRIS, **8**).[118–120] The organic salt [HMT][AOT], which is prepared from the cyanine dye, 1,1′,3,3,3′,3′-hexamethylindotricarbocyanine iodide (HMT-I, **9**), and the anionic surfactant, sodium bis(2-ethylhexyl)succinate, is added to the gel as the active component.

Structures 8, 9



8 **9** (HMT-I)

When the concentration of SDC is relatively low, the crystallinity and the mechanical strength of the hydrogel increase with increasing TRIS concentration (Fig. 15). Indeed, sample A existed as a soft gel with high fluidity. The strength of the gel increased in the series

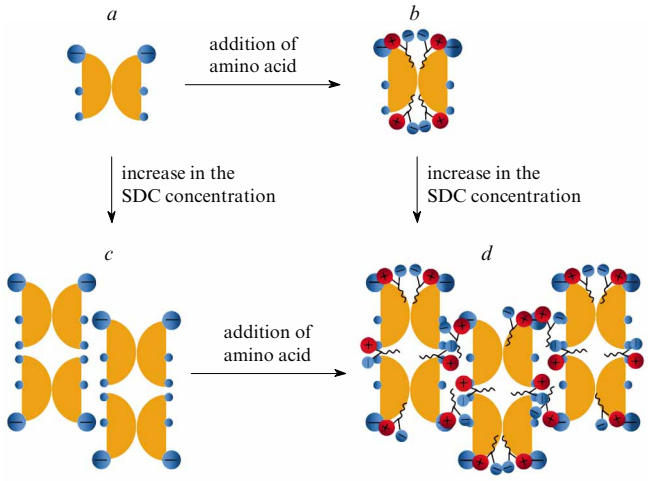


Figure 14. Aggregation of SDC in aqueous solution: SDC dimers (*a*); SDC dimers in the presence of amino acids (*b*); secondary SDC aggregates (*c*); SDC aggregates in the presence of amino acids (*d*).[116] Water molecules are not shown.

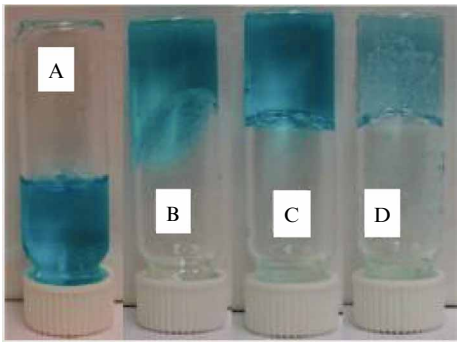


Figure 15. Physical state of sodium deoxycholate (20 mmol $litre^{-1}$) in water at various TRIS concentrations, mmol $litre^{-1}$: 25 (A), 100 (B), 250 (C) and 500 (D).[118]
The colour of the gel is caused by the presence of [HMT][AOT].

A ≪ B < C < D. In addition, a change in the pH [the gelator exists as the neutral or charged form or a mixture of both forms above, below or around pK_a (6.8 for SDC), respectively] affects the gel–solution transition temperature and the crystallinity and strength of the hydrogel.[119]

The hydrogel microstructures that can be adjusted upon the change in the conditions serve as templates for the synthesis of nanoparticles.[121] The [HMT][AOT] nanoparticles with the absorption spectrum in the near-IR region formed in the TRIS-modified SDC hydrogel are about 70–200 nm in size and have rather low polydispersity. A typical feature of nanoparticles is the sensitivity of their spectral characteristics to the microenvironment. The absorption spectra of the [HMT][AOT] salt in the gels are presented as the sum of Gaussian components (curve *1* in Fig. 16), which correspond to three types of aggregates, namely, J-, H- and randomly oriented aggregates (curves *2*, *3* and *4* in Fig. 16, respectively). The J-aggregates formed upon the dipole head-to-tail stacking are responsible for a relatively narrow, bathochromically shifted absorption band (see Fig. 16 *a*) and relatively high fluorescence intensity (Fig. 17). Conversely, H-aggregates are formed upon parallel stacking of dipoles. Their absorption band is broadened and shifted to higher frequencies (hypsochromic shift, see Fig. 16 *a*). As the TRIS concentration increases, the proportion of H-dimers in the absorption spectrum of the [HMT][AOT] salt rises and fluorescence virtually disappears, in conformity with the exciton theory[122] (see Figs 16 *b*; 17).

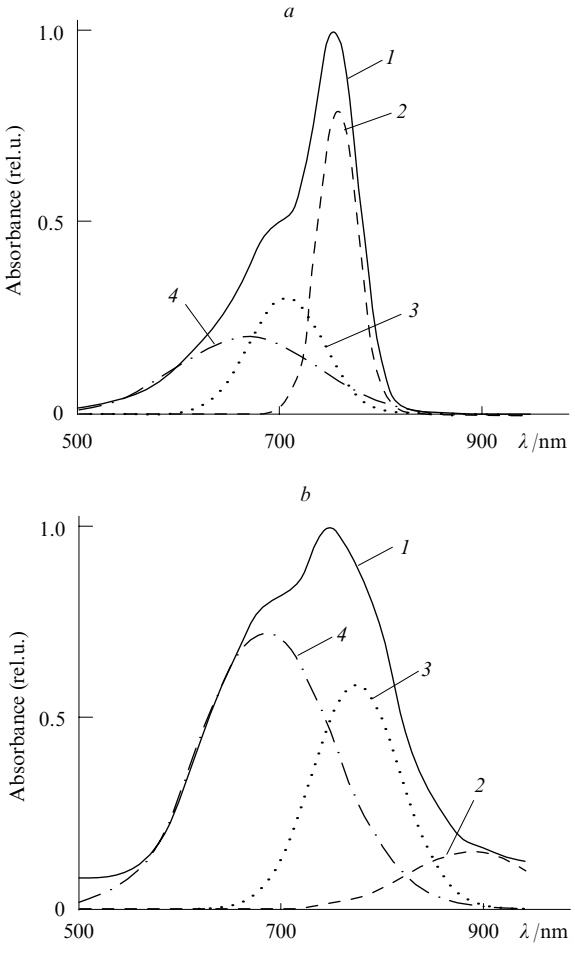


Figure 16. Absorption spectra of the [HMT][AOT] nanoparticles in the TRIS-modified SDC hydrogels that are shown in Fig. 15: in gel A (*a*) and gel D (*b*).[118]
For explanations, see the text.

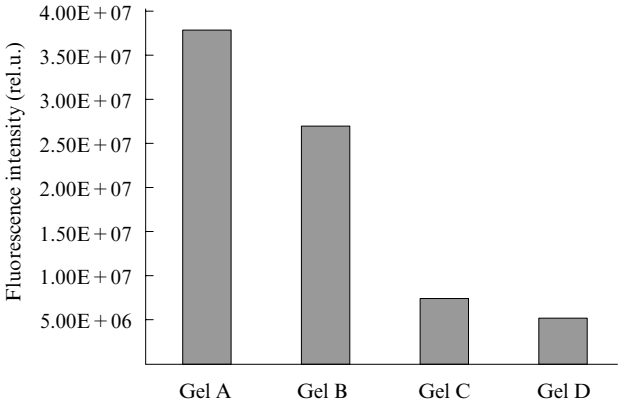


Figure 17. Fluorescence intensity in the absorption maximum of [HMT][AOT] nanoparticles in hydrogels A–D (see Fig. 15).[118]

The TRIS concentration also affects the release of model compounds, *e.g.*, fluorescein or bovine serum albumin, from the loaded SDC hydrogel. This is especially obvious in the case of bovine serum albumin, the release rate of which increases with increasing TRIS concentration, sample crystallinity and increase in the cavity (pore) size of the hydrogel.[118]

IV.5. Sodium lithocholate: modification of gelation

Bile acids form gels in the presence of amines.[123] In mixtures of chiral lithocholic acid with ethanolamine (EA), diethanolamine (DEA) or triethanolamine (TEA) in aqueous solution, supramolecular assembly takes place.[124] The ability of LCA–amine systems to form hydrogels is determined by the degree of alkylation of amine (the number of hydroxyalkyl groups at the nitrogen atom). Indeed, lithocholic acid does not dissolve in the presence of TEA, but in DEA–LCA mixtures, the hydrogel is formed at a very low acid concentration (~0.17 mass %, *i.e.*, ~12 000 water molecules are immobilized by one LCA molecule). This is not the lowest achieved critical concentration of a component for gelation,[125] but this is indicative of the super gelation capability of the given system.

The temperature and mechanical stimulation influence the physical state of the DEA–LCA system. According to cryo-TEM data, the gel consisted of nanotubes ~60 nm in diameter combined into a 3D network. With the same reactant concentrations as in the case of DEA–LCA, the EA–LCA system was a birefringent solution, in which transition from spherical vesicles to nanotubes took place with increasing concentration of lithocholic acid. The hydrogel was also formed for the ethyl derivative of the lithocholic acid amide.[126] When lithocholic acid was added to a micellar solution of dodecyldimethylamine oxide (C_{12}DMAO), the solution–gel transition took place at room temperature.[127] As described by Song *et al.*,[124] hydrogels were also formed at very low critical gelator concen-

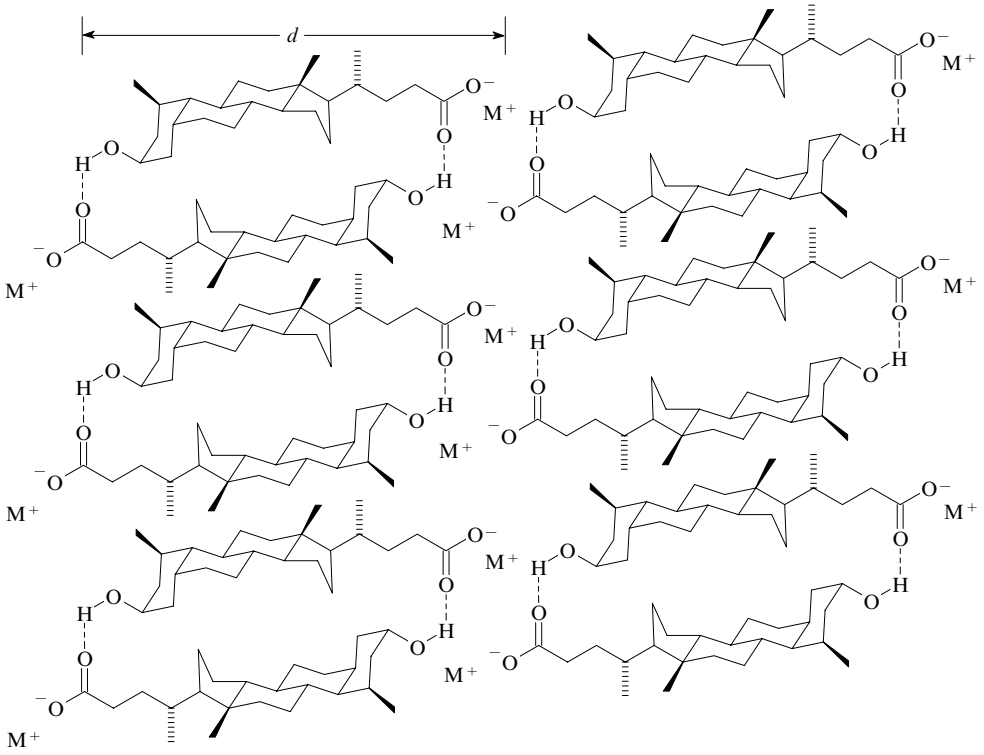


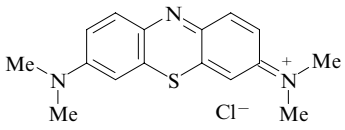
Figure 18. Schematic image of self-assembly of the lithocholate anions with singly charged inorganic cations (M^+).[128]

tration (< 0.1 mass %) and were distinguished by high mechanical strength (super-gels).

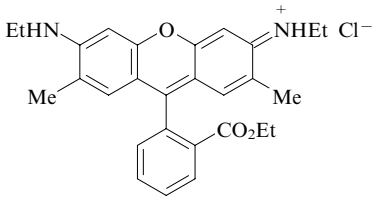
Hydrogels with a network microstructure composed of intertwined nanotubes and other large aggregates were formed upon the introduction of singly charged M^+ (M = Li, Na, K, Rb, Cs) or NH_4^+ cations into an aqueous solution of sodium lithocholate at room (or lower) temperature.[128] This system differed from aqueous solutions of sodium cholate or deoxycholate by a larger set of cations affecting the gelation and the possibility of greater diversity of properties. The mechanical strength of the hydrogel increased with temperature. Figure 18 shows the structure formed upon the assembly of lithocholate anions with M^+ cations. The hydrogelation involves electrostatic interactions and hydrogen bonding between the only hydroxyl group and the carbonyl group of the lithocholate carboxylate anion. The distance between the parallel planes of the crystal lattice (d) was in the 1.7 – 2.1 nm range, which is somewhat longer than the LCA molecule core (1.5 nm).[128] The concentration of cations did not have a noticeable influence on the position of the lithocholic anion in nanotubes. In the case of the NH_4^+ cation, partial hydrolysis of the salt resulted in a decrease in the pH and a change in the gel formation conditions as compared with other singly charged cations.

The use of lithocholate as the gelator promoted a considerable increase in the mechanical strength of BS-based gels. The tubular hydrogels with a negative charge of the surface of microstructures based on the lithocholate anion possessed a high adsorption efficiency and capacity towards oppositely charged dyes.[128] For gels obtained in the presence of the above-indicated cations, the adsorption capacity towards methylene blue (**10**) and rhodamine 6G (**11**) dyes as guest molecules were in the ranges of 0.87 – 1.10 and 1.12 – 1.42 g g^{-1} of LCA, respectively, with short adsorption times (minutes).[128]

Structures 10, 11



10 (methylene blue)



11 (rhodamine 6G)

The dried DEA – LCA gels actively absorbed metal ions — Cu^{2+}, Co^{2+}, Ni^{2+}, Pb^{2+} and Hg^{2+}. An effect of binding of doubly charged metal ions by bile salts was also demonstrated for SDC systems.[129]

IV.6. Role of hydrogen bonds and electrostatic interactions in the formation of sodium deoxycholate-based gels

Deoxycholate gels are 3D networks consisting of nanotubes, helical structures and nanofibres joined by numerous non-covalent interactions. As noted above, the conditions of gelation can be markedly dissimilar. In one case, the formation of the SDC gel involved NaCl and occurred at pH values close to pK_a of deoxycholic acid (6.6);[104] in

another case, gelation took place in the presence of rather strong organic acids;[112] in some other case, the gel was obtained at low pH values (~4) and then the effects of temperature, NaCl and amino acids on the gel–solution phase transition were studied.[34] Therefore, it is pertinent to analyze the effect of pH and inorganic salt on the mechanism of deoxycholate gelation in an aqueous medium. This issue was considered by Zhang *et al.*[130]

For the first system (SDC–NaCl), the attention was concentrated on the role of electrostatic interactions in the gelation. For the second system, the role of hydrogen bonding was investigated; the system consisted of deoxycholic acid, tetramethylammonium hydroxide added for DCA dissolution and acetic acid, which served to maintain a definite pH. This system was devoid of Na^+ ions, while the Me_4N^+ ions (unlike NH_4^+) are unable to gelate SDC.[128] In the third instance, NaCl was introduced into an SDC solution at various pH, *i.e.*, the cooperative contributions of both types of interaction were studied. The following conclusions were drawn.

1. Supramolecular gel is formed in all three systems, but under different conditions.

2. At pH ~ 8.5, sodium deoxycholate, which is almost completely dissociated, forms gels with the participation of inorganic cations (Na^+) only through electrostatic interactions. The SDC concentration range in which the gel is formed is 20–90 mmol litre^{-1}. An increase in the NaCl concentration is favourabe for gelation. However, when [SDC] > 90 mmol litre^{-1}, the increase in NaCl concentration gives rise to the solution–precipitate two-phase system.

3. In the case of an equimolar mixture of DCA and Me_4NOH (neutralization takes place), a transparent solution with pH ~8.5 containing virtually only a deoxycholate anion (DC^-) is formed. With decreasing pH, the formation of the DC^-–DCA complex facilitates the gelation. As a result, the hydrogel is formed without participation of the inorganic cation at pH 6.7–7.3 close to physiological pH values; at pH < 6.7, a mixture of a gel and a precipitate is formed, while increasing the pH to 7.3 induces a gel–solution transition. It was noted that the DCA concentration should be above 160 mmol litre^{-1}.

4. The effect of pH on the SDC–NaCl system was studied in the range of pH 6.7–7.3. When both factors (hydrogen bonds and electrostatic interactions) act, the SDC gel is formed at lower concentrations of SDC and NaCl than in the first system, namely, 75 and 30 mmol litre^{-1}, respectively (at pH 7.0).

5. Since the initial systems differ in the capacity for gelation and in the gelation mechanism, the obtained gels markedly differ in the microstructure and mechanical strength. A combination of hydrogen bonds and electrostatic interactions considerably promotes the gelation and increases the mechanical strength of the gel. These gels were examined for microstructure (by TEM) and rheological properties; conclusions about the mechanism were drawn considering the IR spectroscopy and small-angle X-ray diffraction data.

Hence, gelation of SDC involving electrostatic interactions, hydrogen bonds or both types of contacts proceeds in aqueous solutions at nearly physiological pH and requires fine tuning of external parameters. The formation of hydrogen bonds is also the key driving force in the formation of lithocholic acid-based gels. For example, in the case of the LCA–C_{12}DMAO system, the formation of fibrils (gelation) occurs apparently *via* multiple repetition of the structural motif consisting of two LCA molecules pointing to different directions and four C_{12}DMAO molecules as the [C_{12}DMAO-H]$^+$–C_{12}DMAO pairs.[127]

V. Metallogels based on bile salts

The search for systems able to change the structure and properties in response to external stimuli is a principal task of modern materials science, because such systems have a wide scope of applicability. A rapidly developing trend is the design and investigation of metallogels for the manufacture of functional materials.[131–133] The ability of BS-based gels to accumulate metal ions can be increased by introducing chelating groups into the molecule. In addition, metals can be present in covalently bound groups. However, the most popular approach is based on the formation of coordination complexes, in particular, carboxylate ones, between a low-molecular-mass anionic gelator and an ion, *e.g.*, transition metal ion. Furthermore, the *in vitro* introduction of metal ions is important for understanding of the role of BS and their aggregates (complexes) in *in vitro* physiological processes. We will give several examples of modification of BS-based hydrogels by introducing metal ions. More detailed discussion of this issue can be found in a review[134] devoted to supramolecular gels based on steroid molecules, including organic gels and metallogels.

The introduction of doubly charged metal ions into BS solutions influences the size and shape of micelles and also facilitates the formation of mixed micelles and their conversion to vesicles. A study[135] of samples obtained by the reaction of aqueous solutions of $CuCl_2$ and SDC showed the following.

1. The composition of copper deoxycholate complexes, $Cu(DC)_2$, formed in the $CuCl_2$–SDC system depends on the component concentrations. The complex $Cu(DC)_2(H_2O)_5$ is formed when the SDC concentration is either below or above the CMC, but the concentration of Cu^{2+} ions is high.

2. The dissolution of $Cu(DC)_2$ in an aqueous solution of SDC results in the formation of large particles (30–90 nm in diameter), which are mixed $Cu(DC)_2$ and SDC micelles. They are formed with the participation of two metal ions (Cu^{2+} and Na^+).

3. The composition of the gelator and the coordination complex depends on the component ratio.

The complexes $Co(DC)_2(H_2O)_3$ are formed in the reaction of Co^{2+} ions with the SDC monomer, *i.e.*, at [SDC] < CMC. The Co^{2+} interaction with SDC micelles leads to gel-like non-stoichiometric compounds $Na_nCo_m(DC)_{n+2m}$.[129] Like in the $CuCl_2$–SDC system,[135] in this case, too, this gives rise to large micelles 30–80 nm in diameter with Co^{2+} ions acting as bridges. The vibration frequencies of the carboxylate group are different: in the case of $Co(DC)_2(H_2O)_3$, the CO_2^- vibrations correspond to chelate and pseudochelate modes, whereas for the $Na_nCo_m(DC)_{n+2m}$ gel the bridging mode is observed.

The presence of hydroxyl groups differing in the reactivity, their number and the chirality of bile acids in combination with ready accessibility and low cost make bile salts perfect building blocks for new synthetic applications. A number of metal ions, mainly doubly charged ones, promotes efficient gelation of sodium cholate (Table 4). Doping of a calcium ion-containing hydrogel with transition and main group metal ions (Cu^{2+}, Co^{2+}, Zn^{2+}, Cd^{2+}

Table 4. Gelation upon mixing of aqueous solutions of metal salts (30 mmol litre^{-1}) and sodium cholate (60 mmol litre^{-1}).[136]

Metal salt	Gelation details
$CaCl_2(H_2O)_2$, $Ca(NO_3)_2(H_2O)_2$	Transparent gel is formed within 5 min on mixing the solutions heated to 50 °C
$Co(NO_3)_2(H_2O)_6$	Transparent gel is formed on mixing the solutions at room temperature
$CuSO_4(H_2O)_5$, $Cu(NO_3)_2(H_2O)_3$	After mixing of the solutions, a precipitate is formed and then dissolved in 45 min to give a transparent gel
$CdCl_2$	Transparent gel is transformed to a semitransparent one in 15 – 20 min
$Zn(NO_3)_2(H_2O)_6$, $Zn(ClO_4)_2$	The same
$HgCl_2$	The precipitate that appears after mixing is dissolved during ultrasonic treatment to give a transparent gel
$AgNO_3$	Transparent gel is formed immediately after mixing the solutions
$Mn(OAc)_2(H_2O)_4$	Turbid gel is formed during ultrasonic treatment within 1 min

and Hg^{2+}) accelerates the gelation — the gel is already formed at room temperature. A Ca^{2+}-modified hydrogel based on sodium cholate proved to be a convenient supramolecular matrix for the synthesis and stabilization of nanoparticles.[136] For example, 1 – 2 nm particles (for Au/AgNP metals, see below) and 3 – 10 nm particles (for sulfides CdS, HgS and ZnS) are formed in calcium cholate nanohelices. This is promoted by numerous weak interactions between the inorganic precursor and hydrogel nanowires.

A luminescent hybrid hydrogel was obtained by assembly of sodium cholate with Eu^{3+} or Tb^{3+} ions or their mixture in aqueous solution. The coordination of a cholate anion to a lanthanide ion and self-assembly to 1D nanowires protected the Eu^{3+} ion from fluorescence quenching in an aqueous medium. The maximum emission in the hybrid gel was achieved at the $Eu(NO_3)_3$: sodium cholate ratio of 1 : 3. The emission band (hybrid hydrogel colour) was determined by the introduced ion or doping ion. Using this hybrid hydrogel as a template, photoluminescent inorganic nanotubes of lanthanide oxosulfides were obtained under mild conditions.[137, 138] According to high-resolution TEM data (HR-TEM) and field emission scanning microscopy (FE SEM), the microstructure of the SDC – $Eu(NO_3)_3$ hybrid hydrogel was composed of microfibres combined with small particles.[139] The mechanical strength of hydrogels increased with increasing concentrations of both $Eu(NO_3)_3$ and SDC. The luminescence lifetime of, for example, terbium increased by approximately 250% after it was encapsulated into SDC-containing hydrogels [aqueous solution of SDC, systems SDC – silica gel and SDC – single-walled carbon nanotubes (SWCNT) – silica gel].[137] The degree of participation of various non-covalent interactions, including coordination ones, in the formation of metallogel was dictated by the nature of the metal and the surfactant – metal salt ratio.

Combination of the reducing ability of SDC aggregates formed upon self-assembly in an aqueous solution of L-ascorbic acid and $AgNO_3$ added for the reduction of $HAuCl_4$ and growth of particles, respectively, promotes the formation of plasmon dendritic gold nanoparticles (GNP) with a high degree of branching.[140] In the absence of SDC, only spherical Au nanoparticles are formed. The absorption spectrum and morphology of gold nanoparticles that grow in the matrix from supramolecular SDC aggregates depend on the salt concentration. Branched GNP with a size of about 47 nm (a 10 – 20 nm branch and a 20 nm core), dendritic morphology and plasmon absorption at λ_{max} = 740 nm were formed at a SDC concentration of 1.4 mmol litre^{-1}, *i.e.*, at approximately the CMC (Fig. 19).

This system demanded that conditions of synthesis be maintained rather strictly. For example, at a high concentration of sodium deoxycholate ([SDC] ≫ CMC, system in the gel state), the particle shape changed: they stuck together and captured simultaneously a large amount of SDC. The plasmon resonance peak shifted from 740 to 510 nm. Fast reduction of Au^{3+} upon mixing of the seed particles and the reaction solution (growth solution) gave rise to a mixture of spherical and branched particles at a SDC concentration of 4.8 and 36.1 mmol litre^{-1}, respectively. The excess of $AgNO_3$ (> 10 mmol litre^{-1}) decreased the GNP aspect ratio and the number of branchings.

Thus, the synthesis of plasmon dendritic gold nanoparticles possessing strong absorption in the near-IR region (740 nm), which is necessary for effective photo and thermal therapy, is characterized by the use of supramolecular SDC aggregates as the matrix in aqueous medium. Treatment of the particles with thiol-terminated carboxy polyethylene glycol and then with the cyclic peptide, cyclo(Arg-Gly-Asp-D-Phe-Glu), facilitates the penetration of GNP into the cell and, hence, increases the GNP efficiency, which was demonstrated in *in vitro* experiments on model systems and *in vivo*.[140]

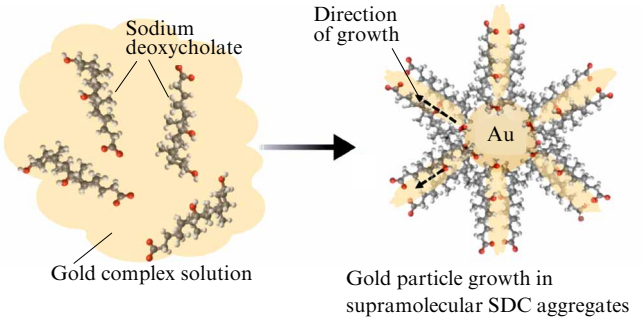


Figure 19. Schematic image of the formation of branched gold particles in the presence of SDC.[140]

VI. The systems sodium deoxycholate – carbon materials

Bile salts are among the best surfactants for solubilization of hydrophobic carbon nanoclusters in aqueous media.[141] Ultrasonic dispersion of single-walled carbon nanotubes in highly concentrated aqueous solutions of SDC ([SDC] ≫ CMC) gives rise to hydrogels.[142] Owing to exceptional viscoplastic properties, the hydrogel can be elongated 50-fold in the direction of the applied force.

For preparation of the SDC–GO–PBS composite hydrogel (GO is graphene oxide, PBS is phosphate buffer), an aqueous dispersion of GO, a solution of SDC of a known concentration and buffer solutions with various pH were used.[10] Mixing of the solutions in a definite ratio resulted in the formation of the SDC–GO–PBS hydrogel; both components (PBS and GO) stimulated the hydrogelation. The state of the SDC–GO–PBS system changed from a semi-gel to a thick hydrogel with increasing [PBS] at a constant GO concentration. In the presence of graphene oxide, the mechanical strength of the SDC-based composite hydrogel was enhanced, because the number of hydrogen bonds between GO and SDC molecules increased owing to the presence of hydrophilic groups on the oxide surface. The adsorption of the model compound [methylene blue (**10**)] on graphene oxide was not accompanied by destruction of the SDC–GO–PBS composite hydrogel. As compared with simple SDC hydrogel, the use of composite gel solves another practically important task. Whereas in the former case, the goal is to release the drug delivered to the target by the gel,[104] in the latter case, the goals are adsorption and excretion of a potentially toxic bioactive compound.[10] Both types of SDC-based hydrogels are useful for medical and biological applications.

A graphene-containing hydrogel was prepared by mixing graphene nanosheets and sodium deoxycholate in water.[143] The introduction of graphene nanosheets improved the viscoelastic properties of the hydrogel. These properties depended on the concentration of graphene nanosheets in the hydrogel and the ability of SDC to form various structures upon self-assembly. Indeed, when the SDC content was ~40%, nanotubes with diameters of tens of micrometres and length of >1 cm were formed in the aqueous medium. Upon dispersion, graphene nanosheets were homogeneously distributed in the SDC matrix. Unlike SWCNT, graphene nanosheets can hardly be encapsulated inside the SDC aggregates because of their large lateral dimensions.

The SWCNT-modified SDC hydrogel can be useful as 'solid ink' for the manufacture of materials for nanoelectronics.[142] A hydrogel based on graphene nanosheets with good and controlled elastic and electrically conductive properties can be employed as the base for the 2D and 3D printing ink and for fabrication of electronic circuits with appropriate size and conductivity by the ink-jet printing process.[143]

VII. Binding of guest molecules by micelles and hydrogels based on bile salts

Supramolecular structures usually have several rather than one binding sites in the host molecule and complementary geometric structures and electronic properties of the host and the guest; this allows the host to selectively bind guest molecules of strictly defined structure and polarity (molecular recognition principle). Complexes with large numbers of bonds between the complementary host and guest are characterized by a high degree of structural organization.

The amphiphlic nature and definite combination of groups in the molecule makes BS a promising class of compounds in supramolecular chemistry meant for molecular recognition, formation of host–guest complexes, biomimetic chemistry and so on. The molecular and crystal structures of host–guest assemblies based on steroids including bile salts, their diversity and hierarchy, and chirality of supramolecular aggregates are subjects of a review.[144]

The BS micelles and aggregates have small free spaces (cavities). Since hydrophobic interactions and hydrogen bonds are responsible for different stages of formation of BS micelles, characterstics of the binding sites (size, rigidity and polarity) differ as regards the inclusion of guest molecules.[145] The cavities in small micelles are rather hard and hydrophobic, whereas those in large micelles are more polar, softer and relatively spacious. The non-polar cavities of BS micelles can solubilize hydrocarbon molecules, whereas polar, rather large guest molecules are encapsulated in aggregates. This Section presents examples of application of bile salts. These include solubilization of poorly soluble objects, change in the product stereochemistry, influence on the state of the active component in solution and so on. The sequence of BS aggregation in water and encapsulation of guest molecules in the cavities is illustrated in Fig. 20.

Among supramolecular systems, the soft cavities of bile acids are considered as microreactors which can change the photochemical behaviour of guest molecules encapsulated in a confined space.[146] An example is photodimerization of

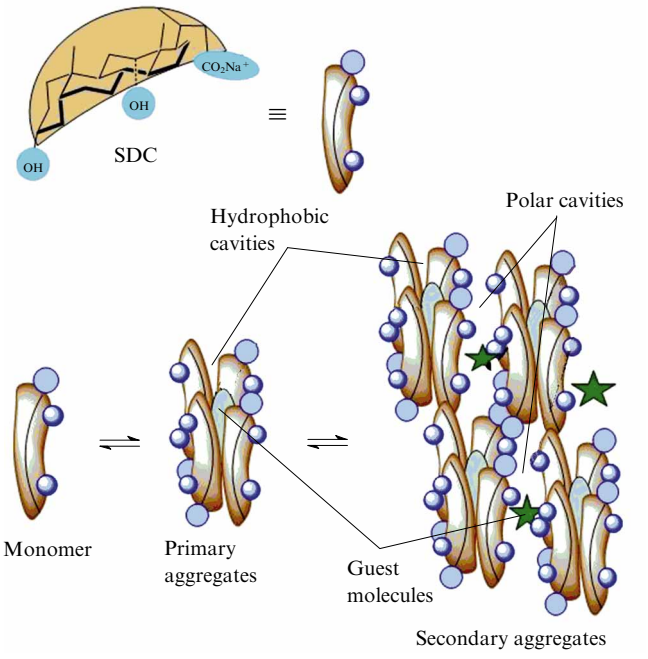
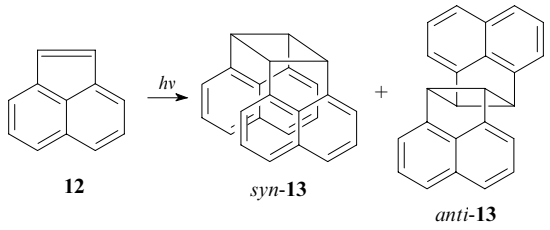


Figure 20. Aggregation of bile salts in aqueous medium and encapsulation of guest molecules in the cavities.[146, 147]

acenaphthene **12** (non-polar guest) taking place in sodium cholate micelles in aqueous medium § (Scheme 2).[147]

Scheme 2



The yield of the dimer with *syn*-naphthalene moieties (*syn*-**13**) increased with increasing SC concentration (Table 5). In the SC aggregates, the yield of dimers **13** in the photodimerization remained nearly constant. As the concentration of acenaphthene increased at a constant concentration of the host (aggregates), the *anti*:*syn* ratio remained, on average, 4.4. In the atmosphere of N_2 or O_2 (triplet quencher), the yield of *syn*-**13** was 83% or 94%. In the presence of eosin-Y (triplet sensitizer), the contents of *syn*-**13** were 56% and 44% for micelles and for hexane, respectively. Thus, small-size non-polar hydrocarbon cavities within SC micelles promote the formation of the *syn*-isomer, the molecule of which is smaller (7.26×6.6 Å) than the *anti*-isomer molecule (6.86×11.8 Å).[148]

Table 5. Selectivity of photodimerization of acenaphthene (**12**) with the change in sodium cholate concentration in an aqueous solution of NaCl.[147]

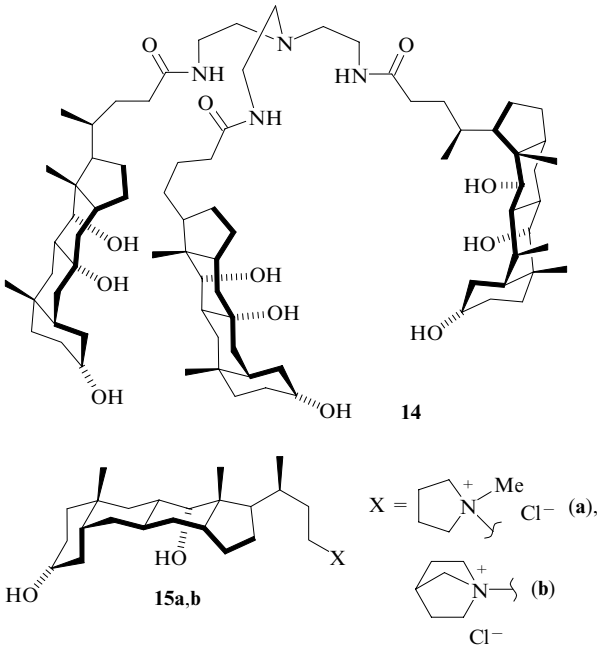
Concentration /mmol litre^{-1}	Type of sodium cholate association	Content (%)		Ratio *syn*-**13**:*anti*-**13**
		syn-**13**	*anti*-**13**	
5	Monomer	66	34	1.94
20	Micelle	71	29	2.45
40	Micelle – aggregate	78	22	3.55
90	Aggregate	84	16	5.55
140	"	87	14	6.29
190	"	86	12	6.14
250	"	88	13	7.33

Note. The acenaphthene concentration is 0.66 mmol litre^{-1}. The sodium cholate solution was prepared using a 25 mmol litre^{-1} aqueous solution of NaCl. Conversion was 30% – 40% in all cases; the yields are average over three runs.

The selectivity of the photodimerization of acenaphthene was analyzed for acetic acid – water mixtures, phosphate buffer and for micelles and hydrogels based on compounds **14**, **15a**,**b** and SDC.[149]

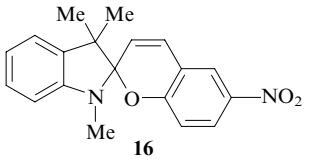
The ratio of *anti*- and *syn*-dimers **13** was higher for gels than for micellar solutions of cationic (compounds **15a**,**b**) or anionic (sodium deoxycholate) bile salts, which is attributable to the dynamic nature of micelles. The selectivity of the reaction is correlated with the gel strength: the *anti*:*syn* ratios of the photodimers are 11 and 2 for the gel with the highest mechanical strength obtained from compound **15b** and the weakest gel obtained from compound **14**, respectively. For the gel based on anionic SDC in the phosphate buffer, the *anti*:*syn* ratio is 3.5, whereas in the case of acenaphthene photodimerization in the phosphate buffer, it is 1.2. Thus, as compared with micelles, the gels based on the above-indicated compounds ensure a harder environment for the guest molecule, which results in a higher selectivity of the photochemical reaction.

Structures 14, 15



For solubilization of aromatic compounds, BS micelles were shown [150, 151] to be adaptable supramolecular systems: the guest structure (shape, size) can largely determine the arrangement of host molecules. The change in the ionic strength of the medium upon introduction of NaCl also changed the properties of the host. Sodium deoxycholate can also function as a guest molecule upon the reaction with dendrimers.[152] In water, bile acid salts solubilize various photochromic compounds, for example, 1′,3′,3′-trimethyl-6-nitrospiro[2*H*-1]benzofuran-2,2′-indoline (**16**), their photochromic activity being retained.[153]

Structure 16



We will consider several examples of binding of bile salts to guest molecules, including hydrocarbons, dyes and drugs, in particular antibiotics used in chemotherapy.

Drug solubilization by bile salts is of interest for pharmacology.[154] The capability of self-assembly and formation of mixed micelles with hydrophobic compounds, including lipids (solubilization), as well as biocompatibility,

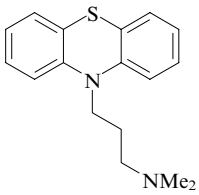
§ Since acenaphthene does not dissolve in water in any reasonable concentration for NMR spectroscopy, the characteristic signals of aromatics (guest) present in the spectrum together with the signals of the aliphatic protons of sodium cholate (host) served as evidence for acenaphthene encapsulation into SC micelles.

made bile salts applicable as vehicles for drug and cosmetic delivery. Doxorubicin (**5**) was less toxic and had higher *in vitro* antitumour activity when used in mixed SDC–Tween-80 micelles rather than in solution.[82] The DOX encapsulation in SDC hydrogels and release upon the change in pH were considered above.[104]

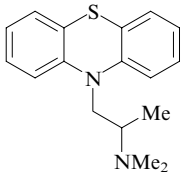
The rate of release of bovine serum albumin from the BSA-loaded SDC hydrogel increased with increasing concentration of the gel-modifying component and increasing crystallinity and pore (cavity) size in the hydrogel.[118]

The CMC values for mixed micelles of phenothiazine derivatives — promazine (PMZ, **17**) and promethazine (PMT, **18**) hydrochlorides — with BS are considerably lower than the CMC of single components.[155]

Structures 17, 18



17 (promazine)



18 (promethazine)

This decreases the toxicity of the dosage form and increases its uptake and bioavailability. The stoichiometric ratios, binding constants and free energy change for the formation of complexes of phenothiazines and BS were determined by the spectrophotometric and fluorescence titration of solutions of phenothiazine derivatives **17** and **18** with BS solutions followed by Beneshi–Hildebrand data processing. The results of measurements are linearized at phenothiazine : BS $\approx$ 1 : 2. The equilibrium constants for PMZ + SC and PMZ + SDC reactions (1244 and 10 414 litre^2 mol^{-2}, respectively) attest to stronger binding to SDC than to SC.[155] The degree of participation of electrostatic and hydrophobic interactions in the formation of BS complexes with phenothiazine derivatives depends on the component concentrations and ratio.

Binding, orientation and location of macrolide molecules¶ as guests with different hydrophobic properties and polarity in BS micelles were studied by NMR spectroscopy.[156] Although the macrolides bind to BS micelles in SC, SDC and STC solutions, the preferred orientation and location of their molecules could not be determined in these experiments. This might be associated with the specific planar diphilic BS structure and rather arbitrary orientation of molecules in the micelle. The latter is consistent with the high mobility of BS molecules in the micelles, which was ascertained in the molecular dynamics simulation of salt aggregation.[102] An increase in the hydrophobicity of macrolides and BS micelles not only enhances the interaction between them but can also reduce the therapeutic effect.

Micelles based on the rigid hydrophobic SDC molecule formed the microenvironment that efficiently protected 9-methoxycarbonylanthracene (9-MA, **19**), a chloride ion channel blocker, from the aqueous medium (Fig. 21).[157]

¶ Macrolides are a group of drugs, mainly antibiotics, the chemical structure of which is based on the 14- or 16-membered lactone macrocycles with attached one or several carbohydrates.

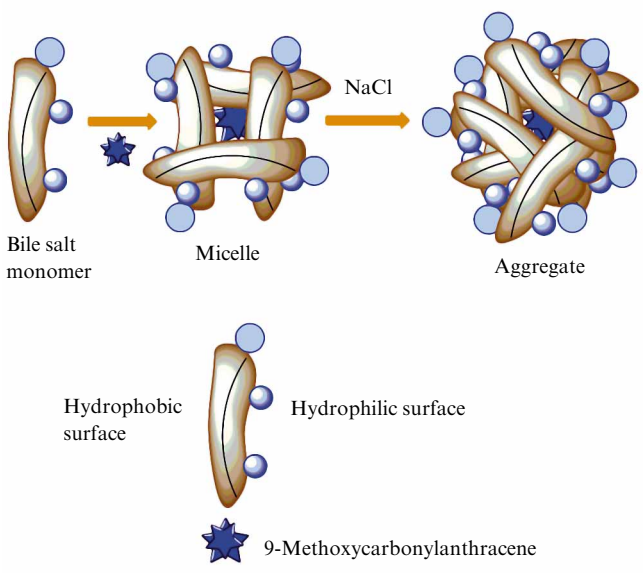
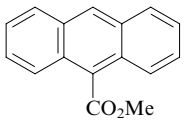


Figure 21. Schematic image of encapsulation of 9-methoxycarbonylanthracene in bile salt solutions (sodium cholate, sodium deoxycholate and sodium taurocholate).[157]

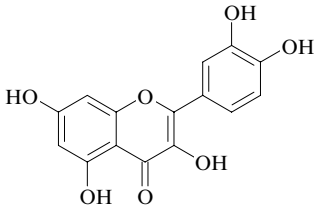
This is indicated by longer fluorescence lifetime and rotational relaxation time of the 9-MA molecule in SDC micelles in comparison with SC and STC micelles and confirmed by the lower degree of quenching of 9-MA emission by the hydrophobic microenvironment created in the SDC micelle.[157]

Solubilization of quercetin (**20**) by sodium cholate aggregates leads to higher absorbance and fluorescence intensity, owing to shielding of the molecule from the aqueous medium.[158] Also, equilibrium constants for the host–guest complex increase up to 0.7×10^3, 0.7×10^4 and 1.1×10^4 litre mol^{-1} for SC concentrations of 9, 15 and 20 mmol litre^{-1}, respectively. According to fluorescence anisotropy data, quercetin exists in a more hydrophobic environment in the secondary SC micelles than in dimers or primary micelles.

Structures 19, 20



19 (9-MA)



20 (quercetin)

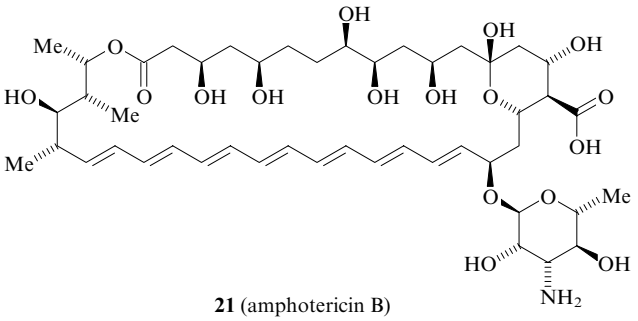
In aqueous solution, amphotericin B (AmB, **21**), a polyene macrocyclic antibiotic, occurs in the aggregated state. In SDC solutions, higher AmB aggregates are destroyed to give monomers and dimers, the latter being present even at high SDC concentrations.[159,160] At low concentrations of the steroid surfactant, the interaction between AmB and SDC provides efficient deaggregation to give antibiotic **21** in the monomeric form. In the case of

more hydrophobic salts (SDC and TSDC), the AmB aggregates undergo faster degradation than in the case of trihydroxy acid salts.

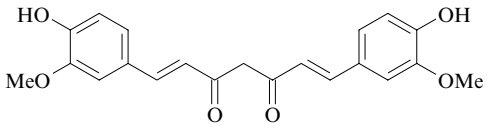
The degree of degradation of curcumin (**22**) — a natural polyphenol poorly soluble in water and known for its antioxidant, anticancer, antimicrobial and other properties — is markedly reduced when it is solubilized upon encapsulation as a guest in the cavities of the STC, SC and SDC aggregates.[161] The hydrophobic environment of the curcumin molecule has a protecting effect and leads to higher fluorescence intensity and hypsochromic shift of the emission band. Sodium taurocholate was most efficient among the studied BS.

In order to increase the liposolubility of insulin, a hydrophobic ion pairing method was developed in the aqueous phase. Insulin was mixed with SDC in water and the precipitated insulin – SDC cmplex was rapidly separated from the dissolved insulin.[162] The ion pair formation reduces the solubility of insulin in water.

Structures 21, 22



21 (amphotericin B)



22 (curcumin)

In the pre-micellar region of BS, Nile blue A (**23**) exists mainly as H-dimers. The degree of dimerization is higher in solution of SDC than SC.[163] When the BS concentration is above CMC, *i.e.*, when micelles are formed, the dye is monomerized. The binding constant and the efficiency of distribution of the dye between micelles and water (the proportion of the micelle-encapsulated dye) is higher for sodium deoxycholate: at 298 K, the binding constants are 6.18×10^{-2} and 5.77×10^{-2} litre mol^{-1} for SDC and SC, respectively.

The microstructure of SDC-containing hydrogels can largely dictate the type of aggregation — the formation of J-aggregates of fluorescein (**24**) proved to be more favourable than the formation of H-aggregates.[164] As opposed to the gel, no preferred dye aggregation was observed for micellar solutions of SDC. The molecules of the amido black 10B dye (structure **25**) were actively sorbed by the xerogel obtained by drying of the LCA – dodecyldimethylamine oxide superhydrogel (Fig. 22).[127] According to the absorption spectra, upon xerogel introduction into a solution, the dye concentration first rapidly decreased and then decreased slowly to reach a constant value after 15 h. The maximum dye absorption by the xerogel was 202 mg g^{-1}.

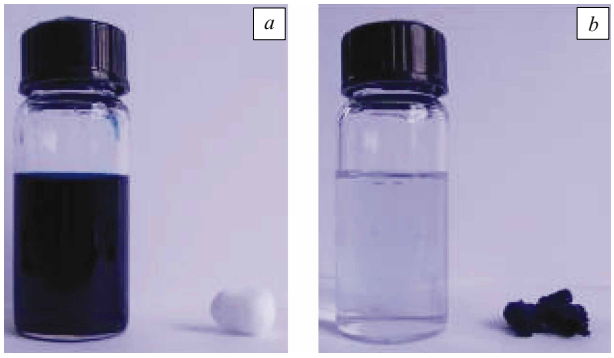
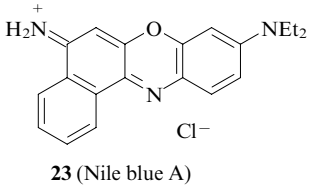
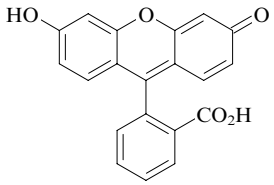


Figure 22. Solution of amido black 10B dye (**25**) and dried gel before (*a*) and after adsorption (*b*).[127]

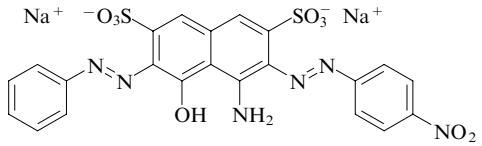
Structures 23 – 25



23 (Nile blue A)



24 (fluorescein)

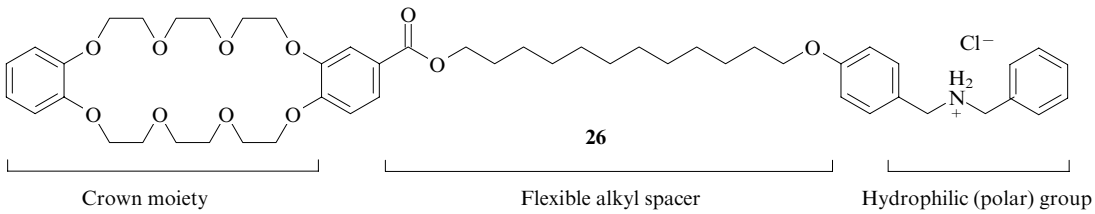


25 (amido black 10B)

VIII. Macrocyclic compounds as gelators

Nanomaterials are distinguished by higher level of drug adsorption, encapsulated forms being able to circulate in the blood stream for long periods of time.[165] A simple way of preparing a multifunctional nanomaterial for theranostics is, for example, the reaction between Fe^{III} phthalocyanine (FePc) chloride and sodium deoxycholate in the $CH_2Cl_2 - H_2O$ (2 : 1) two-phase system.[166] The ion metathesis gives the salt [FePc][DC] (DC is deoxycholate); the introduction of this salt as a THF solution into aqueous phosphate buffer resulted, after some period of time, in the formation of nanoparticles. The physical properties of this salt (fluorescence and magnetism) are provided by the metal phthalocyanine complex, while the deoxycholate anion ensures the system response to external stimulus, in this case, the change in the pH. At physiological pH values, the [FePc][DC] nanoparticles are rather stable. They could be useful as drug delivery agents, and their pH sensitivity could serve for therapeutic purposes: for the subsequent release of the delivered compound. For example, owing to hydrophobic properties and $\pi - \pi$ interactions, doxorubicin can be encapsulated into [FePc][DC] nanoparticles.[166] About 17% of doxorubicin encapsulated into [FePc][DC] nanoparticles are released over a period of 3 h at physiological pH, and complete drug release occurs at pH 5.5. Thus, modified SDC-based nanoparticles in weakly acidic media proved to be applicable in tumours and bacterial infections.

Structure 26



Crown ethers refer to the first generation of supramolecular macrocyclic host molecules. Owing to high selectivity in binding to a broad range of metal ions, organic salts and neutral molecules,[167, 168] crown ether compounds are convenient bases for the fabrication of aggregates sensitive to various types of stimulus. For example, compound **26**, which has high gelation properties, comprises a crown ether moiety (dibenzo-24-crown-8) and a secondary ammonium group.[169]

The former is involved in the recognition and binding of cations, while the latter responds to a change in the pH. A long flexible alkyl chain connects these active moieties. Its role is to increase the compound solubility and ability to form a gel (organogel). The interaction between the active groups *via* the formation of N—H···O hydrogen bonds apparently facilitates the self-assembly. The molecules are self-assembled through van der Waals and electrostatic interactions to give a physical network, which functions as a gel matrix. Among the solvents tested as the gelation media for compound **26**, the lowest critical micelle concentration (0.06 mass %) was attained in acetonitrile; in water, this value was 0.37 mass %.

The self-assembly of phthalocyanine **27** molecules containing four annulated 18-crown-6 ether rings with eight alkyl groups at the periphery through π–π interactions gives micrometre-long columnar stacks, while in chloroform, an organogel is formed.[170–172] The phthalocyanine Q-bands in the electronic absorption spectrum of the organogel are shifted hypsochromically and broadened, which is typical of aggregated Pc forms. According to TEM data, every fibre in the three-dimensional network of the organogel is composed of molecular threads arranged in parallel. The organogel structure can be represented by a multi-core molecular cable in which each thread consists of electron transfer channel (π–π-stacked phthalocyanine macrocycles) and four ion channels (crown ether rings) and is surrounded by an insulating layer (alkyl groups). The presence of a chiral centre in the substituent alkyl group gave rise to optically active helical systems based on phthalocyanine.[173] After the introduction of alkali metal ions, which bind to crown ether macrocycles, the chirality disappeared, indicating that the helix transformed into a straight thread.

Consider, probably, the first example of hydrogelation involving phthalocyanine in water. It was shown (see Ref. 18 and references cited therein) that crown-substituted phthalocyanines are solubilized in aqueous micellar solutions of synthetic anionic surfactants (dodecyl sulfate and sodium dodecylbenzenesulfonate) to give monomers and dimers at a surfactant concentration roughly equal to or below the CMC. Magnesium phthalocyanine complex **28** ($Mgcr_8Pc$) containing eight benzo-15-crown-5 ether moieties exists predominantly in the monomeric state in SDC solutions upon increase in the ionic strength.[174] Solubilization of $Mgcr_8Pc$ by micellar SDC solutions points to the possibility of encapsulation of this compound into supramolecular hydrogels.

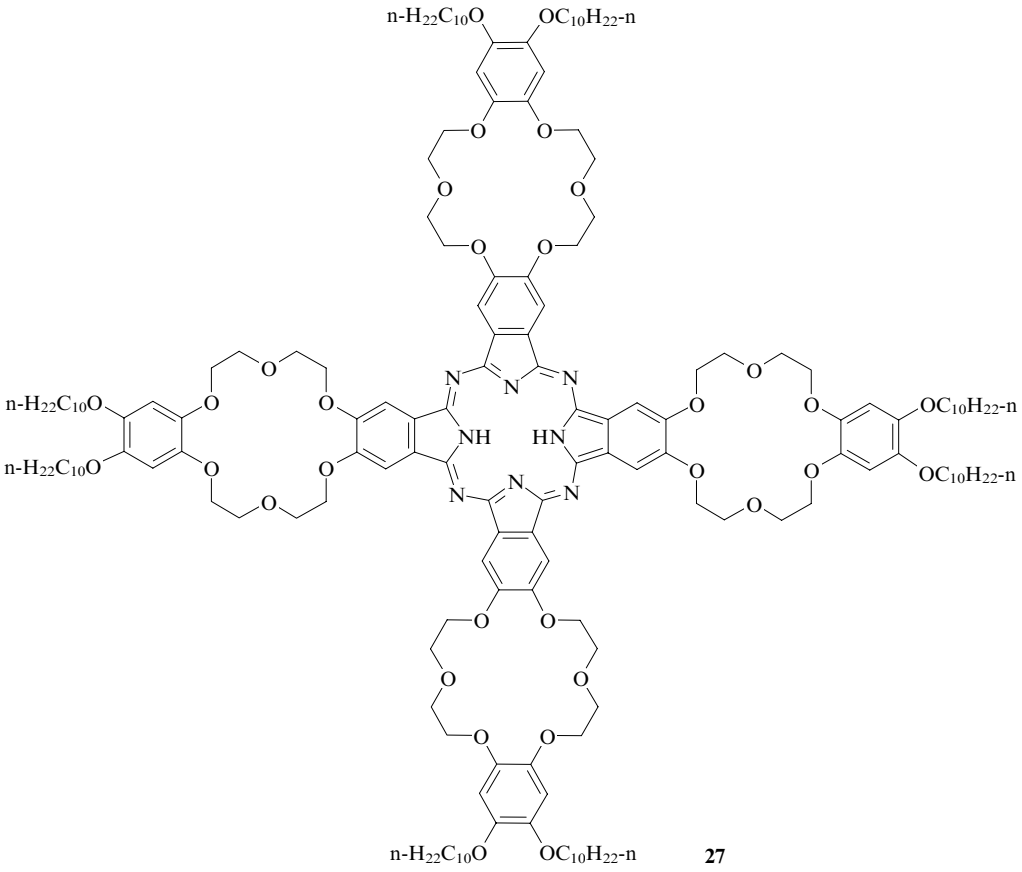
As components of supramolecular gel, lysine hydrochloride, SDC and $Mgcr_8Pc$ (as the model compound) were chosen. The information about the phthalocyanine molecular state and environment is provided by the Q-band region of its electronic absorption spectrum.[18] The broad band at 630–750 nm attests to an aggregated state of $Mgcr_8Pc$ in water. Meanwhile, the bands characteristic of the solid phase of phthalocyanine are absent from the spectrum.[175]

The $Mgcr_8Pc$-containing gels are formed upon mixing of reactants ('direct' gel) or upon diffusion of phthalocyanine from aqueous solution to the gel formed from SDC and Lys·HCl ('diffusion' gel). Figure 23 shows the time dependence of the absorbance of an aqueous solution of $Mgcr_8Pc$ upon successive introduction of Lys·HCl and SDC. At a low concentration of Lys·HCl, the absorption spectrum in region *1* barely differs from the spectrum of an aqueous solution of $Mgcr_8Pc$, which exhibits a broad band at 630–750 nm, indicative of aggregation of phthalocyanine molecules.[176] When sodium deoxycholate is added to the $Mgcr_8Pc$–Lys·HCl system, the absorbance near the Q-band increases (regions *2* and *3*), as in the case of pure SDC.[174] For concentrations of Lys·HCl comparable with the NaCl concentration, *i.e.*, about 0.1 mol litre^{-1}, the absorbance at 686 nm decreases (see the inset in Fig. 23) and gelation takes place. The thick gel thus formed retains the shape and position in the vessel when turned upside down, which is the traditional test for gelation (see the photograph in Fig. 23). On vigorous shaking, the gel behaves as a thixotropic liquid.

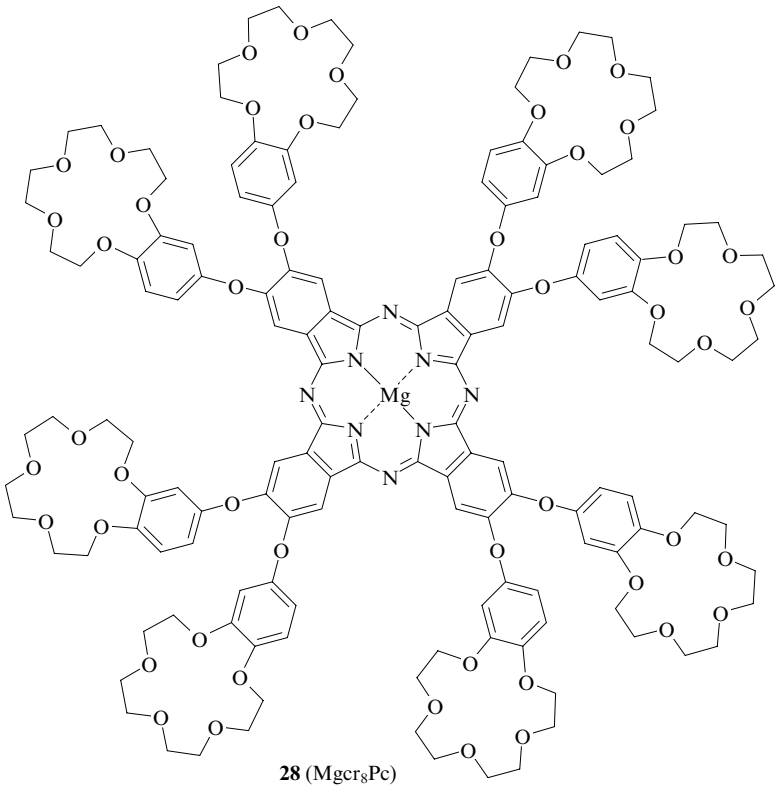
According to the electronic spectral data, at room temperature, gel-encapsulated $Mgcr_8Pc$ is mainly in the aggregated state, which remains unchanged for a long period of time (Fig. 24). The invariability of electronic spectra and their similarity for both types of gels ('direct' and 'diffusion' ones) are indicative of the attained stationary state. If the electronic spectra are qualitatively represented as sums of Gaussian components, the spectra of $Mgcr_8Pc$ in the hydrogel and in an aqueous solution of the SDC–Lys·HCl mixture are similar in the component number, position and shape. The spectra contain some components that, according to their absorption peaks, can be taken as evidence indicating that the gel contains not only aggregates, but also monomers of $Mgcr_8Pc$, resulting from Pc solubilization by SDC or SDC–Lys·HCl micelles, which exist in the microheterogeneous environment.

Heating of the gels, $Mgcr_8Pc$–SDC–Lys·HCl and $Mgcr_8Pc$–SDC–Lys·HCl–NaCl, in the 45–55 °C range is accompanied by melting (see Fig. 24, inset *I*). The temperature range of melting depends on the component ratio. A change in the physical state of the system leads to considerable changes in the electronic absorption spectra of the gel-solubilized $Mgcr_8Pc$, in particular, increase in the

Structures 27, 28



27



28 ($Mgcr_8Pc$)

absorbance in the Q-band region and a change in the Q-band shape (see Fig. 24, inset *II*). In the $Mgcr_8Pc$ – SDC – Lys · HCl – NaCl hydrogel melt, phthalocyanine exists in a state similar to its state in an $Mgcr_8Pc$ – SDC – NaCl aqueous solution, *i.e.*, mainly as a monomer.[177] The $Mgcr_8Pc$-containing hydrogels are thermally reversible and

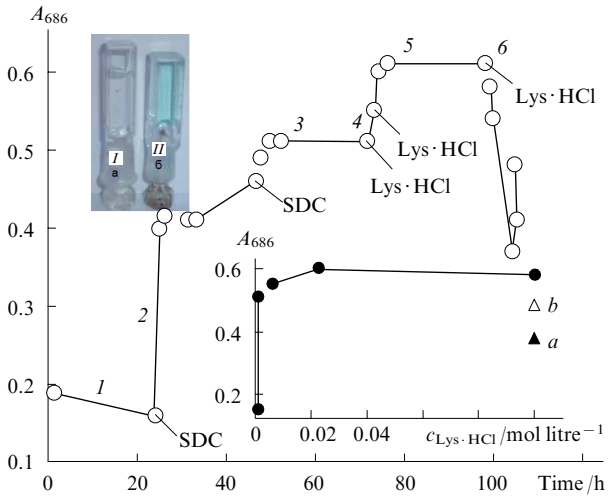


Figure 23. Time variation of the absorbance (A_{686}) of an aqueous solution of $Mgcr_8Pc$ after the addition of lysine hydrochloride (region *1*, [Lys·HCl] = 1.25 mmol litre^{-1}), sodium deoxycholate (regions *2* and *3*, [SDC] = 9.9 and 21.7 mmol litre^{-1}, respectively, [Lys·HCl] = 1.25 mmol litre^{-1}), lysine hydrochloride (regions *4*, *5* and *6*, [Lys·HCl] = 6.2, 22.7 and 100 mmol litre^{-1}, respectively, [SDC] = 21.7 mmol litre^{-1}).[176]
Inset: A_{686} *vs.* [Lys·HCl]; the hydrogel absorbances at room temperature (point *a*) and on heating to ~35 °C (point *b*).
Photograph: samples of dense liquid SDC – Lys·HCl (*I*) and hydrogel SDC – Lys·HCl – $Mgcr_8Pc$ (*II*).[176]

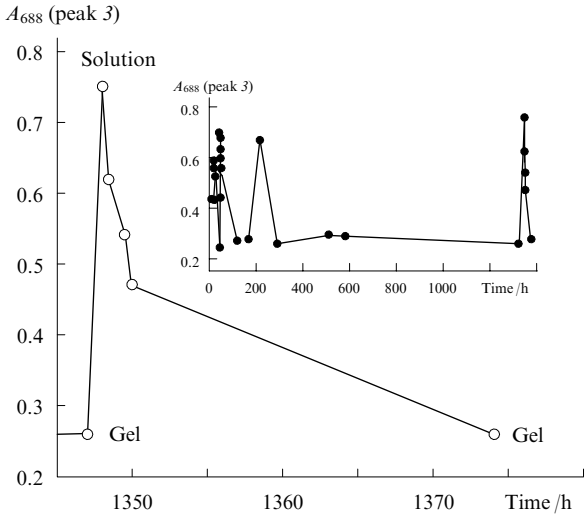


Figure 25. Absorbance of peak *3* (A_{688}) derived from decomposition of the spectral curve for the $Mgcr_8$ Pc – SDC – Lys·HCl – NaCl – H_2O gel into Gaussian functions *vs.* time: gel (20 °C) → solution (~50 °C) → gel (20 °C). The repeating fragment of the plot is shown.[177]
Inset: Full time dependence of A_{688}.

the heating – cooling stages can be repeated many times (Fig. 25). The photobleaching of the gel-solubilized $Mgcr_8Pc$ in a scattered light in air is slower than in micellar

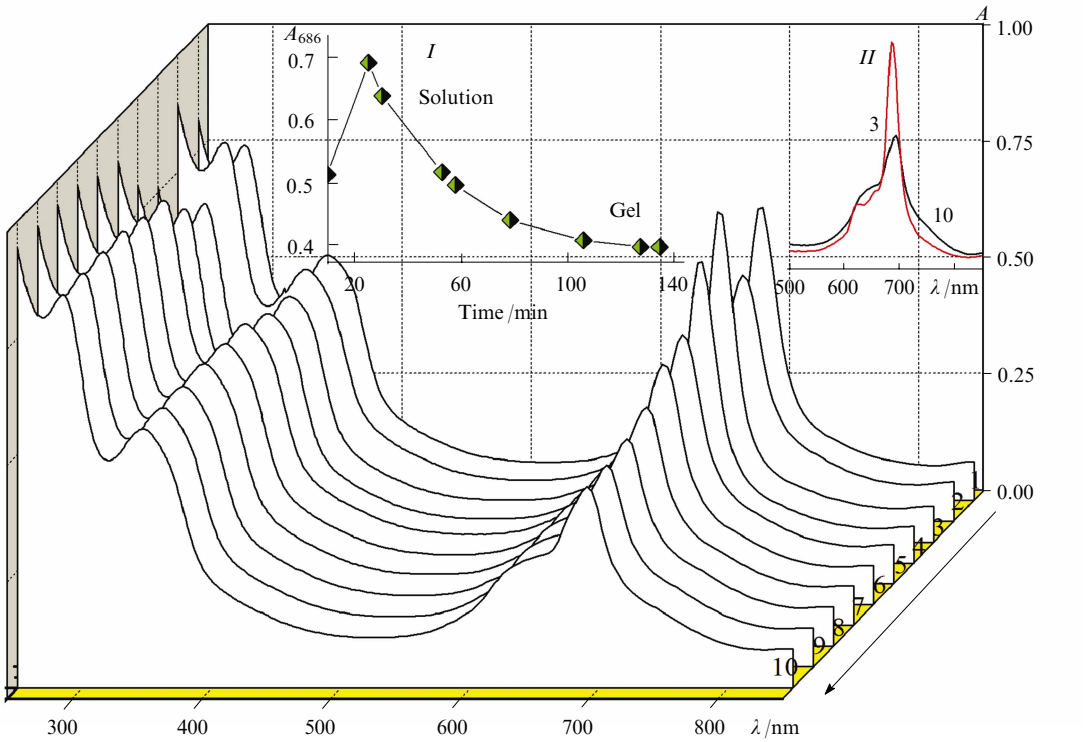


Figure 24. Variation of the electronic absorption spectrum of the 'direct' gel formed (1 – 10 are the numbers of spectra).[177]
Inset *I*: formation of the dense hydrogel $Mgcr_8Pc$ – SDC – Lys·HCl – NaCl – H_2O from a melt (55 °C) during cooling the melt to room temperature (18 °C).
Inset *II*: absorption spectra of the solution (melt) of the hydrogel (spectrum 3) and dense hydrogel (spectrum 10), $Mgcr_8Pc$ – SDC – Lys·HCl – NaCl – H_2O.

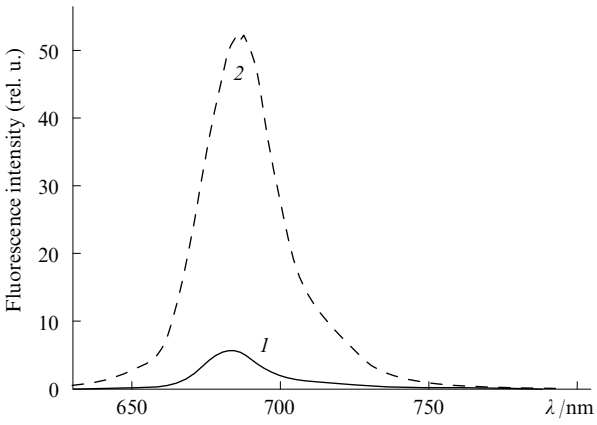


Figure 26. Emission spectra of the $Mgcr_8Pc$ – SDC – Lys · HCl – NaCl – H_2O gel (*1*) and melt (*2*) at λ_{excit} = 614 nm.[177]

Pc solutions[178] in which it exists mainly as a monomer. This is attributable to fast monomer – aggregate – monomer transitions upon the change in the system physical state and to the protecting action of the gel.

Heating of the gel leads to the release of $Mgcr_8Pc$ as a micelle-encapsulated monomer and increase in the Pc fluorescence intensity by an order of magnitude (λ_{excit} = 614 nm) in the melt as compared with the gel (Fig. 26). This supports the conclusion drawn from absorption spectroscopy data about micelle encapsulation of the $Mgcr_8Pc$ monomer, because the aggregates and H-dimers exhibit no fluorescence.

The supramolecular organization of the SDC gel is determined by the amphiphilic properties of sodium deoxycholate. Similarly to singly charged cations, the polar hydrophilic NH_3^+ group in Lys · HCl in the absence of a hydrophobic group promotes the formation and strengthening of a gel comprising SDC and Pc, while barely influencing the degree of aggregation of complex **28** in aqueous solution. In this case, $Mgcr_8Pc$ occurs in the gel mainly in the aggregated form. The existence of Pc as a monomer becomes more favourable in the presence of sodium chloride. A change of the system physical state on temperature rise results in the destruction of the 3D network formed *via* weak but numerous interactions, including hydrogen bonds in water. The complexation of the Na^+ ion with the crown ether cavity, together with electrostatic and hydrophobic interactions induce the release of $Mgcr_8Pc$ as a micelle-encapsulated monomer, similarly to the $Mgcr_8Pc$ – SDC – NaCl system.[174] Cooling of the gel and restoration of the interactions between molecules, including hydrogen bonds, reproduces the medium in which Pc molecules tend to be aggregated. Only a minor portion remains in the monomer form, which influences the fluorescence intensity. The results obtained by IR spectroscopy for the $Mgcr_8Pc$ – SDC – Lys · HCl gel and air-dried gel samples are consistent with these views.

IX. Conclusion

A trend of modern chemistry is the design of new functional materials, including those that change properties in response to external stimuli. This fully refers to supramolecular hydro- and organogels based on natural compounds (amino acids and their derivatives, sugars and bile acids). The similarity of the properties of synthetic gels and living tissues, such as reversible sorption of a large amount of water, biocompatibility, the ability to retain the active component, deliver it and release in response to an external stimulus, promote further investigation of gelation involving natural and synthetic compounds. Bile acids and bile salts are synthesized in liver from cholesterol, thus regulating simultaneously the rate of cholesterol degradation. They participate in digestion by solubilizing food lipids and fat-soluble vitamins and are promising components of the gels based on low-molecular-mass compounds. Of particular interest are gels formed with the participation of crown-substituted tetrapyrroles and carbon nanomaterials, for example, carbon nanotubes, graphene and graphene oxide possessing unique physicochemical properties.

The above examples demonstrate that SDC gelation involves either electrostatic interactions or hydrogen bonding, or a combination of both types of interaction. The gelation proceeds in aqueous solutions at physiological pH values, which is indicative of formation of an environmentally safe gel. Bile salts usually possess a rigid amphiphilic structure (planar diphilicity), which distinguishes them from traditional surfactants and accounts for the specific self-assembly behaviour of bile salts. Owing to the core rigidity, specific distribution of hydrophilic and hydrophobic domains and the involvement of hydrophobic interactions and hydrogen bonds, bile salt molecules form ordered supramolecular assemblies, one-dimensional structures (micelles, tubes and fibres) and low-molecular-mass gels.

In analysis of the research dealing with bile salts, a number of vigorously developing areas should be distinguished.

1) Bile salt micelles and gels as potential drug delivery systems.

The unique character of biocompatible bile salts is determined by the presence of two types of binding sites. Therefore, they can solubilize both hydrophilic and hydrophobic molecules (drugs) and biologically active molecules — cholesterol, lipids, fatty acids and so on. In some cases, BS-based supramolecular hydrogels melt at about 37 °C, which opens up the prospects for using them as drug delivery vehicles. Amino acids loosen the gels *in vitro* and facilitate release of the active component. The amphiphilic BS molecules and aggregates based on them show the unique ability to transport compounds and ions across biological tissues and membranes. For example the rate of release of rutin — a bioactive component model — across an artificial membrane [SDC hydrogel (0.5%) in a phosphate buffer with 5% mannitol] was higher than the rate of its exit from the hydroxyethylcellulose – sodium polyacrylate composite gel.[179]

Solubilization of drugs in aqueous solutions of sodium deoxycholate and modification of supramolecular SDC hydrogels by active components followed by release of the active components are exemplified by phenothiazine derivatives and doxorubicin in the former case and dyes (methylene blue, amido black 10 B), DOX and crown-substituted phthalocyanines in the latter case. The use of SDC-based molecular gel as a vehicle solves the task of drug delivery to the target and release, whereas modification of the gel with carbon nanomaterials is meant for adsorption and excretion of potentially toxic biologically active compounds. Both

types of hydrogels are useful for medical and biological applications. The use of natural compounds for the manufacture of materials that respond to external stimuli improves the biocompatibility and decreases the potential toxicity of decomposition products in biomedical applications.[180] Cholanology (bile acid science) plays an important role in biotechnology and pharmaceutical industry. Bile salts and their priority role at certain stages of drug uptake are the subjects of a review of Holm *et al.*[181] and the prospects of bile acid application for drug delivery are surveyed by Stojančević *et al.*[182]

2) Micelles and gels as matrices for the synthesis and stabilization of inorganic and organic nanoparticles.

Bile salts and metal salts are used to obtain coordination supramolecular hydrogels. Using hybrid gels, it was possible, for example, to fabricate photoluminescent inorganic lanthanide oxosulfide nanotubes under mild conditions. Environmentally safe photoreduction of metals, in particular, silver and gold, in a bile salt microheterogeneous environment at a SDC concentration approximately equal to CMC gives rise to branched Au nanoparticles with a high aspect ratio and absorption spectrum in the near-IR region — the therapeutic window needed for effective photo and thermal therapy. The formation of gold and silver nanoparticles also opens up the way to catalytically active materials, in particular, for C – H bond activation,[183] and antibacterial materials, respectively. Fluorescent probes are protected from the action of water and, as a consequence, from fluorescence quenching by being encapsulated in bile salt-based micelles; this is of interest for the development of diagnostic and therapeutic agents.

3) Hydrogels based on bile salts as sorbents.

Superhydrogels formed by supramolecular nanotube structures assembled from small gelator molecules, for example, sodium lithocholate, are proposed to be used as simple, readily accessible and environmentally benign adsorbents for the removal of heavy metals from industrial waste effluents. Superhydrogels (xerogels) also showed high efficiency and sorption properties towards dyes in water. Of particular interest is the fact of enhancing the mechanical strength of the SDC-containing supramolecular gel by adding a number of modifying agents, such as inorganic salts, carbon nanomaterials and so on.

4) Miscellaneous applications.

Gels modified by nanocarbon materials can be useful for the design of drug delivery systems, sensors, antibacterial materials, 2D- and 3D-printing ink for fabrication of electronic circuits with appropriate size and conductivity for nanoelectronics.

Thus, analysis of the literature devoted to the preparation of supramolecular hydrogels reveals the promising line of research: development of the synthetic strategy and study of properties of supramolecular hydrogels based on bile salts. Despite the progress in the studies of gelation, currently there is no common principle to predict the properties of compounds as gelators based on their molecular structure. This accounts for the active interest in bile acids and bile salts — natural steroid surfactants with unique surfactant properties, the formation of organo- and hydrogels involving these compounds, synthesis of BS derivatives and composite materials, extension of the range of modifying agents for hydrogels in order to fabricate environmentally safe systems with new properties and so on.

Labile supramolecular assemblies of both small-molecule and polymeric gelators act as excellent hosts for the insertion of a variety of guests, including nanomaterials. As this manuscript was being prepared, a review was published [184] devoted to the synthesis, properties and applications of various soft composite gels formed from various nanoparticles based on metals or nanocarbon (fullerenes, nanotubes and graphene) with supramolecular (small molecules) or polymeric physical organogels or hydrogels with specified properties.

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