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Stimuli-responsive bile acid-based metallogels forming in aqueous media

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ABSTRACT

The synthesis and gelation properties of a picolinic acid conjugated bile acid derivative in the presence of metal salts along with the stimuli-responsiveness of the systems are reported. The gels are formed in the presence of Cu^{2+} ions in the solvent systems composed of 30–50% of organic solvent (MeOH, acetonitrile, or acetone) in water. The gels respond to various stimuli: they can be formed upon sonication or shaking, and their gel–sol transformation can be triggered by a variety of chemical species. NMR, MS, and SEM techniques are exploited in order to gain a deeper insight on the self-assembled systems.

1. Introduction

The formation of highly ordered nanostructures from small molecules through non-covalent interactions, such as hydrogen bonding, π–π stacking, metal coordination, solvophobic forces, and van der Waals interactions, has widely been utilized as a bottom-up approach to design and prepare nanostructured materials with interesting properties [1,2]. Of these materials, supramolecular gels derived from low molecular weight gelators have attracted ever increasing attention because of the wide range of applications in which they may find use in our daily life. These applications range from *e.g.*, optoelectronics, light harvesting, and hybrid materials to tissue engineering, regenerative medicine, and drug delivery, as exhaustively reviewed several times [3–7].

The interest in the investigation of metal complexes as supramolecular metallogelators has been increasing only in the past decade. The availability and the diversity of metal ligand coordination that could readily induce or control the self-assembly process leading to the gel formation and thereby influence the properties of the formed gel has raised the interest towards metallogels. Especially the utilization of transition metal complexes as metallogelators has been found to lead to materials exhibiting interesting optical, catalytic, and magnetic properties [8]. In general, the incorporation of the metallic elements into the gel matrix can be achieved by either physical entrapment of noncoordinating metallic elements or by exploiting the metal–ligand interactions as the major driving force leading to the gel network formation. Metallogels have been shown to be responsive to external stimuli and exploit a range of spectroscopic, magnetic, catalytic, and redox properties that are inherent to the metals they contain.

Steroids are widespread natural products having a large and rigid steroidal nucleus combined with derivatizable functional groups leading to an adjustable polarity profile, which makes them attractive building blocks when designing novel low molecular weight gelators [9]. Bile acids are a group of steroidal compounds biosynthesized in the liver through several complementary pathways. Besides the rigid steroidal nucleus composed of four fused rings they have a short aliphatic side chain containing a carboxylic acid group in its end. In higher vertebrates the rings A and B of the steroidal nucleus are in *cis*-fusion, causing curvature to the steroidal nucleus, and thus making the molecules facially amphiphilic. The hydroxyl groups are located on the concave α-face, whereas the convex β-face possesses the three methyl groups [10]. Besides as low molecular weight gelators, bile acids and their derivatives have found use in pharmacology [11–13], asymmetric synthesis and chiral discrimination [14], or as receptors for molecular and ionic recognition [15,16], to name a few.

Herein, we report the synthesis and gelation properties of an aminoethyl amide derivative of deoxycholic acid conjugated *via* amide bond with picolinic acid (**4**, Scheme 1) in the presence of Cu^{2+} salts, along with the stimuli-responsiveness of the formed metallogels. Gelation properties of a series of aminoalkyl amides

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of different bile acids have been systematically studied by us lately [17]. *N*-(2-aminoethyl)-3α,12α-dihydroxy-5β-cholan-24-amide (**3**, Scheme 1) employed as a starting compound in the current study was not, however, shown to be capable of self-assembly leading to gelation in the conditions studied. Inspired by the free amino group of the compound we were prompted to synthesize a new conjugate with the desire of gaining better gelation capabilities. Because picolinic acid (**2**, Scheme 1) is known to act as a chelating agent in the human body, it was chosen as the compound to be conjugated with the deoxycholyl derivative. Indeed, compound **4** was shown to form gels in the presence of Cu^{2+} ions in the solvent systems composed of 30–50% of methanol, acetonitrile, or acetone in water. Moreover, the gels were shown to respond to various stimuli: they could be formed upon sonication or shaking, and their gel–sol transformation could be triggered by a variety of chemical species.

2. Experimental

2.1. Materials

Pyridine-2-carboxylic acid (**1**) (99%) was purchased from Aldrich. Other reagents used in the synthetic steps as well as the solvents used in chromatography and gelation studies were of analytical grade. Triethylamine and ethyl chloroformate were distilled prior to use. The mixed anhydride method used in the preparation of the target molecule and slightly modified by us has been reported previously [18–20].

2.2. Synthesis of compound 4

Compound **4** was synthesized by conjugating the freshly prepared pyridine-2-carboxylic acid anhydride (**2**) with *N*-(2-aminoethyl)-3α,12α-dihydroxy-5β-cholan-24-amide (**3**) prepared according to the previously reported synthetic protocol (Scheme 1) [17].

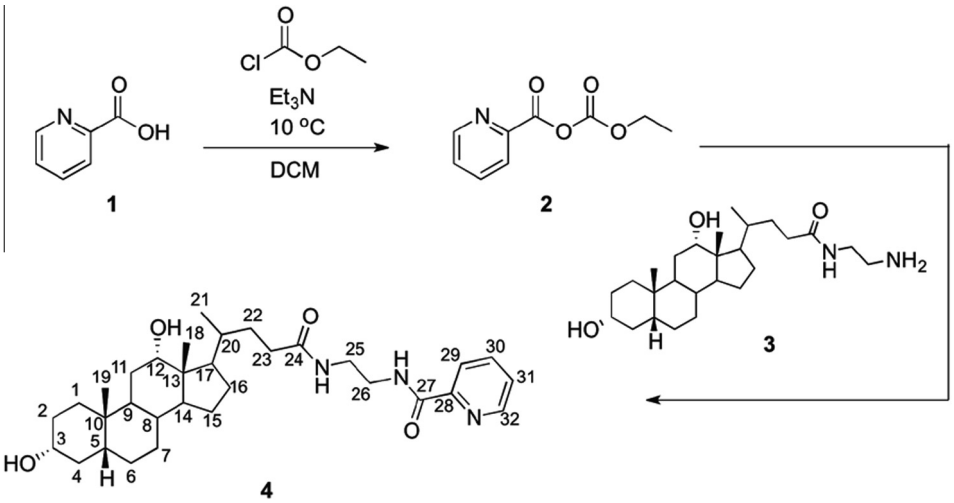
Synthesis of compound **4** was performed in N_2-atmosphere. In a round-bottomed three-necked 250 mL flask picolinic acid (pyridine-2-carboxylic acid; 5.3 mmol, 1 eq.) and dry dichloromethane (40 mL) were cooled on an ice-water bath to +10 °C, after which triethylamine (6.9 mmol, 1.3 eq.) was added to the solution from a dropping funnel, followed by a dropwise addition of ethyl chloroformate (6.9 mmol, 1.3 eq.) in dichloromethane (3 mL). The mixture was stirred at rt for 40 min, after which *N*-(2-aminoethyl)-3α,12α-dihydroxy-5β-cholan-24-amide (5.3 mmol, 1 eq.) in dichloromethane (30 mL) was added dropwise to the freshly prepared picolinic acid anhydride. The stirring was continued for 20 h on an oil bath (40 °C). The crude product obtained after the evaporation of the volatiles was dissolved in $CHCl_3$ (100 mL) and washed with water (2 × 75 mL), 0.1 M HCl solution (2 × 75 mL), water (75 mL), and finally with brine (2 × 75 mL). Then the yellowish organic layer was dried (Na_2SO_4), filtered, and the volatiles evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, CH_2Cl_2:MeOH 90:10) to yield the compound as a white solid.

2.3. Compound 4

Yield 84%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.56 (d, 1H, 32-CH), 8.38 (m, 1H, NH), 8.18 (d, 1H, 29-CH), 7.86 (m, 1H, 30-CH), 7.44 (m, 1H, 31-CH), 6.46 (m, 1H, NH), 3.94 (m, 1H, 12β-H), 3.61 (m, 3H, 3β-H + 26-CH_2), 3.49 (m, 2H, 25-CH_2), 2.24 (m, 1H, 23α/β-H), 2.09 (m, 1H, 23α/β-H), 1.89–0.96 (m, 26H), 0.95 (d, 3H, 21-CH_3), 0.89 (s, 3H, 19-CH_3), 0.63 (s, 3H, 18-CH_3). ^{13}C NMR ($CDCl_3$, 126 MHz, ppm): δ 174.3 (C-24), 165.6 (C-27), 149.5 (C-28), 148.1 (C-32), 137.5 (C-30), 126.4 (C-31), 122.4 (C-29), 73.1 (C-12), 71.8 (C-3), 48.3 (C-14), 47.1 (C-17), 46.5 (C-13), 42.1 (C-5), 40.4 (C-25), 39.4 (C-26), 36.5 (C-4), 36.0 (C-8), 35.3 (C-1), 35.2 (C-20), 34.1 (C-10), 33.7 (C-9), 33.4 (C-23), 31.6 (C-22), 30.5 (C-2), 28.7 (C-11), 27.4 (C6/7), 27.1 (C6/7), 26.2 (C-16), 23.6 (C-15), 23.1 (C-19), 17.4 (C-21), 12.7 (C-18). ESI TOF MS: $[M+Na]^+$ m/z = 562, $[M+K]^+$ m/z = 578. M.W. ($C_{32}H_{49}N_3O_4$) = 539.75. Elemental analysis: Found C, 70.73; H, 9.13; N, 7.67. Calc. for $C_{32}H_{49}N_3O_4 \cdot 0.25H_2O$: C, 70.62; H, 9.17; N, 7.72.

2.4. NMR spectroscopy

^{1}H, ^{13}C, ^{13}C DEPT-135, and 2D PFG ^{1}H,^{13}C HMQC and HMBC NMR spectra used for characterization of the prepared compound were recorded with a Bruker Avance DRX 500 MHz spectrometer equipped with a 5 mm diameter broad band inverse detection probehead operating at 500.13 MHz in ^{1}H and 125.77 MHz in ^{13}C experiments, respectively. The ^{1}H NMR chemical shifts are referenced to the signal of residual $CHCl_3$ (7.26 ppm from internal TMS). The ^{13}C NMR chemical shifts are referenced to the centre peak of the solvent $CDCl_3$ (77.0 ppm from internal TMS). A composite pulse decoupling, Waltz-16, has been used to remove proton couplings from ^{13}C NMR spectra. Assignment of the ^{13}C NMR



Scheme 1. Synthesis route leading to compound **4**.