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Chiral effect on the self-assembly of chiral molecules synthesized from cholesterol

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ABSTRACT

One predesigned chiral steroid base compound cholesteryl 4-(carbonyloxy) 4-(hexyloxyl) benzoate (CCH*) and two achiral compounds with various alkyl chain length oxalyl acid N',N'-di(4-(hexyloxy)benzoyl)-hydrazide (AG6) and oxalyl acid N',N'-di(4-(undecyloxy)benzoyl)-hydrazide (AG11) have been successfully synthesized. Formation of asymmetric self-assembled constructions via self-assembly of achiral molecules in chiral environment was investigated. Due to steric hindrance, CCH* could not form gel in any kind of organic solvents. On the other hand, AG6 and AG11 formed achiral gels in many kinds of solvent. The results suggest that polarity, side branch and intermolecular forces are the key factors for the gelation. Temperature-dependent ^{1}H NMR analysis of the fabricated gels show that van der Waals forces and π-π interactions are key factors leading to self-assembly of molecules result in three-dimensional networks. In addition, CCH* was used as a chiral dopant added into achiral compounds forming asymmetric self-assembled constructions. The results indicate that doping of CCH* into achiral gelators giving a chiral environment leads to the formation of helical constructions. The fabricated asymmetric constructions were confirmed using circular dichroism (CD) spectroscopy and small angle X-ray scattering (SAXS).

1. Introduction

Supramolecular chirality, in last decades, has developed as a dynamic non-covalent chemistry which involves reversible, noncovalent and interaction, with dynamic diversity [1]. In nature, DNA molecule and protein give a sample how it can re-organize molecule to produce nanoconstruction such as, double helix, fibers, sheets and helical structures [2–5]. Driving forces of the self-assembly is non-covalent interaction, for instance, hydrogen bonding, p-p stacking and van der Waals forces [4–12] that it can stimulate by external induction of light, pH, temperature and metal cation [8,13–16]. Cooperation of the secondary forces builds some constructions which stable in thermodynamic and kinetic [9–12]. The Inspired of nature, this phenomenon is widely used in many application like a cosmetic, food, bio-medicine and environment, etc. [5–8,14–16]. Actually, not only the relative weak interaction has particular needed to create nanoconstruction, but also at least one stereogenic center or chiral molecule in self-assembly process [6], which purpose to tune ability the self-assembly.

Recently, chirality has been induced, amplified, memory and transferred from molecule to supramolecular level [14–20]. Transfer chirality can be achieved through noncovalent interaction in gel state condition. There are three possibilities ways to transfer chirality, which are pure chiral molecule [18–24], mixed chiral and achiral molecule, and exclusively pure achiral molecule [20–25]. Combination chiral and achiral molecule as a dopant and how chirality can transferred from chiral to achiral molecule to fabricate nanoconstruction has more issues. Some researcher reported that metal cation can transferred chirality in catalysis process (metal transfer), chiral molecule recognized the guest molecule in chiral separation (chiral separation) [25–28], and chiral drug targeted in our body in medical application [26–32].

Researcher reported some designed molecule which may be able to induce and transfer chirality, such as achiral guest molecules (halide ions) to clickamers [22,33–37], achiral porphyrin to a chiral gelator, chiral Zn II Schiff-base complexes to porphyrin [9,39]. In addition, Some literatures [29–37] reported that combination a chiral gelator and an achiral Schiff base can transferred the chirality via alkyl chain and covalent chain due to Schiff base group. To the best of our knowledge, chiral steroid base is rarely reported as a chiral dopant to induce and transfer chirality into achiral gelator. In our group, we focus on chiral compound and develop some functional group to investigate effect of chirality.

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Recently, we have designed chiral steroid base which appended one or two steroid group [38–40], studied about characteristic chirality and applied for chemosensor, especially for metal cation.

In this paper, one predesigned chiral CCH* and two achiral gelators AG-6 and AG-11 were synthesized. Gelation of the synthesized compounds in various organic solvents was carried out. CCH* chiral dopant was found to induce asymmetric constructions when it was used as a dopant for the gelation of achiral AG-6 and AG-11. The fabricated asymmetric constructions were confirmed using circular dichroism (CD) spectroscopy, scanning electron microscope (SEM) and small angle X-ray scattering (SAXS).

2. Materials and methods

2.1. Materials

4-Hydroxybenzoic acid (99%), potassium hydroxid (KOH, extra pure), potassium iodide (KI, extra pure), Ethanol (C_2H_5OH, extra pure), 1-chlorohexane (95%), hydrochloric acid (HCl, 37%), hydroquinone (99.5%), triethylamine (Et_3N, 99.5%), dry dichloromethane (CH_2Cl_2, ACS), cholesteryl chloroformate (97%), anhydrous magnesium sulphate $MgSO_4$ (extra pure), 4-dimethyl-aminopyridine (DMAP, 99%), N,N'-dicyclohexylcarbodiimide (DCC, 99%), ethyl 4-hydroxybenzoate (ACROSS, 98%.), potassium carbonate (Fisher, 99%), acetone (ACS), 1-bromohexane (Panreac, 98%), chloroform (Panreac), hydrazine hydrate (Shimakyu Pure Chemical, 85%), oxalyl chloride (TCI), 1-bromoundecane (ACROSS, 99%), dry tetrahydrofuran (THF, ACS).

2.2. Instrumentations

Fourier transform infrared (FT-IR) spectra were recorded using a Thermo Nicolet 6700. ^{1}H NMR spectra were obtained using a Bruker AV-500 MHz instrument. The $CDCl_3$ singlet at 7.26 ppm was selected as the reference standard with tetra methyl silane (TMS) as an internal standard. For Temperature-dependent ^{1}H NMR measurement, the gel sample was prepared in an NMR tube containing gelator and selected solvent and the chemical shifts of the gel sample were detected at a temperature between 30 °C and 80 °C with temperature increment 10 °C. The sample morphologies were imaged using High Resolution Scanning Electron Microscope (HR-SEM, Hitachi SU8010) and Transmission Electron Microscope (TEM): Hitachi H-7500. The xerogel for the measurements (SEM and TEM) was prepared by vacuum freeze-drying of the gel formed in the solvent at the critical gelation concentration (CGC) for 12–24 h. The dried samples held on glass substrates were attached to a copper holder for SEM using a conductive adhesive tape and were coated with platinum. For TEM, the gel was placed on a carbon-coated copper grid and then dried under vacuum. The X-ray diffraction (XRD) measurements of the fabricated xerogels were monitored using a Rigaku RINT2000. Circular dichroism (CD) and UV–vis spectra were recorded using a JASCO J-710 and Ultraviolet-visible Absorption Spectrometer (UV–vis) Jasco V-550) which were the sample concentration of 10^{-4} M to 10^{-5} in an optical cell (0.1 mm optical path length).

2.3. Synthesis of chiral steroid base (CCH*)

2.3.1. 4-(hexyloxy)benzoic acid (1)

4-Hydroxybenzoic acid (12.06 g, 0.1 mol), potassium hydroxide (16.83 g, 0.3 mol) and a catalytic amount of potassium iodide (KI) were dissolved in EtOH/H_2O (120 ml, 7:3 v/v). 1-Chlorohexane (13.81 g, 0.1 mol) was added dropwise into the above mixture under stirring at 353 K and refluxed for 24 h. The resulting mixture was cooled to room temperature and poured into deionized water and neutralized with diluted HCl until solid precipitate (about pH 3–4) formed. The white solid precipitate was filtered and dried. Thus obtained crude product was extracted with dichloromethane and washed with water and brine solution. Then the organic phase was collected and concentrated. The resulting product was purified by recrystallization from ethanol. Yield = 46%. ^{1}H NMR ($CDCl_3$, δ in ppm): 1.0 (s, 3H, CH_3), 1.2–1.3 (s, 2H, CH_2), 1.3–1.4 (m, 2H, CH_2), 1.4–1.5 (t, 2H, CH_2), 1.8 (t, 2H, CH_2), 4.0–4.1 (t, 2H, OCH_2), 6.9 (d, 2H, Ar-H), 8.0 (d, 2H, Ar-H). FT-IR (KBr, ν_{max}/cm^{-1}): 1315 (CO–O), 1693 (C=O), 2590 (CH).

2.3.2. Cholesteryl 4-hydroxyphenyl carbonate (2)

Hydroquinone (2.75 g, 25 mmol) and triethylamine (Et_3N) (3.27 g, 30 mmol) were dissolved in dry CH_2Cl_2 (100 ml) in a 250 ml double neck round bottom flask. Cholesteryl chloroformate (8.98 g, 20 mmol) dissolved in dry CH_2Cl_2 (20 ml) was added dropwise into the solution under nitrogen atmosphere and the solution was stirred for 24 h. Then the resulting solution was washed with water in a separating funnel for three times and the organic phase was collected and dried over anhydrous $MgSO_4$, and evaporated the solvent using a rotary evaporator. Thus obtained crude product was purified by column chromatography using silica gel with eluent of ethyl acetate/hexane = 1/3. Yield = 55%. ^{1}H NMR ($CDCl_3$, δ in ppm): 0.6–0.7 (s, 3H, CH_3 in chol.), 2.5 (s, 2H, CH_2CH in chol.), 4.6 (m, 1H, OCH in chol.), 5.4 (d, 1H, HC=C in chol.), 6.8 (s, 2H, Ar-H), 7 (s, 2H, Ar-H). FT-IR (KBr, ν_{max}/cm^{-1}): 1207 (CO–O), 1731 (C=O), 2947 (CH).

2.3.3. Cholesteryl 4-(carbonyloxy) 4-(hexyloxyl)benzoate (CCH*)

Compound (1) (1.11 g, 5 mmol), compound (2) (2.56 g, 4.9 mmol) and 4-dimethyl-aminopyridine (DMAP) (0.61 g, 5 mmol) were dissolved in dry CH_2Cl_2 (100 ml) and stirred under nitrogen atmosphere for 0.5 h. N,N'-dicyclohexylcarbodiimide (DCC) (1.55 g, 7.5 mmol) was dissolved in dry CH_2Cl_2 (10 ml) and then added dropwise into the solution. The reaction mixture was stirred for 24 h at room temperature. The resulting solution was filtrated and washed with water for three times. The organic phase solution was collected and dried over anhydrous MgSO4, and the solvent was removed using a rotary evaporator. The crude product was further purified by column chromatography using silica gel with eluent of ethyl acetate/hexane = 1/3. Yield = 79%. ^{1}H NMR ($CDCl_3$, δ in ppm): 0.6–0.7 (s, 3H, CH_3 in chol.), 2.5 (s, 2H, CH_2CH in chol.), 4.0–4.1 (m, 2H, OCH), 4.6 (m, 1H, OCH in chol.), 5.4 (s, 1H, HC=C in chol.), 6.9–7.0 (d, 2H, Ar-H), 7.2–7.3 (m, 4H, Ar-H), 8.1 (t, 2H, Ar-H). FT-IR (KBr, ν_{max}/cm^{-1}): 1245.8 (CO–O), 1504, 1604 (C=C in Ar), 1758.8 (C=O), 2999.8376 (CH). Scheme 1 shows the synthetic process of the chiral dopant CCH*. Elemental analysis: $C_{47}H_{66}O_6$ (726): Calculated, C: 77.7%, H: 9.1%, O: 13.2%; Found, C: 78.2, H: 8.85, O: 12.95.

2.4. Synthesis of achiral gelators

2.4.1. Ethyl 4-(hexyloxy)benzoate (a1)

Ethyl 4-hydroxybenzoate (6.65 g, 40 mmol) and potassium carbonate (13.82 g, 100 mmol) were dissolved in 150 mL of acetone. 1-Bromohexane (6.93 g, 42 mmol) was added dropwise into the solution under stirring and then refluxed for 24 h. After cooled down to room temperature, the solid precipitates were removed by filtration and the residue was washed with 100 mL of acetone and 100 mL of chloroform twice. The combined filtrate was concentrated. Thus obtained crude product was dissolved in 100 mL of chloroform and then washed with aqueous NaOH and followed by brine solution. The organic layer was collected and dried over anhydrous $MgSO_4$ and the solvent was removed using a rotary evaporator. The product was purified by recrystallization from hexane. The yield of the product was 8.81 g. Yield = 88%. ^{1}H NMR ($CDCl_3$, δ in ppm): 0.9 (s, 3H, CH_3), 1.2–1.3 (m, 3H, CH_3), 1.3–1.4

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