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Synthesis and self-assembly properties of a glycyrrhetinic acid conjugate containing uracil and 2,6-diaminopyridine units†

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A novel glycyrrhetinic acid conjugate containing uracil and 2,6-diaminopyridine units was synthesized and the exclusive supramolecular dimeric structure through six intermolecular hydrogen bonds was characterized by NMR spectroscopy and ESI-MS. The supramolecular dimeric structure could recognize the polar molecule in aprotic polar solvents.

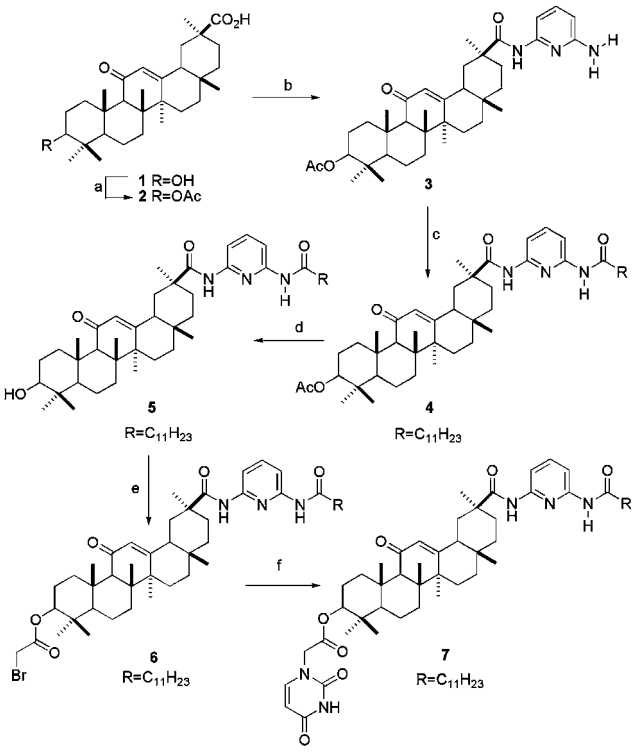
Glycyrrhetinic acid (**1**) is a facile pentacyclic triterpenoid presenting in the form of free acids or aglycones from medicinal plants.[1–3] It has always been noted for the anti-inflammatory, anti-viral and anti-tumor effects.[4–8] However, there are few reports about triterpenoids in supramolecular chemistry.[9–13] Due to their rigid chiral structures, multiple reaction sites and biocompatibility, they has begun to attract more and more attention as scaffolds in supramolecular self-assembly and recognition.

Self-assembly allows access to novel supramolecular architectures with remarkable structural variety, such as linear, cyclic or three dimensional arrays, which is difficult for conventional synthesis.[14–20] So self-complementary molecular structures, which could assemble to form well-defined supramolecular systems through hydrogen bonds, have been designed more and more in recent years.[21–26] Meanwhile, nucleobases have frequently been exploited for the construction of supramolecular structures because of strong degree of interaction.[27–30]

In our previous work, a kind of oleanolic acid derivatives with good gel ability and a glycyrrhetinic acid based receptor for Hg^{2+} were found.[31,32] Here, we report the synthesis of a novel glycyrrhetinic acid bioconjugate containing uracil and 2,6-diaminopyridine units and self-assembly property by hydrogen bonds for the first time.

The synthesis of glycyrrhetinic acid conjugate **7** is outlined in Scheme 1. Glycyrrhetinic acid (**1**) reacted with acetic anhydride in pyridine to give **2**,[33] which was then coupled with 2,6-diaminopyridine to afford **3** in high yield, which subsequently reacted with lauroyl **4** with potassium carbonate, followed by treatment with bromoacetyl bromide to give **6**. Finally, compound **7** was obtained by reaction of **6** with uracil in DMF with 86% yield.

Conjugate **7**, in which glycyrrhetinic acid offered the rigid chiral structure, the complementary 2,6-diaminopyridine and uracil provided the intermolecular six hydrogen bond pairs, and the aliphatic chain containing carbonyl groups facilitated the molecular rotation respectively, was expected to form assembly structures. Initial evidence for assembly of **7** came from ^{1}H NMR spectroscopy studies carried out at 298 K in $CDCl_3$ (Fig. 1). Compared to the corresponding signals of compound **4** and the reference compounds,[34] there were significant downfield shifts of H^a ($\Delta\delta \approx 3$ ppm) and H^g ($\Delta\delta \approx 1$ ppm) of conjugate **7** (70 mM, $CDCl_3$) in ^{1}H NMR spectrum, which clearly indicated the formation of an



Scheme 1 a) Ac_2O, DMAP, pyridine, rt; b) i. $SOCl_2$, Et_3N, benzene, 60 °C; ii. 2,6-diaminopyridine, Et_3N, THF, rt; c) lauroyl chloride, Et_3N, $CHCl_3$, rt; d) K_2CO_3, CH_3OH–THF, rt; e) $BrCH_2COBr$, K_2CO_3, $CHCl_3$, rt; f) uracil, K_2CO_3, DMF, r.t.

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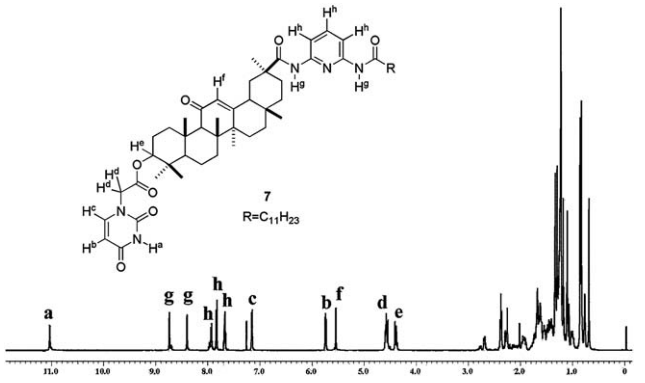

Fig. 1 ^{1}H NMR (300 MHz) spectrum of conjugate **7** (70 mM) in $CDCl_3$.

assembled structure involving hydrogen bonding between the 2,6-diaminopyridine and uracil units.

The appearance of sharp NMR signals further suggested that the hydrogen bonds have not lead to polymeric aggregates. We studied the concentration dependence of signals of **7** in ^{1}H NMR spectrum in the concentration range 0.004–0.095 M ($CDCl_3$, 300MHz) (Fig. 2). It was observed that the shifts of H^a and H^g at the uracil and 2,6-diaminopyridine moieties of **7** moved upfield on dilution and the 1 : 1 dimerization mode was confirmed by plotting the changes in the chemical shift of H^a upon dilution at the uracil moiety. The dimerization constant (41 M^{-1}) was calculated[35] and the self-association of **7** resulted in head-to-tail structure (Fig. 3).

The additional evidence for the formation of intermolecular hydrogen bonds between the 2,6-diaminopyridine and uracil moieties was provided by variable temperature ^{1}H NMR measurements of **7** (70 mM) from 20 °C to 50 °C in $CDCl_3$ (300 MHz) (Fig. 4). As the temperature increased, upfield shifts of H^a (0.021 ppm/K) and H_g (0.009 ppm/K) were observed.

It was further confirmed by ESI-MS to form intermolecular head-to-tail self-assembly of the conjugate **7**. The monomer peaks at *m*/*z* 896.6 $(M + H)^+$ and 918.6 $(M + Na)^+$ were assigned to the quasi-molecular ions in ESI mass spectra. Meanwhile, there were significant signals for the dimer at *m*/*z* 1792.6 $(2M + H)^+$ and 1814.6 $(2M + Na)^+$ in the ESI mass spectra, which were assigned to self-assembly of the conjugate **7** to form dimer (Fig. 5). No signals for higher aggregates were observed.

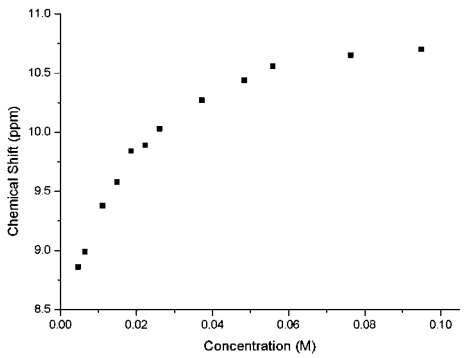

Fig. 2 Dilution shift for H^a of conjugate **7** in the concentration range from 0.004–0.095 M in $CDCl_3$ (300 MHz).

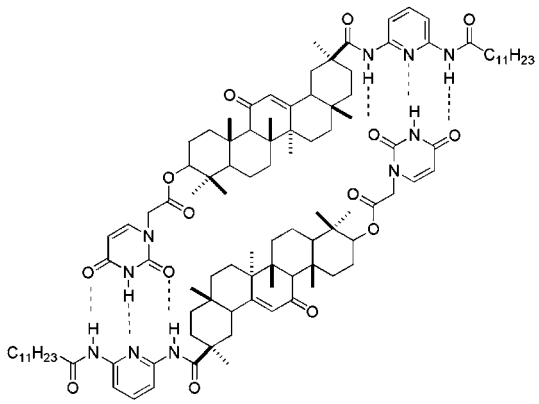

Fig. 3 Self-assembly of conjugate**7** into dimeric species.

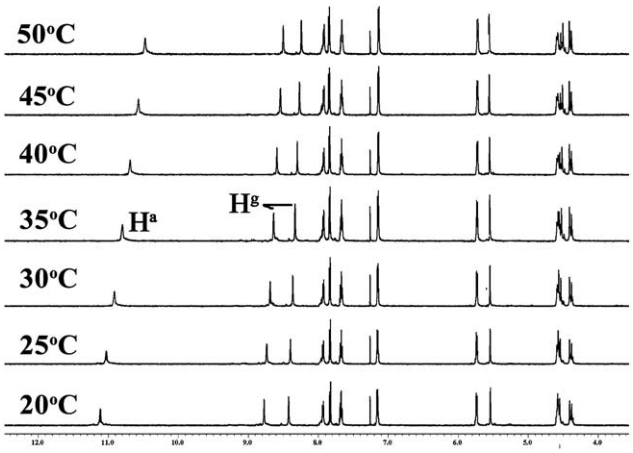

Fig. 4 Variable temperature ^{1}H NMR on increasing the temperature from 20 to 50 °C ($CDCl_3$, 300 MHz) of conjugate **7**.

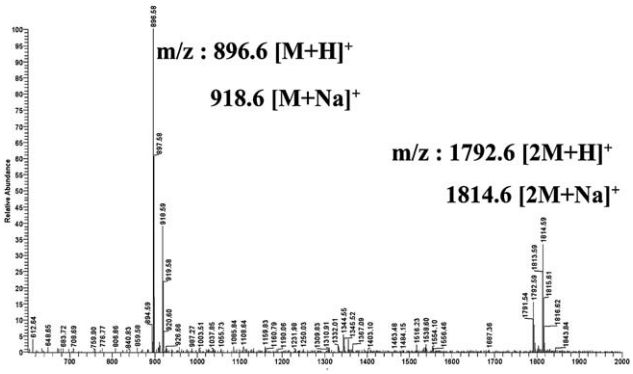

Fig. 5 ESI-MS spectrum of conjugate **7**.

In order to confirm the supramolecular dimeric structure could recognize the polar molecules by both hydrogen bonds and the specially formed cavitary skeleton, the solubility of cresol red sodium (CR, a hydrophilic dye) was investigated with **7** in chloroform (an aprotic polar solvent) based on solid-liquid extraction measurement (Fig. 6).[36] The result showed that the amount of dye extracted increased linearly with the concentration of **7**, while compound **4** and **5** have no effect for the dye encapsulation. It suggested that this cyclic

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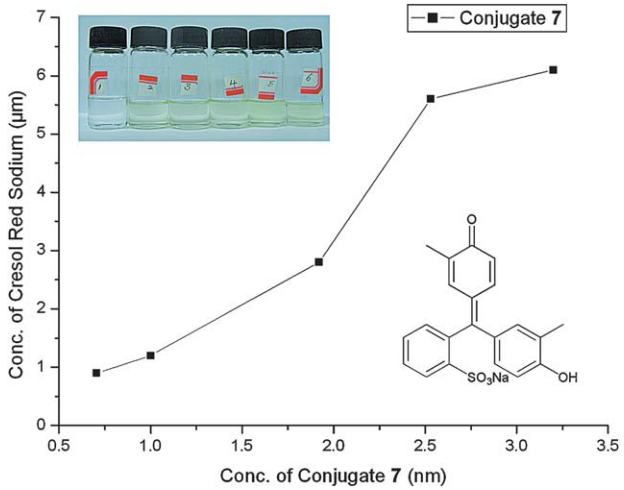

Fig. 6 Solubilization of CR by conjugate **7** (insert: extraction of CR by increasing concentrations of **7**. Left to right: [**7**] = 0–3.2 mM).

dimer could be used to increase the solubilization of polar molecules in aprotic polar solvents due to its suitable cavity and hydrogen bonds.

Meanwhile, the ^{1}H NMR signals of **7** were compared with those of CR's extraction of **7** (Fig. 7). It showed that the signal of H^a of **7** appeared as broader in the extraction of CR (65 mM, 25 °C, $CDCl_3$) than that of **7** alone and upfield slightly (0.06 ppm). It indicated that the H^a of **7** participated the extraction of CR in chloroform.

Based on the above results, the assumption model of exclusive supramolecular dimeric structure was proposed as Fig. 8. The intermolecular hydrogen bonds, the carbonyl groups on linker and triterpenoid skeleton might play important roles in the extration of polar molecule in aprotic polar solvents. This supramolecular dimeric

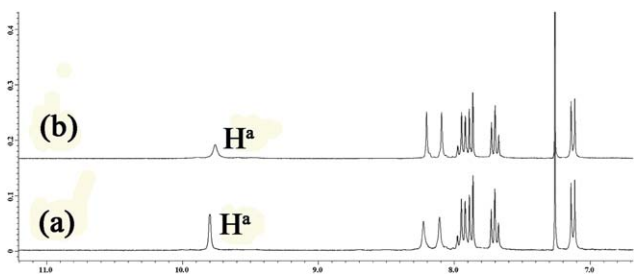

Fig. 7 Partial ^{1}H NMR spectra of (a) conjugate **7** and (b) extraction of cresol red sodium of conjuate **7** ($CDCl_3$, 300 MHz).

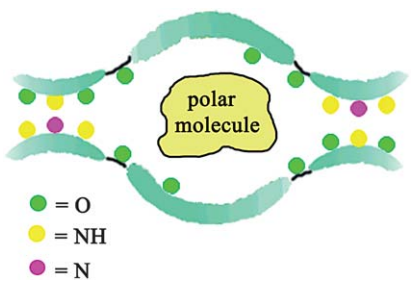

Fig. 8 The assumed model of the exclusive dimeric supramolecular structure.

structure might be used as the potential selective host–guest encapsulation in biomaterial.[37–40]

In conclusion, the glycyrrhetinic acid conjugate **7** containing 2,6-diaminopyridine and uracil units could assemble a stable cyclic dimer exclusively through six intermolecular hydrogen bonds. This head-to-tail self-assembled symmetrical cavity structure showed package effects for polar molecules in nonpolar solvents, and it might be used for potential selective encapsulation in biomaterials.

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