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Unprecedented α-cyclodextrin metal-organic frameworks with chirality: Structure and drug adsorptions

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ABSTRACT

An assembly of cyclodextrin metal-organic frameworks (CD-MOFs) has aroused extensive research interests due to their excellent encapsulation capacity and biocompatibility. In this work, starting from the chiral building block α-cyclodextrin (α-CD), a novel α-CD-MOF compound with left-handed chiral helices, $[Na(H_2O)(C_{36}H_{60}O_{30})]\cdot H_2O$ (Na-α-CD-MOF), was synthesized through changing the diffusion solvent, and then structurally characterized. Single crystal X-ray diffraction analysis reveals that Na-α-CD-MOF exhibits a 3D left-handed helical chiral framework with large cavities (740 $Å^3$). The result of a drug adsorption assay shows Na-α-CD-MOF possesses a more efficient drug adsorption capacity than α-CD matrix, and the solubility of the drug adsorbed in Na-α-CD-MOF can be greatly enhanced. All the results, including the lower cytotoxicity, indicate that Na-α-CD-MOF is an excellent kind of renewable, environmental friendly and biocompatibility drug carrier material.

1. Introduction

Metal-organic frameworks (MOFs) [1] represent an extensive class of porous crystalline solid material, which are being evaluated for numerous applications, such as adsorption, [2] separations [3] and drug delivery [4]. However, the vast majority of MOFs reported to date are composed of organic struts derived from non-renewable petrochemical feedstocks and transition metals, only a handful of MOFs have been derived from natural products. As a special class of carbohydrates, cyclodextrins (CDs) consisting of six, seven or eight α-1,4-linked D-glucoses (α-, β- or γ-CDs, respectively) display the –OCCO-binding motif on both their primary (1°) and secondary faces (2°) (Scheme 1), auguring well for forming extended structures with metal cations (named as CD-MOFs). Note, CD-MOFs can combine the porous features of MOFs with the excellent encapsulation capacity of CD for drug molecules, [5] which can bring about more excellent performance. More importantly, CD-MOFs are "green" in the sense they can be synthesized from renewable sources that are themselves derived from water, CO_2 and non-toxic metal salts.

Recently, many α-, β- and γ-CDs based MOFs have been reported, being prepared through the vapor diffusion method, [6,3c] solvothermal method [7] and conventional syntheses [8]. Due to the weak non-covalent interactions between the CDs and metal ions, many parameters, such as initial reactants and their stoichiometry, pH and temperature, can significantly affect the structures of the resultant CD-MOFs. Just like professor Stoddart reported [6f], merely changing the CD from γ-CD to α-CD with the same synthetic protocols has resulted in the formation of a very different class of extended structures. So the construction of homogeneous and novel CD-MOFs is challenging and a difficult task. Recently, the Stoddart group reported a series of CD-MOFs comprised of γ-CD coordinated to alkali metal cations [6], and our group also synthesized some CD-MOFs based on β-CDs and alkali metals, which exhibit fascinating structures and good drug delivery [7,8]. In our ongoing investigation of CD-MOF materials, we found that Rb-α-CD-MOF [6f] exhibits porous, infinitely long, fascinating left-handed helical channels, but it is with regret that Na/K-α-CD-MOF failed to be isolated successfully by similar protocols. Herein, by changing the diffusion solvent, a new CD-MOF compound, $[Na(H_2O)(C_{36}H_{60}O_{30})]\cdot H_2O$ (Na-α-CD-MOF), was successfully isolated. In addition, in order to elucidate the drug adsorption capacity of Na-α-CD-MOF, 5-Fluorouracil (5-FU), Silybummarianum (SL), Methotrexate (MTX), Ferulic acid (FA) and Quercetin (QT) (Scheme S1) as drug models are chosen in this work.

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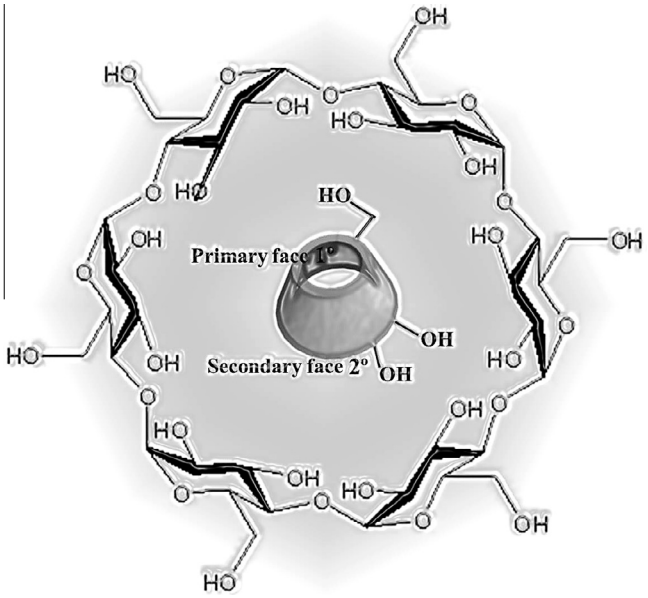

Scheme 1. Structure formula of α-cyclodextrin (α-CD) with its C6 symmetry, and the six C6 hydroxy (OH) groups and six glycosidic ring oxygen atoms constituting the primary face (1°) of α-CD molecules, and the 12 C_2 and C_3 OH groups constituting the secondary face (2°).

2. Experimental section

2.1. Materials and general methods

α-Cyclodextrin (α-CD, 98%) was purchased from Shanghai Jinsui Bio-Technology Co., Ltd, tetramethylammonium hydroxide solution (25%), 5-FU, SL, MTX, QT and FA from SCR (Shanghai), Counting Kit-8 from Beyotime Institute of Biotechnology and all the organic solvents from Aladdin-reagent (Shanghai). Double distilled water was used to prepare all the solutions. HepG2 cells were provided by Basic Medical College, Jiamusi University. Elemental analyses were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer (C and H) and a Thermo Fisher Ice3500 Atomic Absorption Spectrometer (Na). The IR spectra were obtained on an Alpha Centaurt FT/IR spectrometer with KBr pellets in the 400–4000 cm^{-1} region. XRPD patterns were obtained with a Rigaku D/max 2500V PC diffractometer with Cu-Kα radiation, the scanning rate was 4°/s and 2θ ranged from 5° to 40°. UV–Vis absorption spectra were recorded on a 756 CRT UV–Vis spectrophotometer.

2.2. Synthesis of $[Na(H_2O)(C_{36}H_{60}O_{30})]\cdot H_2O$ (Na-α-CD-MOF)

α-CD (650 mg, 0.5 mmol), NaOH (0.16 g, 4 mmol) and tetramethylammonium hydroxide solution (25%, 0.2 mL) were dissolved in H_2O (10 mL). The aqueous solution was filtered and MeOH (ca. 30 mL) was allowed to vapor diffuse into the solution over the period of a month. White needle crystals (Fig. S1), suitable for X-ray crystallographic analysis, were isolated, filtered and washed with MeOH. Yield: 68% (based on α-CD). *Anal.* Calc. for $C_{36}H_{64}NaO_{32}$ (1031): Na, 2.23; C, 41.90; H, 6.21. Found: Na, 2.21; C, 41.78; H, 6.37%.

2.3. Drug adsorption assay

Dissolving 5-FU (50 mg) and α-CD (50 mg) in ethanol (10 mL), over 2.5 days, yielded a heterogeneous solution. The mixture was then centrifuged and the solid (5-FU-α-CD) was filtered, washed with ethanol and dried at room temperature. The 5-FU content was calculated through UV/Vis results (λ = 264 nm) (ESI†). According to the same method, SL-α-CD, MTX-α-CD, FA-α-CD, QT-α-CD, 5-FU-Na-α-CD-MOF, SL-Na-α-CD-MOF, MTX-Na-α-CD-MOF, FA-Na-α-CD-MOF and QT-Na-α-CD-MOF were prepared (λ = 288 nm for SL, 266 nm for MTX, 320 nm for FA, 377 nm for QT). The standard curve equation in ethanol is as follows:

$$A_{5-FUethanol} = 0.0573C + 0.004 \quad R^2 = 0.9991$$
$$A_{MTX\ ethanol} = 0.0343C - 0.0102 \quad R^2 = 0.9997$$
$$A_{SL\ ethanol} = 0.0499C - 0.0524 \quad R^2 = 0.9991$$
$$A_{FA\ ethanol} = 0.0965C - 0.01403 \quad R^2 = 0.9997$$
$$A_{QT\ ethanol} = 0.0659C + 0.05001 \quad R^2 = 0.9997$$

The adsorption percentage (q) of CD-MOFs towards drug was calculated as follows:

$$q_t = \frac{V(C_0 - C_t)}{W} \times 100\%$$

where *qt* is the loading rate at contact time *t*, *V* is the volume of drug solution (mL), C_0 is the initial concentration of drug (mg m L^{-1}), C_t is the concentration of drug at contact time *t* (mg m L^{-1}) and W is the weight of the compounds (mg).

2.4. In vitro cytotoxic assay

The human hepatoma carcinoma cell line HepG2 was cultured in a 37 °C humidified incubator at 5% CO_2 with DMEM (Gibco, USA), containing 10% FBS (Gibco, USA), 100 units/ml penicillin and 100 units/ml streptomycin. The cytotoxicity study of compound on HepG2 cells was tested by the Cell Counting Kit-8 (CCK-8) experiment. The experiments were divided into five groups: blank group (without cells), negative control group (cells with no drug), drug group, compound group (α-CD and Na-α-CD-MOF), drug-loading group (5-FU-α-CD, MTX-α-CD, 5-FU-Na-α-CD-MOF and MTX-Na-α-CD-MOF). The respective liquid was added to each group to give a final concentration of 100, 50, 25, 12.5 and 6.25 μg ml^{-1}, and then cultured for 48 h. Finally CCK-8 (each hole 10 μL) was added, and the cellular survival rate was monitored at BIV-TEK INSTRUMENTS INC (λ = 540 nm).

2.5. Solubility test assay

An excess of the drug compounds were put in phosphate buffer solution (10 mL, pH = 7.4), respectively, and shaken at 2 °C for 48 h until a dissolution equilibrium was reached. The mixture was then centrifuged and filtered. Meanwhile, the drug-loading compounds were also processed in the same way. The drug value of the solution was determined by the UV/Vis results (ESI†). The standard curve equations in PBS are as follows:

$$A_{5-FU\ PBS} = 0.0505C + 0.0037 \quad R^2 = 0.9991$$
$$A_{MTX\ PBS} = 0.0314C - 0.0116 \quad R^2 = 0.9997$$
$$A_{SL\ PBS} = 0.035738C - 0.0227 \quad R^2 = 0.9991$$
$$A_{FA\ PBS} = 0.090813C + 0.011 \quad R^2 = 0.9997$$
$$A_{QT\ PBS} = 0.0165C + 0.1057 \quad R^2 = 0.9997$$

2.6. X-ray crystallographic study

Crystal data for Na-α-CD-MOF was collected on an Agilent Technology Eos Dual system with focusing multilayer mirror optics and a Mo-Kα source (λ = 0.71073 Å). Empirical absorption corrections were applied to the intensities using the SADABS program [9]. The structure was solved using the program SHELXS-97 [10] and refined with the program SHELXL-97 [11]. The positions of the hydrogen atoms on the carbon atoms were calculated theoretically. A