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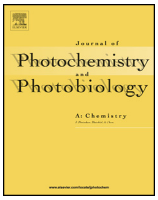

Invited feature article

Modulating the reactivity of chromone and its derivatives through encapsulation in a self-assembled phenylethynylene *bis*-urea host

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ABSTRACT

This manuscript reports on the modulation of the photoreactivity of a series of chromones, also known as benzo-γ-pyrones, by absorption into a porous self-assembled host formed from phenylethynylene *bis*-urea macrocycles. Chromone and four derivatives namely 6-fluorochromone, 6-bromochromone, 7-hydroxy-4-chromone, and 3-cyanochromone are unreactive in the solid-state. Each of these derivatives was loaded into the nanochannels of self-assembled phenylethynylene *bis*-urea macrocycles to form solid host·guest complexes, which were subsequently UV-irradiated at room temperature under argon atmosphere. We observed that chromone and 6-fluorochromone underwent selective [2+2] photodimerization reactions to produce *anti*-HT dimers in high selectivity and conversion. The 6-bromochromone also reacted in high selectivity and conversion to afford an aryl coupling adduct. In each case, the products were extracted, and the crystalline host recovered. In comparison, 7-hydroxy-4-chromone, and 3-cyanochromone were unreactive within the complex. Simple GCMC simulation studies suggest that chromone, 6-fluorochromone, and 6-bromochromone were loaded in orientations that facilitate photoreaction, and correctly predicted that the *anti*-HT dimer would be favored in the chromone case. In contrast, *syn*-HH dimers were predicted by GCMC simulations for the halogen containing derivatives but were not observed. The simulations with 7-hydroxy-4-chromone were in agreement with the observed reactivity. We compare these computational and experimental findings and suggest future methods for optimizing simulation parameters. Our goal is to expand the scope and accuracy of the simulations to be able to predict the reactivity of guests encapsulated within columnar nanotubes.

1. Introduction

Inspired by nature's exquisite control over reactivity within the defined spaces of enzyme active sites, chemists have designed and investigated many molecular and supramolecular hosts as well as examined the use of porous materials to facilitate the reaction of encapsulated guests [1–7]. These 'nanoreactors' provide confined environments to induce selectivity, modulate the reaction pathway, and potentially catalyze the reaction [8]. Our group studies how the photolysis of small organic molecules is altered and influenced by the encapsulation within the cylindrical channels of stable, porous, crystalline hosts [9]. These hosts are formed through the supramolecular assembly of *bis*-urea macrocycles, such as the phenylethynylene *bis*-urea **1**, which self-assembles into columns that contain guest accessible channels of ~0.9 nm diameter (Fig. 1). Here, we investigate the application of this host to uptake chromone and its derivatives and study the effects of this encapsulation on the subsequent photoreactions versus the reactions of these derivatives in their solid-state form. Specifically, this manuscript applies systematic experimental and computational methods to evaluate: (1) the reactivity of chromone and four of its derivatives in the solid-state; (2) the use of GCMC simulations to investigate the organization of guests within the confined channel of a self-assembled phenylethynylene *bis*-urea host and to analyze if neighboring guests are aligned for facile photoreaction; and to evaluate experimentally (3) the uptake of chromones and their subsequent reactivity upon UV-irradiation.

Chromone (4H-1-benzopyran-4-one) belongs to the flavonoid family. Flavonoids play a vital role in plants as secondary metabolites [10]. Chromone serves as a key scaffold in synthetic organic chemistry [11], medicinal chemistry [12], and drug discovery [13]. In solution, simple chromones may undergo photodimerizations and photoaddition reactions [14] with olefins and acetylenes. For example, benzene solution UV-irradiation of

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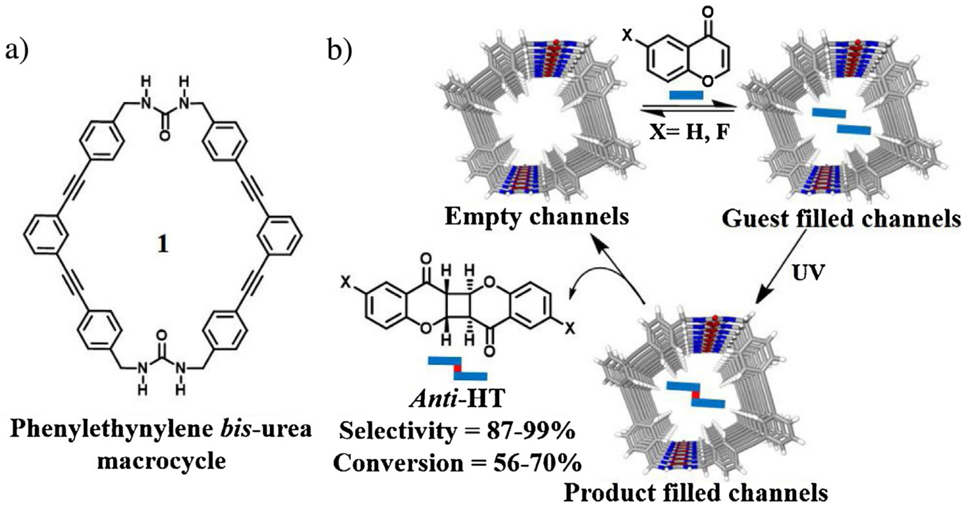

Fig. 1. Self-assembled phenylethynylene *bis*-urea macrocycles used as a confinement for conducting selective photodimerization of chromones. (a) Structure of the phenylethynylene *bis*-urea macrocycle [21]. (b) Loading of chromone and 6-fluorochromone affords host **1**·guest complexes that facilitated the selective formation of the respective *anti*-HT photodimers upon UV-irradiation.

chromone produced *anti*-HT and *trans-fused* HT dimers in $\sim$1:1 ratio with 30% conversion and 99% yield [15]. The dimerization efficiency greatly depended upon the concentration of chromone [16]. Indeed, UV-irradiation of chromone-2-carboxylic esters (methyl, ethyl, or *iso*-propyl) in acetonitrile solutions produced *anti*-HH dimers from the triplet excited state while solid state reactions of methyl and *iso*-propyl chromone-2-carboxylic ester yielded the *anti*-HT dimers, and no solid state reaction was observed in ethyl derivative or for the parent chromone. Hanifin and Cohen reported the photoreactions of chromone with tetramethylethylene, 1-dimethoxyethylene, cyclopentene, and 2-butyne to obtain a variety of cycloadducts [17,18]. Nath et al. employed the photocycloaddition reaction of 2, 3, 7-trimethylchromone with ethylene as a key reaction in the synthesis of two marine natural products [19]. Studies from Valiulin and Kutateladze showed that the Diels–Alder adducts of chromones could undergo an intramolecular $[2\pi+2\pi]$ alkene–arene photocyclization reaction [20].

Herein, we examine the utility of host **1** to bind, organize and facilitate the photoreactions of a series of simple chromones in the solid-state. Host **1** is formed by the columnar self-assembly of a phenylethynylene *bis*-urea macrocycle (Fig. 1a) [21]. This assembly process is driven by the urea hydrogen-bonding motif as the compound crystallized from DMSO. Heating drives off the DMSO solvent leaving open columnar channels, which are accessible to new guests. Our study into the utility of this host proceeded through both experimental investigation of what guests can be loaded into this confined channel as well as through GCMC simulations to predict not only guest absorption but also subsequent effects of this confinement on guest reactivity. The GCMC simulations were carried out using Monte Carlo for Complex Chemical Systems (MCCCS) Towhee [22] plug-in built into Scienomics' Materials Processes and Simulations (MAPS) platform [23] and suggested that the chromone, 6-fluorochromone, 6-bromochromone, and 7-hydroxy-4-chromone would load into the channels of host **1**; however, simulations predict that only the first three compounds would be favorably positioned for photoreactions. Simulations were not carried out on 3-cyanochromone due to incompatibility of the configurational bias settings with the cyano functional group and consistency of the bias settings with previous simulations.

The simulations suggest that the orientation of chromone inside the channel should favor formation of *anti*-HT photodimers. In comparison, the *syn*-HH dimers were predicted for 6-fluorochromone, and 6-bromochromone. Experimentally, we confirmed that the crystalline chromones were unreactive and stable to prolonged UV-irradiation. Host **1** absorbed each of these guests from solution to form solid-state host·guest complexes with the host:guest binding ratios dependent on the size and polarity of the guests (Fig. 1b). We tested if the solid-state photochemistry of chromones was modulated by incarceration within the crystalline host. Upon UV-irradiation of the respective host **1**·guest complexes, both chromone and 6-fluorochromone underwent [2+2] photodimerization reactions within the host in high conversion and selectivity. We observed 70% of chromone and 56% of 6-fluorochromone converted into photodimers. The *anti*-HT dimers were afforded as the major products in these host·guest complexes with 87% selectivity for chromone and >99% for 6-fluorochromone. The 6-bromochromone also reacted within the host complex forming a coupling adduct in high selectivity (>99%) and 70 % conversion. In this case, no [2+2] photocycloaddition was observed. In comparison, 7-hydroxy-4-chromone, and 3-cyanochromone proved to be unreactive within the host·guest complexes. The GCMC simulations predicted the reactivity of chromone, 6-fluorochromone, 6-bromochromone, and 7-hydroxy-4-chromone when encapsulated within the host. However, calculations predicted the observed product selectivity only in the case of chromone, which contains no additional polar functional groups. Our future goals are to synergistically evaluate the reactivity of encapsulated guests while concurrently optimizing GCMC simulations. We are currently addressing the computational simulations by evaluating new force fields, probing the effects of configurational bias settings, and testing variety of MC moves as well as probabilities.

2. Experimental

2.1. Materials and methods

All chemicals were purchased from Aldrich or VWR. Chromone and all its derivatives were further purified by recrystallization prior to loading. The phenylethynylene *bis*-urea macrocycle was prepared and recrystallized from DMSO to obtain host **1**·DMSO according to previous procedures [21]. Thermogravimetric analysis (TGA) was carried out in TA instrument SDT-Q600 to evacuate DMSO solvent from the channels of host **1**·DMSO prior to loading