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Research paper

Mechanistic study of hemicucurbit[6]uril formation by step-growth oligomerization and end-to-end cyclization

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ABSTRACT

The formation of hemicucurbit[6]uril (hCB[6]) from ethyleneurea with formaldehyde in acidic aqueous solution was explored using density functional methods and the implicit solvation model in water. The oligomerization and cyclization barriers were approximately half lower than that of the iminium formation. Thus, the initial iminium formation is the rate-determining step, and the formation of hCB[6] is *kinetically* and *thermodynamically* favored in acidic aqueous solution. In particular, the 'alternate' conformation of hCB[6] is enthalpically and entropically preferred over the 'cone' conformation, which is consistent with the crystal structure of hCB[6].

1. Introduction

Cucurbit[*n*]urils (CB[*n*]) are macrocyclic compounds composed of *n* glycoluril units connected by 2*n* methylene bridges (Fig. 1) and are prepared by the condensation of glycoluril with formaldehyde (FA) under acidic conditions [1–5]. CB[*n*] has a hydrophobic cavity and polar ureido carbonyl groups at the portals, providing a potential inclusion site for nonpolar molecules and binding sites for ions and molecules, respectively [1–5]. The ability of CB[*n*] to form various host-guest complexes has broadened their applications in drug delivery, fluorescence spectroscopy, catalysis, and nanomaterial engineering [5].

Miyahara et al. synthesized hemicucurbit[*n*]urils (hCB[*n*], $n = 6$ and 12) by the condensation of ethyleneurea with FA in acidic medium, where hCB[6] resembles the structure obtained by cutting CB[6] in half along the equator (Fig. 1) [6]. In the crystal structure of hCB[6], the six ethyleneurea units adopted an 'alternate' conformation with *anti*-orientations of two adjacent units [6]. hCB[6] formed complexes with halides and thiocyanate but not with metal cations, except Co^{2+}, Ni^{2+}, and UO_2^{2+}, in aqueous solution [7,8]. Svec et al. reported the synthesis of a cyclic hexamer, bambus[6]uril (BU[6]), which combines the structural features of CB[6] and hCB[6] with glycoluril and ethyleneurea units in alternate orientations [9]. BU[6] was prepared by an acid-catalyzed condensation of 2,4-dimethylglycoluril with FA in HCl solution and showed good affinity for halide anions. Recently, Aav et al. synthesized cyclohexylhemicucurbit[6]uril, which adopted an alternate conformation, with apolar cyclohexyl groups around the openings and polar ureas in the middle, and formed complexes with halides, carboxylic acids, and amines in $CDCl_3$ [10].

Although several nuclear magnetic resonance (NMR) experiments [11] and density functional theory (DFT) calculations [11–17] were performed to elucidate the structures and binding affinities of hCB[6] and BU[6] with various anions, no mechanistic studies have examined the formation of hCB[6] experimentally and computationally. Makrlík and coworkers also studied the complex formation of BU[6] with ionic species such as H_3O^+, $(H_3O^+)_2$, and Cs^+I^- using DFT methods [18,19]. In addition, several DFT studies were performed to explore the mechanisms of iminium as potential Mannich reagents [20–22] and proline-catalyzed Mannich reactions [23–25]. However, no quantum-chemical study reported the pathway to form iminium in Mannich reactions. Here, we explored the formation of hCB[6] by step-growth oligomerization and end-to-end cyclization using DFT methods in water. In particular, two pathways, via *anti*- and *syn*-orientations of two adjacent ethyleneurea units, were considered for the formation of acyclic methylene-bridged ethyleneurea dimer to determine why only the *anti*-orientations exist in the 'alternate' conformation of hCB[6] in crystal.

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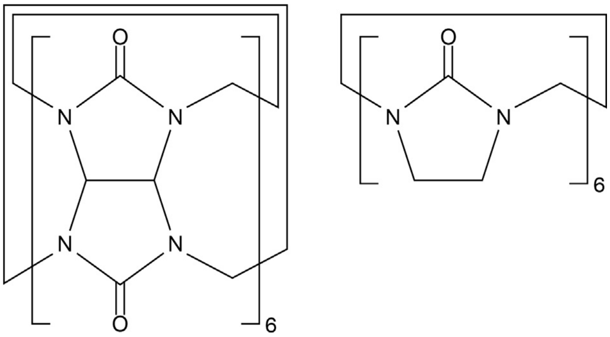


Fig. 1. Chemical structures of CB[6] (left) and hCB[6] (right).

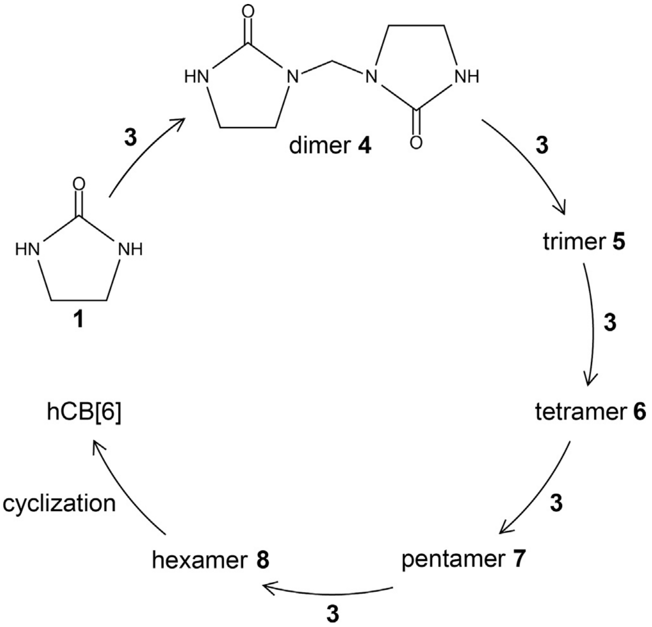
2. Computational methods

2.1. Proposed mechanism of hCB[6] formation

Because hCB[6] was prepared by the condensation of ethyleneurea with FA in acidic conditions, this reaction is similar to the Mannich reaction [26–29]. In Mannich reactions of amines with FA in acidic media, the production of the iminium ion from hydroxymethylamine and its subsequent reaction with the active hydrogen atom to produce the Mannich base was suggested. Recently, the existence of the protonated aldehyde and the iminium intermediate in Mannich reactions catalyzed by the imidazolium-based ionic liquid was confirmed by electrospray ionization (tandem) mass spectrometry [ESI-MS(/MS)] [30]. Specifically, the condensation of glycoluril with less than two equivalents of FA produced a reaction mixture containing acyclic methylene-bridged glycoluril oligomers (dimer–hexamer), which supported the step-growth oligomerization and end-to-end cyclization during CB[*n*] formation [31]. Based on these experimental results, we proposed a stepwise mechanism of hCB[6] formation in water. The pathway of iminium formation is shown in Scheme 1, and the step-growth oligomerization and end-to-end cyclization to yield hCB[6] are presented in Scheme 2.

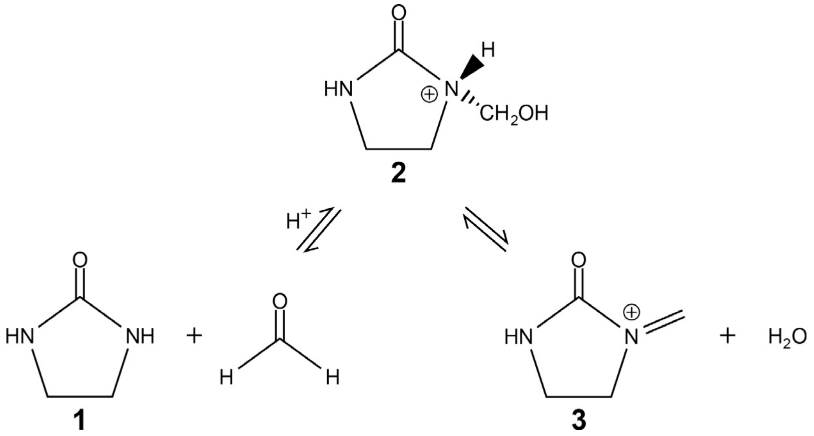
2.2. Computational details

All structures were optimized using the hybrid-meta-GGA M06-2X functional [32] and the solvation model based on the density (SMD) method [33], as implemented in GAUSSIAN 09 programs [34,35]. GaussView [36] was used to edit the peptide structures. All initial structures were optimized at the M06-2X/6-31+G(d) level of theory in the gas phase. Further optimizations were then performed at the SMD M06-2X/6-31+G(d) level of theory in water.



Scheme 2. Formation of the acyclic methylene-bridged ethyleneurea oligomers by step-growth oligomerization and hCB[6] by end-to-end cyclization.

First, the initial structures of the transition states (TSs) ts$_{i1}$ and ts$_{i3}$ for iminium formation were constructed from the optimized structures of hydroxymethylamine (**2**) and iminium (**3**), respectively, in Scheme 1, which was followed by TS optimization. In addition, each TS was verified using the intrinsic reaction coordinate (IRC) method [37,38] to determine whether it connects the reactants and products. However, as in most cases, the IRC calculation did not step all the way to the minimum on either side of the path. Further optimizations were conducted starting from the reactants and products obtained by the IRC method to reach the two minima connected by the TS. However, the torsion angle χ of the C(=O)—NH—CH$_2$—OH sequence of **2** was different for the products (i.e., intermediate I$_1$) from the IRC calculations of ts$_{i1}$ and the reactants (i.e., intermediate I$_2$) from the IRC calculations of ts$_{i3}$, whose values were 76.9° and 178.9°, respectively. From the potential energy scan of the torsion angle χ, ts$_{i2}$ between I$_1$ and I$_2$ was located at $\chi = 127.8°$. The calculated pathway of iminium forma-



Scheme 1. Formation of the iminium derivative from ethyleneurea and FA in acidic aqueous solution.