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Inhibition and Stabilization: Cucurbituril Induced Distinct Effects on the Schiff Base Reaction

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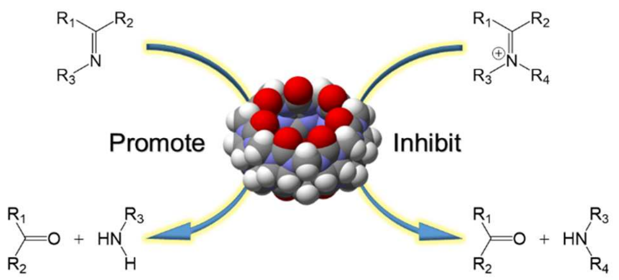
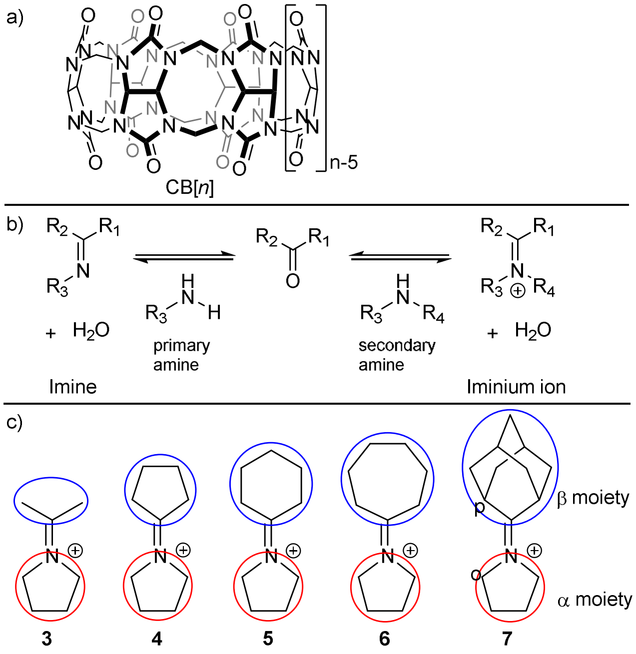
ABSTRACT: The different effects of cucurbit[7]uril (CB[7]) on the Schiff base reactions in aqueous solution were explored by ^{1}H NMR spectroscopy and single X-ray crystallography. With CB[7] the condensation reaction of aldehyde and primary amine is dramatically inhibited. In contrast the presence of CB[7] does tremendously stabilize iminium cation in water through ion-dipole interactions. A single crystal structure of the complex of iminium ion **7** with CB[7] grown in water is reported.



It is always at the heart of synthetic chemistry to develop novel, cleaner, more efficient and selective reactions. To this end, there has been a recent explosion of interest in the use of microenvironments to simulate the catalyst prowess of enzymes.[1-3] Appearing in the late 1990s, nano-reactors (NRs) have attracted considerable attention because of their ability to control reaction processes. Moreover within supramolecular chemistry numerous successes in this area have been achieved using different kinds of hosts. For example, self-assemblies such as cages and "soft ball" have been found to catalyze organic reactions.[4-7] In addition, other cyclic hosts such as crown ethers, cyclodextrins and calixarenes have been also used in different kind of reactions.[8-10]

Among the macrocyclic hosts, cucurbit[*n*]uril (CB[*n*], n = 5-8, 10, Scheme 1a) possess a hydrophobic cavity and two identically open portals with 2*n* carbonyl oxygens. These structural features lead to outstanding molecular recognition properties towards cationic and neutral guests.[11-13] CB[*n*] have showed an exquisite ability as nano-reactors, catalyst, and to the stabilization of highly reactive species.[14-17] Relatedly, several groups have focused on the use of CB[*n*] as protective agent in different reactions.[18,19]

The Schiff base reaction (Scheme 1b), discovered by German chemist Hugo Schiff,[20] is a well known and wildly utilized reaction in numerous domains.[21-23] Furthermore, imines are also important enzymatic intermediates in *vivo* such as the reaction of a common enzyme cofactor PLP and a lysine residue.[24] In this work we investigate the effects of CB[*n*] on the reversible Schiff base reaction and the stability of iminium cations using ^{1}H NMR spectroscopy and single X-ray crystallography.



Scheme 1. Structure of CB[*n*] (a), Schiff base reaction (b) and structure of iminium cation compounds (c).

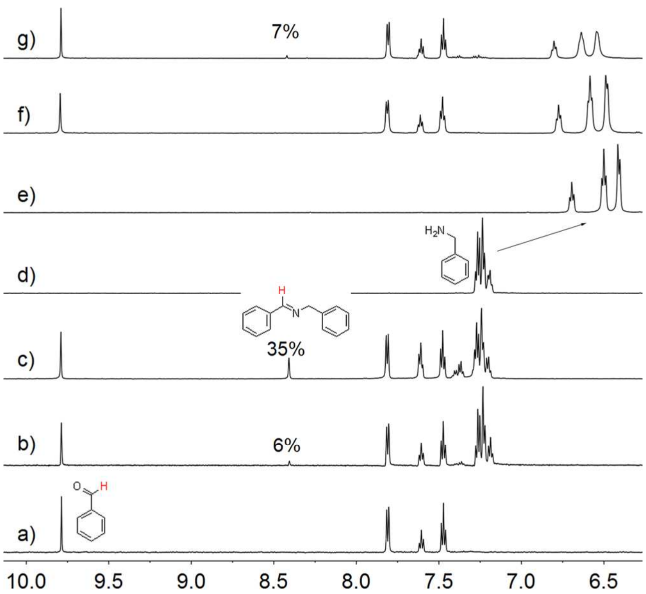
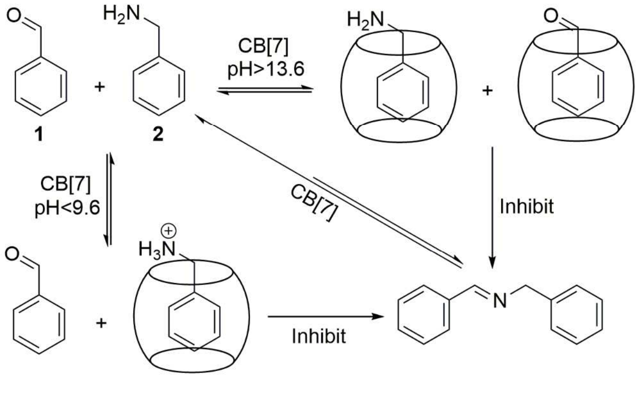


Figure 1. Partial ^{1}H NMR spectra (600 MHz, D_2O) for a) **1** (2.0 mM); b) 5 min after addition of **1** (2.0 mM) to **2** (2.0 mM); c) 20 min after addition of **1** (2.0 mM) to **2** (2.0 mM); d) **2** (2.0 mM); e) 1:1.1 mixture of **2** (2.0 mM) and CB[7]; f) 1 day after addition of **1** (2.0 mM) to a 1:1.1 mixture of **2** (2.0 mM) and CB[7] (pD = 9.6); g) 1h after addition of **1** (2.0 mM) to a 1:1.1 mixture of **2** (2.0 mM) and CB[7] in pD = 11.5.

The condensation reaction of benzaldehyde (**1**) and benzylamine (**2**) with/without CB[7] was first explored by ^{1}H NMR. In the absence of CB[7], a new peak at ~ 8.4 ppm corresponding to the imine product emerged after adding **1** to the solution of **2**, indicating the occurrence of the reaction (Figure 1a, 1b). Within 20 minutes, the content of imine increased to 35% (Figure 1c). Separately, when CB[7] was added to the solution of **2**, the signals for the aromatic protons of **2** underwent significant upfield shifts ($\Delta\delta$ = 0.5 ~ 0.7 ppm), whereas those from the methylene signal underwent a less significant upfield shift ($\Delta\delta$ = 0.15 ppm) (Figure 1d, 1e). These shifts are suggestive of the encapsulation of **2** within CB[7] (fast exchange on ^{1}H NMR time scale). After addition of **1** to the solution of this complex, the signals of **2** shifted slightly downfield due to weak competitive binding of **1** (pD = 9.6) (K_a for both **1** and **2** with CB[7] can be found in Table S1). Importantly, no peak at ~ 8.4 ppm was observed even after the mixture was left for 1 day, indicating the reaction between **1** and **2** is fully inhibited by the presence of CB[7] at pD 9.6 (Figure 1f). To obtain a comprehensive understanding of the role of CB[7], the reaction was carried out at different pD. Although a small peak at ~ 8.4 ppm emerged after 1h at pH 11.5, the content of imine (7%, according to equation 1) did not increase even after 1 day (Figure 1g). When a strong basic solution (pD = 13.6) was used, all signals of protons on both **1** and **2** shifted upfield as a consequence of the encapsulation of two substrates within CB[7] (Figure S1, Table S1). Despite the relatively larger peaks (11%) reflecting more substrates converted to imine**,** the percentage of imine is still smaller compared to those without CB[7] (47%) (Figure S1, S2). Although CB[7] can bind the guests in both weaker and stronger basic condition, obviously it prefers to bind the protonated amine **2**, which is why more imine formed with the increase of pD in the presence of CB[7].

Since protonation of **2** is unfavorable to reaction we sought to probe this inhibition by determining the pK_a values of **2** in the absence and presence of CB[7] (UV/Vis titration). As excepted, encapsulation within CB[*n*] led to an increase in the pK_a of the amino guest:[25] a pK_a shift of **2** from 9.7 to 12.1 (Figure S3). The mechanism of inhibition is therefore quite clear. In a relatively weaker basic condition (pD = 9.6), the reaction of free **2** proceeds because it is only partially protonated. However, in the presence of CB[7] the amino group of **2** is almost fully protonated due to the increase of its pK_a. Hence **2** cannot act as a nucleophile and attack the carbonyl carbon atom of **1**, so that the reaction is fully inhibited (Scheme 2). In contrast, in strongly basic condition (pD = 13.6), both neutral **1** and **2** competitively bind with CB[7], which reduces the chance of their encounter due to the encapsulation inside CB[7]. Moreover, the electronegative oxygen on the carbonyl groups of CB[7] could stabilize the electropositive carbon on the aldehyde group of **1** by electrostatic interactions and so reduce the reactivity of substrate **1** (Scheme 2).[26]

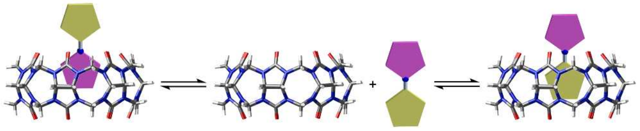


Scheme 2. Plausible mechanism of CB[7]-mediated Schiff base reaction.

To gather more information of the influence of CB[7] on the reaction, the hydrolysis of imine at various pD was also explored. We found that in the absence of CB[7] the percentages of imine at pD = 13.6, 12.5, 11.5 were 47%, 43% and 36%, whereas in the presence of CB[7] the values were 22%, 16%, and 9% (compare Figure S4a with S4b, S4c with S4d, S4e with S4f). Apparently the presence of CB[7] promoted the hydrolysis of imine at all pD values examined. Alone with previous inhibition effect, this promotion on the hydrolysis could be attributed to the higher binding affinity between CB[7] and the hydrolysis products **1** and **2**.

The inhibition effect on the Schiff base reaction by CB[7] lead us to postulate about reactions involving secondary amine that form iminium cations.[27-30] The Raymond group has developed a route to generate and stabilize these species in aqueous solution by trapping the product in an assembled cage host,[31] which suggested that CB[*n*] could play the same role owing to its high binding affinity towards organic cations. Unfortunately we did not observe that CB[7] can generate these species in aqueous solution. However CB[7] does promote the stabilization of iminium cations. Several iminium cations with different size and shape were synthesized by the condensation of ketones and secondary amine (Scheme 1c).[32]

The binding of iminium cations with CB[7] was investigated by ^{1}H NMR (Figure 2, S5-S8), and the complexation-induced chemical shift changes (CIS, $\Delta\delta = \delta_{bound} - \delta_{free}$) exhibited by guest protons were calculated to understand binding behavior.[12,15,33] CIS values (Table S2) reveal that all iminium cation compounds can be encapsulated within the cavity of CB[7]. Since the positively charged nitrogen is located in the middle the guest both the α and β moieties (Scheme 1c) on the guest could conceivably bind to CB[7]. According to the CIS values, it is evident that for iminium cation **4**, both similarly sized moieties have equal affinity for the binding site of CB[7]. A binding model of iminium cation **4** within CB[7] is showed in Scheme 3. This model explains that why the signals for all protons on both five number rings of **4** underwent significant upfield shifts.[34] To explain the CIS data for all guests the packing coefficient (PC)[35] of each moiety (Table S3) were calculated. For example, for iminium cation **3** both the CIS and the PC values for protons on the α moiety are much larger than those on the β moiety. Correspondingly for those having β moieties with larger PC, their CIS values on β moiety are obviously larger than those on α moiety, especially for **7** which has β moiety with a nearly perfect PC value (52.68).[35]



Scheme 3. Kinetic binding model of iminium cation **4** with CB[7].

The binding ^{1}H NMR of iminium cation **7** with CB[7] is shown in Figure 2. Like the other iminium cations, hydrolysis of **7** can be observed in few minutes by ^{1}H NMR (Figure 2a). According to the split of the NMR signals on CB[7] in Figure 2c, the 1:1 inclusion complex CB[7]•**7** exhibits slow exchange on the ^{1}H NMR time scale.

Given the encapsulation of iminium cations inside CB[7], we then focus on the stabilization of these high activity species upon encapsulation. The hydrolysis of **3**-**7** was monitored by ^{1}H NMR spectroscopy in deuterium oxide. All ^{1}H NMR spectra demonstrate that without CB[7], iminium cations hydrolyzed quickly to its corresponding ketone and amine (Figure 2a, 2b and Figure S5-S8). However, in the presence of CB[7] either no peaks correlating to ketone and amine could be observed, or only very small peaks were evident that did not change over time. Apparently, in some cases hydrolysis was observed before the iminium cation was encapsulated by CB[7]. The lifetimes of **3**-**7** were calculated by NMR signal integration (Figure S9, according to equation 2). In all cases with CB[7] there was no evidence of hydrolysis after 1 day, and for the complex CB[7]•**7**, no obvious hydrolysis was observed even after two weeks.

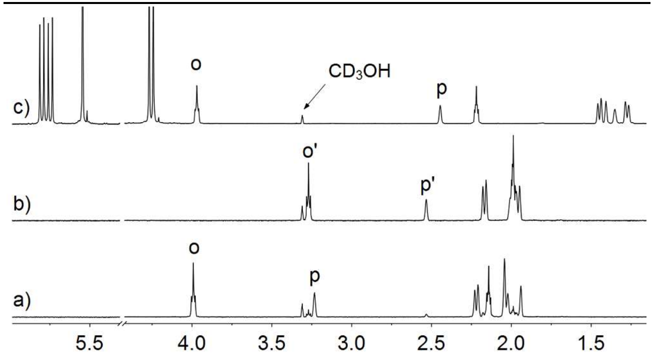


Figure 2. Partial ^{1}H NMR spectra (600MHz, D_2O) of: a) **7** (1.0 mM) (partially hydrolyzed); b) fully hydrolyzed **7** (1.0 mM); c) CB[7]•**7** (1.0 mM) for 1 day.

The single crystal of CB[7]•**7** was successfully obtained assisted by adding a small amount of KI to the aqueous solution of host and guest. This provided direct evidence of the encapsulation and stabilization of iminium ion **7** (Figure 3).[36] The nature of the bound guest was confirmed by: 1) the short bond length of N=C (1.298 Å for N_{86}=C_{145} verses 1.506 Å and 1.540 Å for N_{86}–C_{141} and N_{86}–C_{144} respectively); 2) the planar array of the four atoms covalently linked to N_{86} and C_{145}. Also apparent from the structure was that all seven oxygens on one ureidyl carbonyl portal of CB[7] are involved in forming $C{=}O\cdots N^+$ ion-dipole interactions with the positively charged nitrogen atom on the guest **7**. The average distance from oxygen on the ureidyl carbonyl portal to nitrogen on guest **7** was ~ 4.23 (7) Å, which is slightly shorter than ~ 4.38 (7) Å found in a CB[7] complex with an attomolar dissociation constant reported by Isaacs.[37] Furthermore, the positively charged nitrogen atom is exactly located on the plane composed of seven oxygens on the portal of CB[7], which maximizes the ion-dipole interactions between CB[7] and the guest. Further inspection reveals that the average distance from oxygen on the ureidyl carbonyl portal to C_{145} (carbon on 2 position in 2-adamantanone) on guest **7** (~ 4.39 (7) Å) is very close to that of C_{152} (carbon on 6 position in 2-adamantanone) to the adjacent oxygens on CB[7] (~ 4.43 (7) Å) (Figure S10). The results imply in this case that the 2-adamantyl "perfectly" fits in the cavity of CB[7].

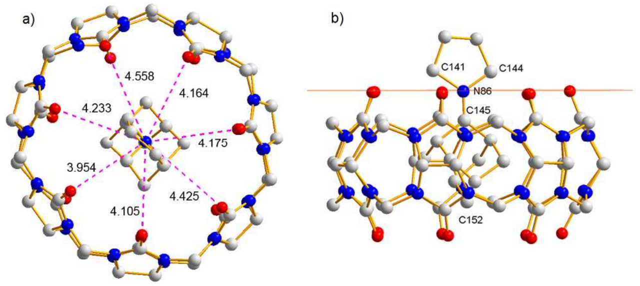


Figure 3. Representation of the X-ray crystal structures of the inclusion complex CB[7]•**7**: a) top view and b) side view.

The binding and stabilization of iminium cations were further extended to smaller CB[6] (Figure S11-S16). To our surprise, although CB[6] has the capacity to hold an aromatic group, no obviously chemical shift changes from the protons of the iminium cations could be observed from the ^{1}H NMR spectra. Nevertheless, by monitoring the progress of the hydrolysis of iminium cations, we found that even though inferior to CB[7], CB[6] indeed provided protection to iminium ions from hydrolysis in aqueous solution. We assume that once upon mixed, iminium cations stay at the portals of CB[6] due to the strong ion-dipole interactions, which slows down the hydrolysis.

In summary, we have demonstrated that CB[7] can play an important role in Schiff base reactions - inhibiting the condensation reaction of aldehyde and primary amine. Although CB[7] could not help to generate iminium cation in aqueous condition, it does stabilize them by host-guest interaction. Also, for the first time we report on the crystal structure of an encapsulated iminium ion grown in water. This preliminary finding further point out that CB[*n*] are able to control the reaction process, either obverse or reverse effect. Stabilization of highly unstable iminium ions in water with CB[*n*] could lead to a new way to switch some reactions involving highly active intermediates from organic condition to aqueous condition.

Experiment Section

General information: CB[6] and CB[7] were synthesized and separated according to literature procedures.[38] Other compounds used in this study were purchased from commercial suppliers and were used without further purification. ^{1}H NMR spectra were collected on Agilent 600 MHz DD2 spectrometers and chemical shifts were recorded in parts per million (ppm). UV/Vis measurement was performed on a SHIMADZU UV-3600 instrument with 1 cm pathlength cells at 298 K. The X-ray intensity data were measured on a Bruker APEX-II CCD system (Data collection temperature was 203K).

General procedure for iminium cation compounds synthesis: All the iminium cations (as perchlorate salt) were prepared according to the literature.[32] To a solution of ketone (10 mmol) and pyrrolidine (10 mmol) in toluene (25 mL) was added ammonium perchlorate (10 mmol). The solution was heated to reflux with continuous removal of the water formed. After cooling down in ice-water bath, the precipitated product was collected by filtration, washed with ether (3 × 10mL), and dried in vacuum.

Hydrolysis of imine experiment: 1 (2.0 mM) and **2** (2.0 mM) was mixed in D_2O/NaOD (pD > 13.6) and left overnight. Then the solution was divided into two parts and one was added with 1.1 equivalent of CB[7]. To above solutions was added DCl to adjust pD, and all samples were monitored by ^{1}H NMR until there was no any change on ^{1}H NMR spectra.

Calculation of lifetime of iminium cations: Due to the high reactivity of iminium cations to H_2O, the concentrated solution of iminium cations was prepared in CD_3OH. However when added to the aqueous solution of CB[7], quick hydrolysis of iminium cation was still observed before it was stabilized by the encapsulation inside CB[7]. In order to simplify the calculation, the first percentage for the complex is set up to 100% and the subsequent values are calculated based on this value.

Calculation equation:

$$\text{imine }\% = \frac{[\text{imine}]}{[\text{imine}] + [\text{aldehyde}]} \qquad (1)$$

$$\text{iminium cation }\% = \frac{[\text{iminium caiton}]}{[\text{iminium caiton}] + [\text{amine}]} \qquad (2)$$

Associated Content

Supporting Information

Experimental and characterization details and additional figures (pdf)

Crystallographic data for CB[7]•**7**

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