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Cucurbituril-Mediated Supramolecular Acid Catalysis

Cornelius Klöck, Roy N. Dsouza, and Werner M. Nau*

School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, D-28759 Bremen, Germany

w.nau@jacobs-university.de

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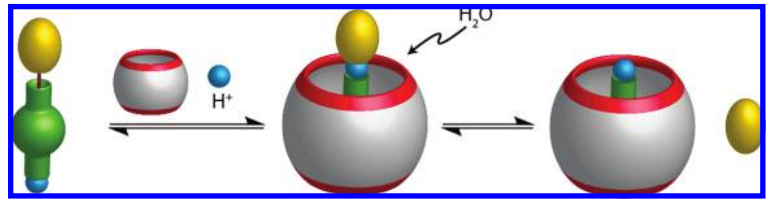
ABSTRACT



The rates of acid hydrolysis of *N*-benzoyl-cadaverine (1), mono-*N*-(*tert*-butoxy)carbonyl cadaverine (2), and benzaldoxime (3) with binding motifs for cucurbit[6]uril (1,2) and cucurbit[7]uril (1,3) were investigated in the absence and presence of these hosts. Significant rate enhancements (up to a factor of ca. 300 for the hydrolysis of 3) were observed. Competitive inhibition due to encapsulation of added cadaverine and the successful use of sub-stoichiometric amounts of macrocycle confirmed the function of cucurbiturils in promoting acid hydrolysis.

Enzyme-mimetic catalysis has been a key focus of the supramolecular chemistry community.[1−5] The confinement imposed by supramolecular inclusion, e.g., by macrocyclic hosts, and the associated variations in substrate reactivity are especially important in these catalytic processes.[6,7] In the case of hydrolysis reactions in acidic or basic media, shifting the pK_a of the substrate by supramolecular or biomolecular interactions has been shown to drastically enhance reaction rates.[8] Raymond and co-workers have previously shown that a highly charged supramolecular metal complex accelerated the acid hydrolysis of orthoformates up to 890-fold at basic pH, which was attributed to a complexation-induced pK_a shift.[9,10] Furthermore, using the same metal complex, the basicity of amines could be shifted by up to 4.5 pK_a units.[11]

Toward the development of efficient enzyme-mimetic acid−base catalysts, inclusion complexes with macrocyclic organic hosts such as calixarenes, cyclodextrins, and cucurbit[*n*]urils have shown up to 4.5 unit pK_a shifts of included guests.[12−15] These commercially available host molecules have the added advantage of forming a vast number of inclusion complexes with a variety of binding moieties.[16−20] Cucurbit[*n*]urils, in particular, are rigid macrocycles with cation-receptor properties that show a strong binding propensity toward numerous neutral and, preferentially, posi-

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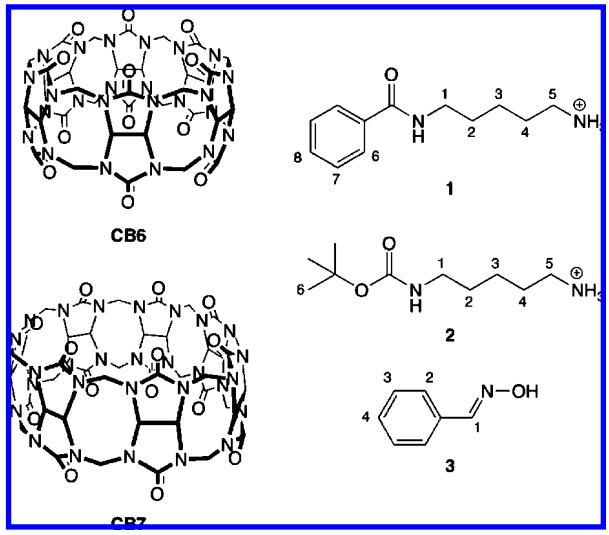
tively charged guests.[18,21] Previously, cucurbit[6]uril (CB6) has been employed to catalyze 1,3-dipolar cycloaddition reactions between alkynes and alkyl azides,[22−24] while cucubit[7]uril (CB7) and cucubit[8]uril have been employed to catalyze different types of photocycloaddition reactions.[25−28] However, although it is known that complexation by cucurbit[*n*]urils can shift the pK_a value of included guests and thereby promote their protonation, the possibility of catalyzing or promoting reactions of acid-labile substrates has been invoked in only a single case.[14] Herein, we find that cucurbit[*n*]urils indeed catalyze the hydrolysis of amides, carbamates, and oximes in acidic aqueous solution or, conversely, allow their hydrolysis under significantly milder conditions.

Our general design principle (see Abstract graphic) is such that we employ acid-labile substrates with anchoring groups that are known to bind strongly to the macrocycle, thereby positioning the reactive groups in the proximity of the cation-receptor sites of the host. This induces guest protonation and catalyzes the hydrolysis. Specifically, we use CB6 and CB7, which bind cations at their upper and lower carbonyl rim, and compounds **1**−**3** as substrates with acid-labile amide, carbamate, or oxime functionalities. With respect to the anchoring group, compounds **1** and **2** possess a cadaverine (1,5-diaminopentane) residue known to particularly strongly bind to CB6,[29] and **3** offers a benzyl anchor for preferential binding with CB7.[21]



As a classical challenge,[30] we have first tackled amide hydrolysis by using substrate **1**. This reaction proceeds via protonation of the carbonyl oxygen in a pre-equilibrium, which makes it susceptible to the rate-determining nucleophilic attack of water. Subsequently, a proton transfer to the nitrogen occurs followed by the cleavage of the intermediate to the amine and carboxylic acid.[30,31] A theoretical study suggests that the nucleophilic attack and the protonation of the nitrogen occur simultaneously, assisted by a second water molecule that accepts a proton from the nucleophile and donates one to the nitrogen.[32] Regardless of the protonation site, the resulting positive charge of the protonated amide functionality should be positioned near the carbonyl portal of the macrocycle and experience a Coulombic stabilization.

Compound **1** has a cadaverine moiety that is known to bind very strongly with CB6.[18,29] The larger phenyl moiety also present in **1** has a 3 orders of magnitude lower affinity to enter the CB6 cavity.[18] Upfield shifts of the aliphatic protons and downfield shifts of the aromatic protons in the ^{1}H NMR spectrum of **1** (Figure 1) confirmed the selective inclusion of the cadaverine moiety experimentally. The larger CB7 macrocycle also binds cadaverine strongly (1.4×10^7 M^{-1})[33] but has a sizable affinity for phenyl rings as well (e.g., 2×10^6 M^{-1} for *p*-aminoaniline and 8×10^6 M^{-1} for *p*-methylaniline).[21] Accordingly, compound **1** showed large upfield (−0.45 ppm) shifts for the cadaverine protons, as well as slight upfield shifts (−0.05 ppm) and signal broadening of the aromatic protons (Figure 1). This can be interpreted as a preferential binding of CB7 to the cadaverine moiety with occasional population of a structure in which the phenyl ring is temporarily included.

The hydrolysis of **1** was followed by ^{1}H NMR at two different pD values at 60 °C in a saturated solution of CB6 as well as in solutions with 1 and 2 equiv of CB7. The concentrations of both reactants and products at different times (up to 2 weeks) were determined from the H-1 and H-5 resonance integrals of **1** along with the α-amino protons of cadaverine (see Supporting Information). The reaction followed first-order kinetics at low conversion (10−30%)[34] for both hosts, and the rate constants (Table 1) were calculated accordingly by linear regression analysis of plots of the logarithmic rates against time.

While the results nicely confirmed our conjecture that cucurbit[*n*]urils accelerate the rate of amide hydrolysis, the absolute magnitude of the effect was much smaller than expected. On the basis of previous observations, pK_a shifts between 2 and 4.5 units should correspond, under the ideal assumption that the reaction rate is unimolecular with respect to the protonated form (as expected for a specific acid catalysis),[35] to an acceleration factor of 100 to 30 000. We speculated that the protonation of the cucurbituril macrocycles (pK_a(CB6) = 3.02 and pK_a(CB7) = 2.20)[36,37] under the harsh

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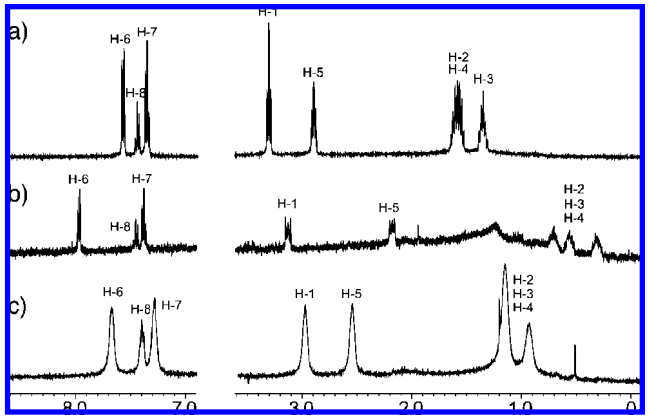

Figure 1. ^{1}H NMR of **1** (3 mM) (a) in D_2O, (b) with 1.5 equiv of CB6 (0.3 mM of **1**), and (c) with 2 equiv of CB7 in D_2O at pD 0.9.

acidic conditions (ca. pH 1) could interfere and therefore extended our search to hydrolysis reactions under milder conditions, namely, carbamate ester (pH 2−3)[31,38,39] and oxime hydrolysis (pH 4−6).[40]

Table 1. Rate Constants[a] for the Hydrolysis of **1** (3 mM) in the Absence and Presence of Cucurbit[*n*]urils and Associated Acceleration Factors at 60 °C

	no host	CB6[b] (1.5 equiv)		CB7 (1 equiv)		CB7 (2 equiv)	
pD	$10^6\ k$ (s^{-1})	$10^6\ k$ (s^{-1})	α^c	$10^6\ k$ (s^{-1})	α^c	$10^6\ k$ (s^{-1})	α^c
0.9	0.062	0.248	4.0	0.299	4.8	0.324	5.2
1.4	<0.014[d]			0.136	>9.8[d]	0.161	>11.6[d]

[a] 5% error. [b] 0.3 mM of **1** was used. [c] Acceleration factor, $\alpha = k_{cat}/k_{uncat}$. [d] Conversion below detection limit (estimated as 1.5%) after 14 days; k_{uncat} specified as maximal rate, α as minimal acceleration factor.

Carbamates are acid-labile and undergo decomposition either by a hydrolysis pathway similar to that known for amides[39] or, in the case of the *tert*-butoxycarbonyl protecting group, by fragmentation. We used commercial mono-*N*-(*tert*-butoxy)carbonyl cadaverine (**2**) as a model carbamate, for which a similar complexation pattern as for **1** was expected. Indeed, ^{1}H NMR spectra of **2** in the presence of an excess of CB6 (Figure 2) exhibited characteristic upfield shifts in the resonances of the cadaverine backbone; the *tert*-butyl protons shifted downfield, indicating their proximity to the portals of the host. In analogy to the amide hydrolysis of **1**, we assessed the reaction progress by using the characteristic protons of the cadaverine moiety, and calculated the pseudounimolecular rate constants accordingly.[34] The resulting data in Table 2 demonstrate that the addition of CB6 efficiently accelerated deprotection. The markedly improved acceleration factor compared to that observed for amide hydrolysis was also gratifying (factor of ca. 30), but it did not further improve by working at higher pH values and still fell below of what we envisioned.

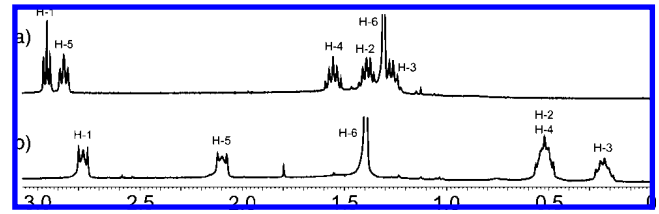

Figure 2. ^{1}H NMR of **2** (0.5 mM) (a) in D_2O and (b) with an excess of CB6 (1.5 equiv) in D_2O at pD 2.9.

We therefore proceeded to oxime hydrolysis as our third and most successful test case to establish the catalytic properties of cucurbit[*n*]urils. Mechanistically, this reaction is known to proceed via the protonation of the oxime-nitrogen, which renders the oximinium carbon susceptible to nucleophilic attack by water. Proton transfer yields an intermediary carbinolamine, which decomposes to the parent carbonyl compound and hydroxylamine. Accordingly, the reaction proceeds fastest in acidic solution. Interesting from a thermodynamic point of view is that the reaction is reversible and that the position of the equilibrium strongly depends on the reaction progress-dependent amount of the weakly basic ($pK_a \approx 6$) hydroxylamine in solution. Thus, the equilibrium can be shifted toward the aldehyde either by working at strongly acidic pH or by trapping the hydroxylamine product.[40−42]

Table 2. Catalyzed and Uncatalyzed Deprotection Rate Constants[a] of **2** (0.5 mM) at Different pD Values

pD	uncat $10^6\ k$ (s^{-1})	CB6 (1.5 equiv) $10^6\ k$ (s^{-1})	α^b
2.4	1.480	40.3	27.1
2.9	0.391	11.3	28.9

[a] 5% error. [b] Acceleration factor, $\alpha = k_{cat}/k_{uncat}$.

We selected (*E*)-benzaldoxime (**3**) as the substrate of choice to study the rate of hydrolysis and the effect of cucurbit[*n*]urils. Since the phenyl residue serves as a poor anchor for CB6 (see above), we focused on the larger CB7 as additive. Efficient and preferential inclusion of the phenyl ring of **3** within CB7 was confirmed by upfield shifts as well as a selective signal broadening of the aromatic protons of **3** (see Supporting

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Information). For comparison, benzaldehyde, the hydrolysis product of **3**, was shown to form inclusion complexes with similar proton upfield shifts (data not shown). Molecular models of the corresponding inclusion complex (Figure 3) showed that the oxime group is positioned near the carbonyl-lined portals of the host, which should allow for both an efficient stabilization of the positively charged intermediate and a facile attack by water.

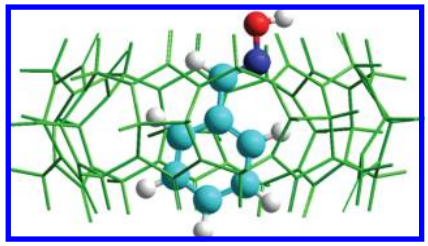

Figure 3. AM1-optimized structure of the CB7·**3** complex.

Table 3. Initial De-oximation Rate Constants[a] of **3** (2 mM) in the Absence and Presence of CB7

pD	uncat $10^6\ k$ (s^{-1})	CB7 (1.5 equiv) $10^6\ k$ (s^{-1})	α^b
4.0	5.5	260	50
4.9	0.75 [0.93][c]	68 [0.98][c]	95
5.4	0.19	27	140
5.8	0.062	17	285

[a] 5% error. [b] Acceleration factor, $\alpha = k_{cat}/k_{uncat}$. [c] Rate in the presence of 2 equiv of cadaverine.

In acidic solution (pH < 4), oxime hydrolysis was too fast to be accurately followed by NMR, and at higher pH values, only partial hydrolysis occurred as a result of the equilibrium nature of the reaction. To ensure a consistent and robust kinetic analysis of the forward reaction (oxime hydrolysis), we employed α-ketoglutaric acid as a known hydroxylamine scavenger.[43] This scavenger as well as its corresponding oxime addition product (which is stabilized by intramolecular hydrogen bonding) are anionic, such that no interference due to complexation with CB7 needed to be considered. Oxime hydrolysis in the presence of the scavenger at higher pH could be followed via the integrals of the aldoxime and aldehyde protons in NMR. Unfortunately, the reaction product (benzaldehyde, $K = (1.2 \pm 0.2) \times 10^5\ M^{-1}$) turned out to bind more strongly to CB7 than the reactant (**3**, $K = (2.1 \pm 0.4) \times 10^4\ M^{-1}$) such that product inhibition presented an obstacle. Nevertheless, the deoximation rates were found to follow first order kinetics at low conversion (10−30%). The deoximation rate constants of **3** such determined at various pD values are shown in Table 3. The difference between the catalyzed and uncatalyzed reaction rates became larger at higher pD values with a peak acceleration factor of 285, which comes close to the previously reported 890-fold acceleration for orthoformate hydrolysis.[9]

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To demonstrate the action of CB7 as an actual catalyst through the formation of an inclusion complex, we investigated the possibility to inhibit the hydrolysis reaction by addition of a competitive binder and to perform the reaction at sub-stoichiometric amounts of macrocycle. In fact, the addition of cadaverine as inhibitor led to a dramatic drop in the reaction rate with a value essentially the same as that in the absence of macrocycle (values in square brackets in Table 3; see also Supporting Information). At sub-stoichiometric amounts of macrocycle, the reaction rate decreased linearly with CB7 concentration (see Figure 4 and Table S-1, Supporting Information). This was indeed expected for a reaction that is accelerated through the competitive formation of an intermediary inclusion complex in pre-equilibrium.

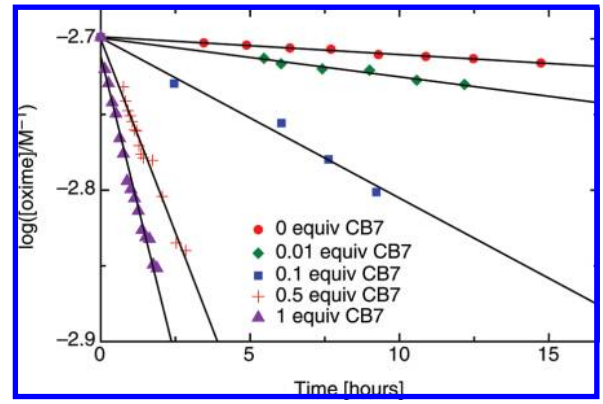

Figure 4. Logarithmic kinetic traces for acid hydrolysis of **3** (2 mM) with sub-stoichiometric amounts of CB7 at pD 4.9.

The combined results on the acceleration of hydrolysis rates at stoichiometric as well as sub-stoichiometric amounts of cucurbituril along with the observed competitive inhibition confirm our conceptual conjecture that these macrocycles can serve as acid catalysts by virtue of complexation-induced pK_a shifts. In essence, the macrocyclic host serves as an unconventional "acid substitute", which facilitates the protonation of the substrate by proper positioning near the cation-binding carbonyl sites of the host, thereby increasing the apparent pK_a value of the substrate. The absolute magnitude of the rate acceleration presumably depends critically on the precise mechanism of acid hydrolysis as well as on the exact positioning of the reactive site within the host. The optimization of the latter is particularly critical to achieve large pK_a shifts and translate this physicochemically interesting supramolecular phenomenon into practically relevant catalytic effects.

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Supporting Information Available: Experimental details and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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