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Cucurbit[6]uril as a potential catalyst for the acidic decomposition of azidoaminoalkanes

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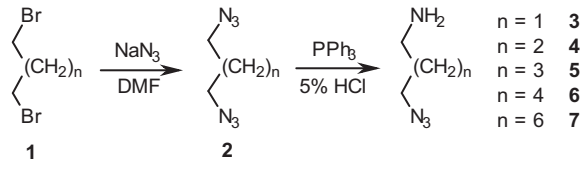
ABSTRACT

Five azidoalkyl-1-amines and *p*-azidoaniline have been synthesized and complexed with cucurbit[6]uril in acidic solutions. Isothermal titration calorimetry has been employed to determine the association constant *K* and the enthalpy of complex formation ΔH of the azidoalkyl- and azidoarylamines. 4-Azidobutyl-1-amine forms by far the most stable complex. Cucurbit[6]uril significantly catalyzes the decomposition of the azidoalkyl- and azidoarylamines studied.

Supramolecular catalysis is a promising field. Indeed, it has already produced very attractive results for easy syntheses of compounds that otherwise would be difficult to obtain under mild conditions and with satisfactory regioselectivity.[1] In order to achieve this goal, in general a host molecule is used to mediate the reaction. Much work has already been done on the basis of self-assembled capsules,[2] calixarenes,[3] hemicarcerands,[4] and cyclodextrins[5] the latter host molecules being especially useful because of their intrinsic aptitude to transfer chirality to entrapped guest molecules.[5a,6] Since the discovery[7] and the rediscovery of cucurbit[n]urils (*n* = 5, 6, 7, 8, and 10) and their complexing ability,[8] this family of host molecules is gaining ever more significance for applications in slightly acidic aqueous media. This is due to their high affinity for positively charged organic molecules such as ammonium compounds, combined with a relatively high specificity owing to their rigidity.[9] With cucurbit[6]uril (CB[6]), Mock has shown their ability to catalyze the 1,3-dipolar cycloaddition of azidoalkylamines to aminoalkynes, leading to the exclusive formation of only one triazole regioisomer.[10] Since then, this approach has been used for the preparation of a self-threading polyrotaxane[11] and for the synthesis of oligotriazoles.[12] Further examples were reported with the highly stereoselective photodimerization of diaminostilbenes[13] and stilbazoles[14] in the larger cavity of cucurbit[8]uril. In contrast, cucurbit[7]uril has been utilized to mediate the dimerization of aminopyridine to a tricyclic compound,[15] producing exclusively the anti-*trans* isomer and being able to stabilize it with respect to decomposition. All these synthetic applications have in common that they are employing protonated nitrogen compounds as a substrate. The presence of this functional group greatly enhances complex formation, and as a consequence, the catalytic efficiency of the system.

In the course of our efforts to investigate the possibilities to improve the synthetic utility of azides and nitrenes, we recently could demonstrate the remarkable regioselectivity of the monofunctionalization of a resorcinarene cavitand using an encapsulated phenyl azide.[3b] Therefore, we now have prepared inclusion complexes of azidoalkyl- and azidoarylamines in cucurbit[6]uril to investigate scope and limitations of this approach. In this Letter, we report about the preparation and the stability of these complexes.

Azidoalkylamines **3**–**7** were synthesized from dibromoalkanes **1** in analogy to a known literature procedure (Scheme 1).[16,17] The first step corresponds to the preparation of diazides **2** by thermal treatment of the corresponding dibromides with NaN_3 in DMF (80 °C, 20 h) followed by reduction of one azido group with PPh_3 using a slightly modified Staudinger reaction.[18] The reduction of



1 2

Scheme 1. Synthesis of azidoalkylamines **3**–**7**.

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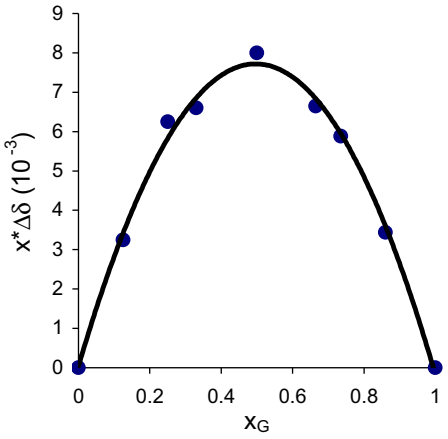

Figure 1. Job plot of **4**$^{+}$@CB[6].

Table 1
Association constants of cucurbit[6]uril complexes **4**$^{+}$ and **5**$^{+}$ in 7.6 M DCl

	4^{+}	**5**$^{+}$
K (M^{-1})	676	108

the second azido group is avoided by use of cold temperatures and a two-phase system: the freshly generated azidoalkylamine is protonated and extracted into the acidic aqueous phase and therefore not available for a second reduction. The hydrochloride salts were obtained by bubbling dry hydrogen chloride into an ethereal solution of azidoalkylamines **3**–**7** in their free base form. For all reactions the yields were uniformly high (85–90%).

The complexes were prepared by dissolution of azidoalkylamine hydrochloride in water followed by addition of cucurbit[6]uril.[19] A putative complex of 4-azidobutyl-1-ammonium **4**$^{+}$ in cucurbit[6]uril is represented in the graphical abstract.[20] The stoichiometry of the complexes **3**$^{+}$@CB[6], **4**$^{+}$@CB[6], and **5**$^{+}$@CB[6] was determined by ^{1}H NMR spectroscopy in 7.6 M DCl using the method of continuous variation (Job plot, Fig. 1). A 1:1 stoichiometry was found for all complexes. The association constants were determined by titration to give 676 M^{-1} for **4**$^{+}$@CB[6],[21] and 108 M^{-1} for **5**$^{+}$@CB[6][22] (Table 1). Some unsuccessful attempts were made to obtain single crystals of the complexes.[23]

We also employed isothermal titration calorimetry (ITC) with 1/1 (v/v) HCO_2H/H_2O as the solvent to determine the binding constants of azidoalkylamines in CB[6] (Fig. 2). This choice of solvent combination was partly dictated by the poor solubility of cucurbit[6]uril in pure water and in common solvents and by the technical requirements of the ITC apparatus used. The binding properties of the four azidoamines **4**, **6**, **7**, and **8** are shown in Table 2. Due to the larger benzene ring, *p*-azidophenylammonium **8**$^{+}$ (K = 655 M^{-1}) is bound about eight times weaker than 4-azidobutylammonium **4**$^{+}$ (K = 5500 M^{-1}) which seems to be a perfect fit for the cavity of cucurbit[6]uril. Chain lengths longer than four carbon atoms led to a much weaker bonding (K = 514 M^{-1} for 6-azidopentylammonium **6**$^{+}$ and K = 713 M^{-1} for 8-azidohexylammonium **7**$^{+}$). This preferential binding for the butyl group can be found again in previous works,[24] where it has been shown that complexation of butylammonium in cucurbit[6]uril leads to a highly negative value for the reaction enthalpy combined with an almost maximal entropic gain among all linear alkylammoniums. However, in comparison to other complexes of alkylammoniums in cucurbit[6]uril,[24] the association constants are relatively low, indicating that the azido group has a negative effect on the stability of the complex, which is probably due to the presence of an electron lone-pair on its nitrogen atoms generating a repulsive interaction with a rim of the host. A second reason for the low measured affinity is the choice of solvent, for example, a strongly acidic solution, which leads to a competition for binding with protons and formic acid.[24] The binding constants of comparable amines are known to be much larger in water[25] or even in 0.05 M NaCl.[24]

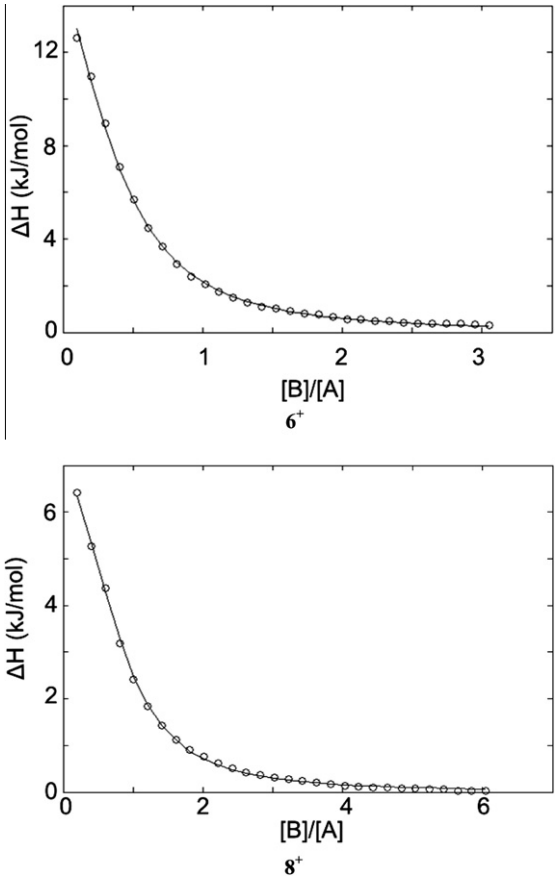

Figure 2. ITC titration curves of **6**$^{+}$ and **8**$^{+}$ with CB[6] in 50% formic acid.

Table 2
Energetic parameters and association constants of the CB[6] complexes in 50% formic acid

	4^{+} Butyl	**6**$^{+}$ Pentyl	**7**$^{+}$ Hexyl	**8**$^{+}$ Aniline
K (M^{-1})	5500 ± 50	514 ± 5	713 ± 5	655 ± 5
ΔH (KJ/mol)	−22.8	−24.1	−26.3	−9.6

Whereas azidoammoniums **4**$^{+}$–**8**$^{+}$ are stable in acidic solution at room temperature, they decompose completely within a week in the dark, when cucurbit[6]uril is added. Considering that pK_a shifts in the magnitude of 4–5 units have already been reported upon complexation,[25,26] a plausible explanation is that protonation of the azido group is facilitated by complex formation, generating a dication, which can be efficiently stabilized by the CO groups at the rims of the host. The decay has been observed by ^{1}H NMR spectroscopy showing the disappearance of azidoammonium **X**$^{+}$ after only a few hours. However, in the liquid phase, no products of low molecular weight could be detected. Similar results showing the efficacy of cucurbiturils as supramolecular acid catalysts have already been published.[27] Our experiments also have shown that the decomposition of an azidoalkylamine in cucurbituril cannot proceed through a catalytic cycle. In fact, stoichiometric amounts of cucurbit[6]uril are required because the major products, the cor-

responding diamines, have a much higher affinity to the host[24,28] than the starting compounds, thereby forming a poorly soluble complex.

In conclusion, azidoalkylamines **3**–**7** and azidoarylamine **8** form complexes with cucurbit[6]uril in acidic aqueous solution. Among these compounds, the best fit is provided by butyl derivative **4** for which an association constant of 5500 M^{-1} has been determined. The solutions of **3**–**8@**CB[6] in 7.6 M DCl have proven to be chemically unstable. Although the studied azidoalkyl- and azidoarylamines can be kept in this solvent at room temperature, they do decompose rapidly in the presence of cucurbit[6]uril.

Acknowledgments

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17. Synthesis of azidoalkyl- and arylamines: NaN_3 (2.275 g, 35 mmol) was added in portions to a stirred solution of the dibromoalkanes (10 mmol) and a catalytic amount of KI (20 mg) in 50 mL of DMF over a period of 30 min. The flask was then covered with aluminum foil to exclude light and the mixture was heated to 80–85 °C for 20 h. The yellowish liquid was poured on ice/water (250 mL) and extracted three times with hexane. The combined organic phases were washed several times with water and finally with brine to remove DMF. The solvent was removed under reduced pressure at room temperature to obtain the diazide as a colorless liquid. **Warning!** Care should be taken during evaporation of the solvent due the explosive nature of the diazides! Also, exposure to sunlight and other light sources should be minimized to prevent decomposition! The liquid residue was dissolved in a 1:1 mixture of ether and hexane (100 mL) and poured into 200 mL of 5% HCl. The mixture was rapidly stirred to ensure proper emulsification and cooled to 0 °C. Then a solution of triphenylphosphine (2.62 g, 10 mmol) in 50 mL of ether was added slowly over 30 min, keeping the temperature at 0 °C. The mixture was stirred overnight. The organic phase was discarded and the aqueous phase was washed several times to remove the majority of triphenylphosphine oxide. The aqueous phase was brought to pH 11, whereby the solution turned turbid. The amine-free base was extracted three times with ether (50 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure at room temperature (**Do not heat!**). ^1H and ^{13}C NMR spectroscopy confirm the absence of traces of the corresponding diamine. Finally, the obtained free base was dissolved in 50 mL of anhydrous ether and dry HCl was bubbled into the solution to obtain the corresponding HCl salt. This was suction-filtered, dried at room temperature in vacuo and stored in the dark at 2 °C. Care should be taken because of the hygroscopic nature of the HCl salts.
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19. Preparation of the complexes: Azidoalkylamine hydrochloride (100 mg) was dissolved in 20 mL of distilled water. Then 3 equiv. of cucurbit[6]uril were added at 45 °C and the resulting suspension was stirred for 4 h at this temperature. Undissolved material was removed by filtration. Subsequently, from the vial with the obtained solution placed in a desiccator over ca. 100 mL of acetone, a white precipitate was produced by vapor diffusion of acetone at room temperature. The crystals were suction-filtered, washed with a small amount of cold acetone and dried in vacuo.
20. Graphical abstract: The Figure in the graphical abstract was obtained by drawing a putative complex of 4-azidobutyl-1-ammonium in cucurbit[6]uril and minimizing the energy of the structure with Spartan 04. The resulting structure was then displayed with Mercury 2.0 and GIMP 2 to obtain the final image.
21. Titration experiments with azidobutylamine (**4**)·HCl and CB[6]: Two stock solutions were prepared: azidobutylamine (**4**)·HCl (0.01 M in 7.6 M DCl) and cucurbit[6]uril (0.01 M in 7.6 M DCl). Under these strongly acidic conditions (7.6 M DCl), for azidobutylamine (**4**)·HCl the spectra also clearly indicate a kinetically stable complex between the amine and CB[6]. The Job plot showed a 1:1 stoichiometry. The association constant K was determined as 676 M^{-1}.
22. Titration experiments with azidopentylamine (**5**)·HCl and CB[6]: Two stock solutions were prepared: azidopentylamine (**5**)·HCl (0.02 M in 7.6 M DCl) and cucurbit[6]uril (0.02 M in 7.6 M DCl). Under the acidic conditions (7.6 M DCl), for azidopentylamine (**5**)·HCl the spectra clearly indicate a kinetically stable complex between the amine and CB[6]. K = 108 M^{-1}.
23. Attempts at crystallization: A 1:1 mixture of the amine hydrochloride and CB[6] in water was carefully heated up to 40 °C for 5 min under exclusion of light, cooled to room temperature and filtered off after 2 h of stirring. The obtained clear colorless filtrate was stored in an open vial in the dark at room temperature (26 °C). After two weeks the solution had turned into a syrupy yellowish liquid and small colorless crystals were formed. These were checked by X-ray analysis. The result clearly showed that the azidoalkylamine was converted into the corresponding diamine and fully included within the cavity of CB[6]. The diamine was highly disordered, so a further refinement failed. Azidobutylamine hydrochloride (**4**)·HCl, azidopentylamine hydrochloride (**5**)·HCl, and azidohexylamine hydrochloride (**6**)·HCl also showed the same behavior.
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