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Two Mechanisms of Slow Host–Guest Complexation between Cucurbit[6]uril and Cyclohexylmethylamine: pH-Responsive Supramolecular Kinetics**

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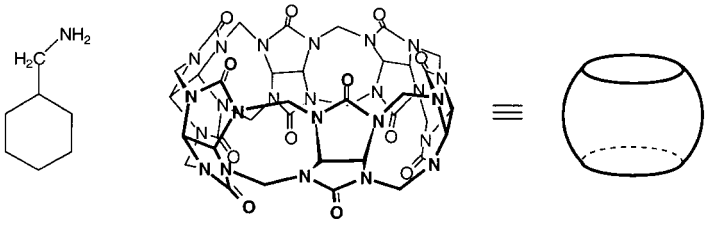
Supramolecular materials capable of performing specific functions are of great current interest.[1–3] Ultimately, their suitability will greatly depend, in particular for the case of prospective supramolecular machines, on the speed by which their operations and functions are performed. A prediction and optimization of this speed requires knowledge of the sequence and the rates by which the elementary supramolecular processes occur, which defines the emerging field of supramolecular kinetics.[4] We have recently introduced a fluorescent probe for measurement of very fast host–guest association processes with cyclodextrins[5] and now report a study of the factors which govern the other extreme of very slow host–guest complexation kinetics between cyclohexylmethylamine (**1**) and the container compound cucurbit[6]uril (CB6). The pH proved crucial for the kinetics and the rate



1 CB6

constants turned out to be unrelated to the thermodynamics of complexation; rather, they are related to the degree of protonation of the guest. The distinct pH dependence of the kinetics of this host–guest complexation process points to two different mechanisms, in which the ingression of the protonated guest is retarded by the formation of an association complex, while the unprotonated guest can enter the cavity directly with a rate constant 20-fold larger. Such a regulation of the supramolecular kinetics between an organic guest and a container-type host molecule through pH is unprecedented.

CB6 is a glycoluril macrocycle with two "crowns" of six ureido-carbonyl groups on both rims suitable of complexing organic ammonium salts through ion–dipole and hydrogen bonding interactions.[6, 7] The small cavity openings of CB6 have been considered as portals, the size of which (about 4 Å)[8] determines whether and how fast complexation occurs. The inner, wider cavity (5.5 Å in width and 6 Å in height)[8] is suitable to accommodate nonpolar organic residues through

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stabilizing van der Waals interactions. CB6 is a water-soluble molecular container compound[9] with molecular recognition properties[3] and forms complexes which closely resemble those of molecule-within-molecule structures,[10, 11] hemicarceplexes,[12] and caviplexes.[13] Besides this function, CB6 has been successfully employed as a supramolecular component in the construction of supramolecular switches,[6] polyrotaxanes,[14, 15] and catenanes.[16] Further, applications for removal of contaminants[17] from air and water have been reported, as well as the use in fluorescent solids.[18] Note also that cucurbit[*n*]urils of different sizes ($n = 5-8$),[19] as well as a permethylated derivative[20] have been characterized.

The complexation kinetics of CB6 with most organic guests is slow on the NMR time scale, which results in a separate set of resonances attributable to the complexed and the uncomplexed components.[6, 9, 21] This has allowed Mock et al. to measure the complexation kinetics of cycloalkylmethylamines by a displacement–competition kinetics or the NMR signal-coalescence method (Table 1).[21] The observed maximum in the binding constants (K) for the medium-sized cyclobutylmethylamine reveals an interplay between stabilizing and repulsive van der Waals interactions between the guest and the walls of the cavity. Interestingly, we have now also observed binding of cyclohexylmethylamine **1**, which has been previously considered as being too bulky to be included.[22] For this large amine the exchange occurs on the time scale of hours to days, which bypasses an indirect assessment through coalescence or competitive reactions[21] and allows a direct monitoring of the kinetics in the classical way, namely by taking spectra at different times.

Table 1. Ingression ($k_{ingress}$) and egression rate constants (k_{egress}) and binding constants ($K = k_{ingress}/k_{egress}$) for the inclusion complexes between CB6 as a host and cycloalkylmethylamines as guests.[a]

Guest	$k_{ingress}$ [$M^{-1}s^{-1}$]	k_{egress} [s^{-1}]	K [M^{-1}]
cyclopropylmethylamine[b]	$\geq 10^6$	$> 10^7$	1.5×10^4
cyclobutylmethylamine[b]	5.9×10^3	1.6×10^{-2}	3.7×10^5
cyclopentylmethylamine[b]	5.5×10^0	1.6×10^{-5}	3.3×10^5
cyclohexylmethylamine **1**[c]	8.8×10^{-4}	1.1×10^{-5}	8.0×10^1

[a] Determined by ^{1}H NMR spectroscopy in a 1/1 (v/v) D_2O/formic acid mixture at 40 °C. [b] Data from refs. [6, 21]. [c] This work with 3 mM CB6 and 6 mM **1**. The error in the values is 5%. Data in a D_2O solution with 0.2 M Na_2SO_4 at 40 °C and pH 7.0 are $k_{ingress} = 8.2 \times 10^{-3}\,M^{-1}s^{-1}$, $k_{egress} = 7.3 \times 10^{-5}\,s^{-1}$, and $K = 1.1 \times 10^2\,M^{-1}$.

The fact that the kinetics of complexation by CB6 (Table 1), which possesses two tight openings, falls far below the values observed for host systems with unobstructive openings like cyclodextrins[5] or calixarenes[23] suggests a physical (steric) barrier towards complexation and decomplexation. The rate constants for ingression ($k_{ingress}$) and egression (k_{egress}) resemble those observed for some hemicarcerands for which the entrance of the guest through the portals is rate-determining.[24–29] Such a *constrictive* binding[30] may also apply for CB6, which resembles hemicarcerands in the size of its portals (about 4 Å).[6, 21, 22] This is supported by the observed decrease of the $k_{ingress}$ values with increasing steric demand of the guest (Table 1) and the slight decrease of the value of k_{egress} upon going from cyclopentylmethylamine to the larger cyclohexylmethylamine (Table 1), which is opposite to the expectations arising from the binding constants of these two amines.

The study of rate constants under varying reaction conditions provides an important mechanistic tool. We have analyzed in detail the pH dependence of $k_{ingress}$ and k_{egress} for **1** and compared it to the binding constants K, which can be obtained from the equilibrium concentrations on sufficiently long time scales (Table 2). The experiment could not be performed at very high pH values due to low binding constants, very fast kinetics, and competitive binding of sodium at the very high NaOH concentrations.[13] The variation in the binding constant with pH (Figure 1b) can be accounted for in a straightforward manner. The complex is destabilized at low pH values (< 2), at which protonation of CB6 occurs,[13] and thereby reduces the driving force for complexation of organic ammonium salts; it is also destabilized at high pH values (> 11), at which the ammonium complex is converted to the amine complex that lacks the stabilizing ion–dipole interactions with the CB6 ureidocarbonyl groups. In between these two extreme pH values, the binding constant reaches a plateau value of 170 M^{-1}.

Table 2. Ingression ($k_{ingress}$) and egression rate constants (k_{egress}) and binding constants ($K = k_{ingress}/k_{egress}$) for the inclusion complex between CB6 and **1** in dependence on pH.[a]

pH	$10^4 k_{ingress}$ [$M^{-1}s^{-1}$]	$10^6 k_{egress}$ [s^{-1}]	K [M^{-1}]
0.6	0.18	0.49	37
1.6	4.0	3.1	130
2.4	6.5	4.0	165
3.6	7.6	4.6	165
4.2	7.6	4.5	170
4.8	8.1	4.9	165
6.0	8.1	4.8	170
7.5	8.1	4.8	170
8.2	8.7	5.2	170
8.6	9.7	5.7	170
10.0	52	30	170
11.0	110	92	120
12.2	140	1100	13
14.0	145[b]	1450[b]	10[b]

[a] Determined by ^{1}H NMR spectroscopy in D_2O at ambient temperature with 3 mM CB6 and 6 mM **1**. The pH was adjusted through addition of D_2SO_4 or NaOH solutions. The total sodium concentration was adjusted to 0.2 M through addition of appropriate amounts of Na_2SO_4 to achieve a sufficient water solubility of CB6. The error in the values is 5%. [b] Extrapolated by fitting Equations (1) and (2) to the experimental data, see text.

The $k_{ingress}$ and k_{egress} values cover a range of more than two orders of magnitude. However, $k_{ingress}$ proved to be unrelated to the driving force for complexation. The data at high pH values demonstrate that although the amine form has a lower binding constant, its $k_{ingress}$ value is higher. Strikingly, a dramatic increase was observed beyond pH 10. Hence, while the equilibrium for inclusion under the experimental conditions was reached only after 1 week at pH 7.5, the same process occurred within hours at pH 10.0 (inset of Figure 1a). On the other hand, guest release from the complex in dilute solution takes place with a half-life of around 40 h at neutral

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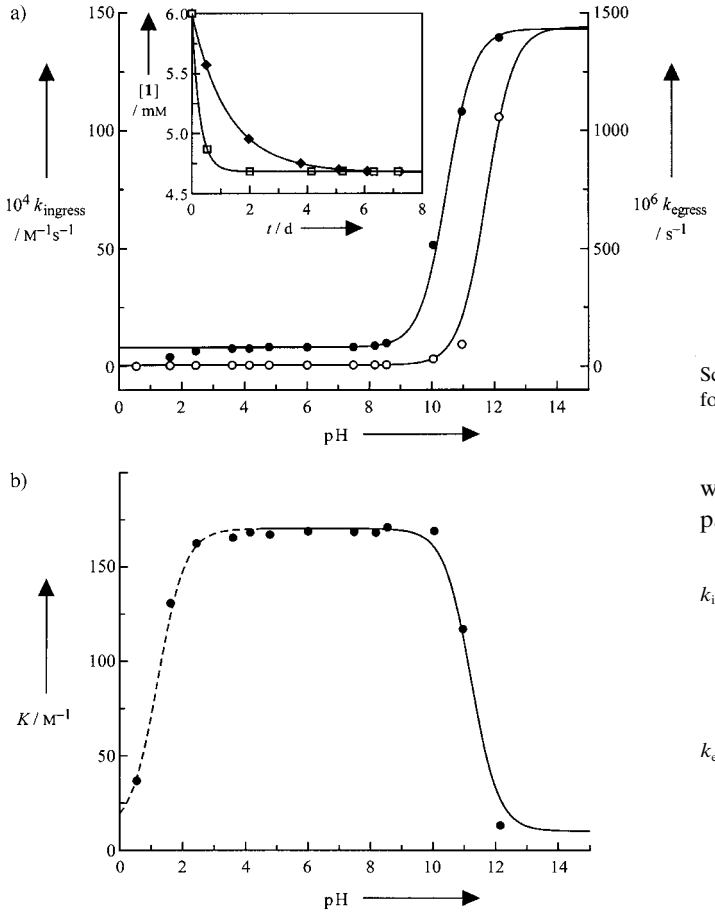
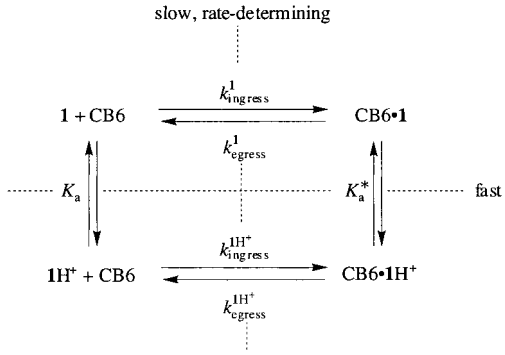


Figure 1. Effect of pH on the kinetics and thermodynamics for complexation between CB6 and **1** according to the data in Table 2: a) Plot of the ingression rate constants ($k_{ingress}$, ●, left scale) and the egression rate constants (k_{egress}, ○, right scale) versus pH. The deviations for the three data points at lowest pH are due to competitive protonation of CB6, see text; these data points were not included in the regression analysis according to Equations (1) and (2) (interpolated lines). The inset shows representative kinetic decays at pH 7.5 (◆) and pH 10.0 (□). b) Plot of the binding constant ($K = k_{ingress}/k_{egress}$) versus pH.

pH but requires merely two hours at pH 11, although the thermodynamics of binding is hardly affected in this pH range.

Since the large change in the kinetics occurred near the pK_a value of **1**, which was determined as 10.50 in this work by ^{1}H NMR, in agreement with a previous report,[31] a competition between ingression and egression processes of the unprotonated and protonated amine and its complex according to Scheme 1 was presumed. Here, the protonation equilibria of the free amine (K_a) and the amine complex (K_a^*) are fast compared to the slow, rate-determining ingression and egression rates. This is confirmed by the fact that the protonated and unprotonated species are in a dynamic equilibrium on the NMR time scale. The larger $k_{ingress}$ and k_{egress} values at high pH values indicate that the amine form (**1**) undergoes faster ingression and egression than the ammonium form (**1**H$^+$). According to Scheme 1, the measured $k_{ingress}$ and k_{egress} values can be expressed as a composite of the rate constants for ingression and egression of the protonated ($k_{ingress}^{1H^+}$, $k_{egress}^{1H^+}$) and unprotonated forms ($k_{ingress}^{1}$, k_{egress}^{1}), each



Scheme 1. Kinetics for ingression and egression and acid–base equilibria for complexation of **1** and its ammonium form (**1**H$^+$) with CB6.

weighted with the fraction of the relevant concentration at a particular pH [Eq. (1), (2)].

$$k_{ingress} = \frac{[\mathbf{1}H^+]}{[\mathbf{1}H^+] + [\mathbf{1}]} k_{ingress}^{1H^+} + \frac{[\mathbf{1}]}{[\mathbf{1}H^+] + [\mathbf{1}]} k_{ingress}^{1} = \left(\frac{[H^+]}{K_a + [H^+]}\right) k_{ingress}^{1H^+} + \frac{K_a}{K_a + [H^+]} k_{ingress}^{1} \quad (1)$$

$$k_{egress} = \frac{[CB6 \cdot \mathbf{1}H^+]}{[CB6 \cdot \mathbf{1}H^+] + [CB6 \cdot \mathbf{1}]} k_{egress}^{1H^+} + \frac{[CB6 \cdot \mathbf{1}]}{[CB6 \cdot \mathbf{1}H^+] + [CB6 \cdot \mathbf{1}]} k_{egress}^{1} = \left(\frac{[H^+]}{K_a^* + [H^+]}\right) k_{egress}^{1H^+} + \frac{K_a^*}{K_a^* + [H^+]} k_{egress}^{1} \quad (2)$$

Equation (1) can be directly fitted to the experimental $k_{ingress}$ values by using the known pK_a of **1**. The fit in Figure 1a provided a value of $0.0145\,M^{-1}s^{-1}$ for the ingression rate constant of the free amine ($k_{ingress}^{1}$), nearly 20-fold larger than for the ammonium form ($k_{ingress}^{1H^+} = 8.0 \times 10^{-4}\,M^{-1}s^{-1}$). Equation (2) can be fitted to the experimental k_{egress} values according to [Eq. (3)] if the unknown K_a^* value of the complex is expressed through the thermodynamic cycle of Scheme 1.

$$K_a^* = \frac{k_{ingress}^{1} k_{egress}^{1H^+}}{k_{egress}^{1} k_{ingress}^{1H^+}} K_a \quad (3)$$

Substitution of Equation (3) into Equation (2) and use of the known values for K_a, $k_{ingress}^{1}$, and $k_{ingress}^{1H^+}$ allows for an excellent fit (Figure 1a) and provides the egression rate constants of the amine and ammonium complexes, k_{egress}^{1} and $k_{egress}^{1H^+}$, as $1.45 \times 10^{-3}\,s^{-1}$ and $4.7 \times 10^{-6}\,s^{-1}$. The ratio of the rate constants for the free amine ($k_{ingress}^{1}/k_{egress}^{1}$) provides a weak binding constant of $10\,M^{-1}$ for the unprotonated complex. The kinetic and thermodynamic constants for the free amine are entered in Table 2 as extrapolated to pH 14 values. These can then be used in Equation (3) to derive a pK_a^* value of 11.75 for the CB6 complex, more than one unit above the free amine. It should be noted that the fitted pH rate profiles in Figure 1a present essentially titration curves, from which the pK_a values and rate constants (plateau values) can be directly read. The increase in pK_a upon complexation (from 10.50 to 11.75) is expected in view of the additional stabilization of the ammonium form due to ion–dipole interactions in the

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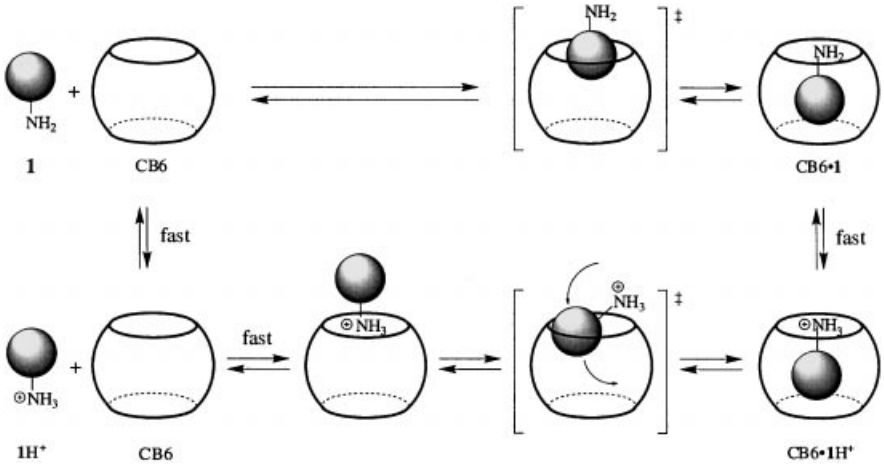
complex. Such complexation-induced pK_a shifts of ammonium ions play an important role not only in supramolecular but also biomolecular systems.[32]

The overall phenomenon can be qualitatively understood in terms of a change of the preferred pathway for complexation and decomplexation (Scheme 1). At low pH, complexation of the free ammonium form and decomplexation of the ammonium complex predominate. Above pH 10 the complexation proceeds mainly through the free amine, but it is only above pH 11 that the decomplexation of the unprotonated complex becomes important and dominates the egression rate. Consequently, and as can be seen from the comparison of the evolution of the thermodynamics and kinetics with pH (Figure 1a versus 1b), there exists a very narrow region between pH 10 and 11 where the binding constant is similar to the value at lower pH but where the kinetics increases dramatically. From a kinetic point of view, it is thus preferable to assemble such complexes at $pH \approx pK_a$. Knowledge of such protonation effects is important, since amino and ammonium groups are frequently used in supramolecular chemistry.[11, 33–35]



Scheme 2. Proposed mechanisms for complexation of **1** and its ammonium form (**1**H$^+$) with CB6.

The fact that the binding constant remains large in a region where most of the free amine is already deprotonated is a consequence of the higher pK_a^* value of the complex. Accordingly, complex formation between pH 10 and 11 does not occur through a direct complexation of the remaining ammonium form but through a faster complexation of the amine form, followed by an immediate protonation of the more basic complex (Scheme 1). Below pH 11 the complex is mainly protonated, such that k_{egress} remains rather constant. Only at larger pH values does deprotonation of the complex become significant, which causes a large increase of k_{egress} and a concomitant decrease in the binding constant. For the present system the binding constant remains similar as the ingression rate constant increases steeply. However, the general reaction mechanism according to Scheme 1 could, in principal, also account for an increase in the binding constant in the $pH \approx pK_a$ region, whenever $pK_a^* \gg pK_a$.

The lower egression rate constant k_{egress} of the ammonium form is consistent with its higher binding affinity. In contrast, the lower $k_{ingress}$ value of the ammonium form is opposite to expectations based on thermodynamic data. A mechanistic explanation must take into account that both the degree of protonation of the amino group (Table 2) as well as the size of the organic residue affect the kinetics (Table 1). Based on the results from molecular dynamics calculations,[36] we suggest the reaction mechanisms in Scheme 2.

Accordingly, the amine enters by a direct penetration of the organic residue into the nonpolar cavity. This pathway is unfavorable for the ammonium ion, which forms rapidly an intermediary *association* complex, in which the ammonium site coordinates with the ureido-carbonyl rim while the organic residue is still exposed to the aqueous phase.[37] The subsequent rate-determining ingression of the organic residue occurs in a flip–flop manner, namely through a *different* transition state. The transition state for conversion of the association to the inclusion complex requires a significant distortion of the portal, which renders this pathway slower than for the amine, but avoids a complete loss of the stabilizing ion–dipole interactions since it allows the ammonium ion to remain at least partly coordinated with the portal. Typical calculated structures for ingression of the amine and the ammonium form are shown in Figure 2. The involvement

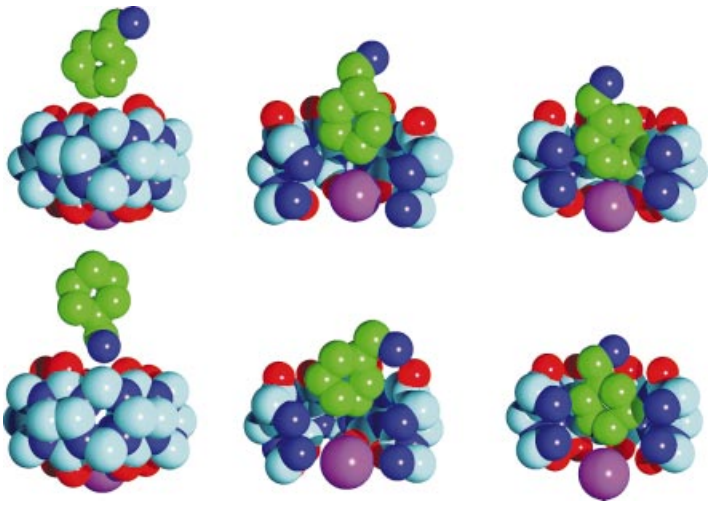


Figure 2. Representative structures obtained in molecular dynamics runs for ingression of unprotonated (top) and protonated (bottom) **1** into CB6. The middle and right-hand structures are shown as intersections. The calculations were run with a sodium cation complexed to the lower portal, which is vital experimentally to promote solubility of the host. Note that the ammonium form (bottom) retains ion–dipole and hydrogen bonding interactions with the carbonyl rim during ingression, while the amine form (top) does not.

of different transition states receives strong support from the rate constants for egression, which differ by more than a factor of 300 for the protonated and unprotonated complex. This difference cannot be entirely accounted for by the ground-state energy difference ($K_a/pK_a^* \approx 18$) and, hence, requires a discrimination of the transition state energies.

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Alternative explanations for the observed kinetic effects were also considered. First, differential desolvation of the amine and ammonium forms cannot be decisive for the observed rates since ion and solvent replacement occur on the much faster nano- to microsecond time scale akin to the fast complexation equilibria of inorganic cations, including ammonium, with crown ethers.[38] Accordingly, the association complexes should be part of a rapid pre-equilibrium, although their spectroscopic properties are not sufficiently distinct to allow direct detection. Further, the possibility that the formation of the association complex reduces the concentration of free ammonium form and uncomplexed CB6, and thereby slows down the kinetics, was also tested. In this case, the association complex does not convert to the inclusion complex, that is, it acts as a dead end and serves merely as a reservoir. However, for such a reservoir effect to cause the observed effect on the ingression rate constant (a factor of 20), a much higher binding constant for the association than for the inclusion complex is required, which contrasts the presumed weak binding in such association complexes.[37] Moreover, a reservoir effect cannot account for the large decrease of the unimolecular egression rate constant which is higher than expected from the ground state energy difference (see above). A different transition state as suggested in Scheme 2 is therefore required. Note that the refined mechanism in Scheme 2 does not require a modification of the kinetic analysis according to Equations (1) and (2) as long as the association complex is in a rapid pre-equilibrium.

The interesting implication from this mechanistic peculiarity is that the ion–dipole and hydrogen bonding interactions, which stabilize the complex thermodynamically, retard the kinetics of complexation through the formation of an intermediary association complex, which prevents direct inclusion. A closely related example in which such an association complex actually retards the kinetics has been documented by Rebek et al. for the slow complexation of organomercury species by crown ethers.[39] Clearly, mechanistic details of the elementary reaction steps, which can be assessed through measurement of rate constants under varying reaction conditions, are crucial for the understanding and optimization of the kinetics and thermodynamics of supramolecular processes. Many supramolecular assemblies rely on a *combination* of different noncovalent interactions like van der Waals forces, hydrogen bonding, π,π interactions, charge-transfer stabilization, or ion–dipole interactions.[1–3] As demonstrated herein for a prototypal host–guest complex, which results from a combination of ion–dipole and van der Waals interactions as well as steric hindrance, the relative rate constants of the processes governed by a particular interaction and the sequence by which they occur may be an important supramolecular design criterion.

Returning finally to the original context of supramolecular *functionality*, we have obtained experimental evidence that the presently examined operation ("inclusion of an organic ammonium ion into CB6") cannot only be "switched on and off" (Figure 1b) but that the operational speed can be "adjusted up and down" by more than an order of magnitude through fine tuning of the pH (Figure 1a). This host–guest system can be considered as a model for a pH-responsive *kinetic regulator* as opposed to a thermodynamic switch. Kinetic regulation of supramolecular functions may be crucial, for example, in the cases of supramolecular drug delivery,[40] to induce an accelerated or retarded release on the time scale of hours to weeks through natural or external stimuli. The pH-responsive guest exchange of CB6 in this attractive yet rarely encountered time range[28, 34, 41] as well as its water solubility in the presence of physiological electrolyte concentrations are promising features along this train of thought.

Experimental Section

The cyclohexylmethylammonium salt was prepared from the commercial amine (Fluka) through precipitation from diethyl ether upon addition of D_2SO_4. CB6 was from Merck; formic acid, NaOH, and Na_2SO_4 were from Fluka (>98%). D_2O (Glaser AG, Switzerland, >99.8%) was used as solvent for all measurements. NMR spectra were obtained at different times after sample preparation on a Bruker DPX 400 MHz Avance spectrometer and the data analysis was performed with the SwaN-MR program.[42]

Kinetic analysis. The kinetics were in line with a reversible 1:1 host–guest complexation. The restricted solubility of CB6 in nonacidic solutions and the relatively low sensitivity of the NMR integration method precluded the adjustment of pseudo first-order kinetic conditions. We have employed the method described by Mauser[43] to extract the rate constants for ingression and egression under second-order kinetic conditions. The decrease of the guest concentration, which could be most accurately followed, is given by Equations (4) and (5), which applies for the present conditions where

$$[\text{guest}] = [\text{guest}]_\infty - \frac{([\text{guest}]_0 - [\text{guest}]_\infty) r e^{-rt}}{r + k_{\text{ingress}}([\text{guest}]_0 - [\text{guest}]_\infty)(r e^{-rt} - 1)} \quad (4)$$

$$r = \sqrt{(k_{\text{egress}} + k_{\text{ingress}}([\text{host}]_0 - [\text{guest}]_0))^2 + 4 k_{\text{ingress}} k_{\text{egress}} [\text{guest}]_0} \quad (5)$$

$[\text{guest}]_0 \neq [\text{host}]_0$ and $[\text{complex}]_0 = 0$. Here, the concentrations of host and guest refer to the sum of the protonated and unprotonated forms, which are in a dynamic equilibrium on the NMR time scale. The kinetics were followed until no further change in concentration was detected. Nonlinear least-squares fitting to the experimental data provided the pertinent rate constants and binding constants in Table 2.

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Combinatorial Discovery of New Photocatalysts for Water Purification with Visible Light**

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Photocatalytic conversion of air and water pollutants belongs to the most promising methods of environmental protection. Irradiation of a semiconducting oxide (SCO) with light of energy equal to or larger than the bandgap energy leads to the generation of electron – hole pairs, which can subsequently induce redox reactions at the SCO surface. Heterogeneous photocatalysis is an environmentally friendly method for the detoxification of water and air by sunlight, by which organic pollutants are converted to CO_2, H_2O, and mineral acids. Recent reviews were published discussing the underlying mechanisms and summarizing the state of the art.[1, 2] Research has been concentrated on anatase (TiO_2), which is photostable, nontoxic, cheap, and active. Due to its large bandgap of 3.2 eV, UV light ($\lambda < 400$ nm) is necessary to generate the electron – hole pairs. This is a major drawback for an efficient water detoxification with TiO_2, since only 3 % of the solar spectrum has wavelengths shorter than 400 nm.

We have discovered recently, that a variety of dopants in sol – gel derived TiO_2, such as Pt, Ir, and even coke, provide photocatalytic activity with visible light at wavelengths > 400 nm.[3, 6, 7, 12] These discoveries have convinced us, that there may be more photocatalytically active materials than presently known, and we have developed a combinatorial high-throughput technique in order to search more effectively for promising novel compositions. In recent years the potential power of combinatorial approaches and high-throughput (HT) screening for materials and catalysts has already been amply demonstrated,[4] while reports on the discovery of superior novel substances are still limited.

The aim of this work was to develop a reliable HT technique for the efficient discovery of new photocatalysts, capable of photodegrading water pollutants with visible light ($\lambda > 400$ nm). Due to their well-known photocatalytic properties, doped titanium oxides were selected as reference materials during the development of the method. Since nothing is known about the photocatalytic properties of the doped SCOs WO_3 or SnO_2 with visible light, these oxides have been selected as base materials for the discovery libraries.

The "library design" chosen consists of 45 transparent HPLC glass flasks (2 mL) arranged in an addressable rack of nine rows and five columns. The potential catalysts were

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