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Elucidating the importance of HCl as cocatalyst for resorcinarene capsule-catalyzed reactions

Jesper M. Köster[b] and Konrad Tiefenbacher*[a,b]

Abstract: This survey of resorcinarene capsule-catalyzed reactions demonstrates that HCl functions as a crucial cocatalyst by increasing the capsule's inherent Brønsted acidity to enable or accelerate cationic reactions. The presence of HCl appeared to be without consequences for other reactions.

Supramolecular catalysts have emerged as promising enzyme mimics,[1],[2] that are able to influence reactions accelerated inside their cavity. The main differences of reactions catalyzed inside a supramolecular container as compared to the bulk solution are:[1i] (1) product selectivity; in several cases different products were obtained inside the supramolecular container; (2) substrate selectivity; this hallmark feature is generally used as a control experiment, where large substrates that do not bind the cavity, or at least to a much lower extent, are converted at significantly reduced rates; (3) multicatalyst tandem reactions, where the encapsulation of the active site enables the simultaneous use of several otherwise incompatible catalysts in solution. One of the more versatile representatives is calix[4]resorcinarene (**1** , Fig. 1a), which self-assembles in apolar solvents such as chloroform and benzene under incorporation of eight water molecules to the hexameric capsule **I** (Fig. 1b).[3] The assembly displays a high affinity for cations, which are stabilized via cation-π interactions with the aromatic cavity walls.[4] [4] Furthermore, capsule **I** was shown to be reasonably Brønsted acidic (pK_A 5.6 - 5.9).[5] It has been employed as a catalyst for the hydrolysis of acetals,[5] the tail-to-head cyclization of terpenes,[6] the intramolecular hydroalkoxylation of alkenes,[7] the cyclodehydration of alkenols,[8] the hydration of isonitriles,[9] [2+3]-cycloaddition reactions,[10] the *Meinwald* rearrangement of epoxides,[11] the hydration of alkynes to ketones,[12] and the oxidation of thioethers.[13] In a recent report concerning the tail-to-head terpene cyclization,[14] it was found that traces of hydrochloric acid, formed via photodegradation of the solvent chloroform, acted as an essential cocatalyst. It was established that HCl protonates the capsule,[14] which is then believed to transfer the proton onto the encapsulated substrate (Fig. 2a, right). Control experiments without the capsule under otherwise identical conditions did not lead to any observable conversion. Additionally, size competition experiments as well as blocking experiments provide convincing evidence that the reaction takes place inside the capsule. It was also found that the presence of HCl traces can be easily detected by inspecting the ^{1}H NMR spectrum of the capsule solution (Fig. 2b). In the absence of HCl, sharp peaks for the phenols and water signals are observed. Traces of HCl lead to a significant broadening of these peaks. In all previously published reactions employing capsule **I** as catalyst, untreated chloroform (not filtered through basic Al_2O_3) was used as a solvent. Therefore, we wondered if the presence of an acid

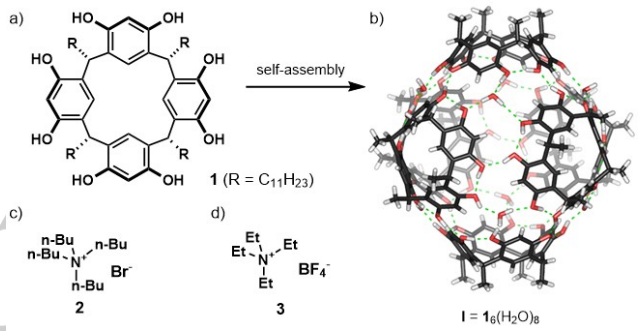

Figure 1. a) Resorcin[4]arene monomer **1** b) Hexameric capsule **I**, C_{11}-alkyl feet have been omitted for clarity c) High-affinity guest tetrabutylammonium bromide (TBAB, **2**) d) tetraethylammonium tetrafluoroborate ($TEABF_4$, **3**).

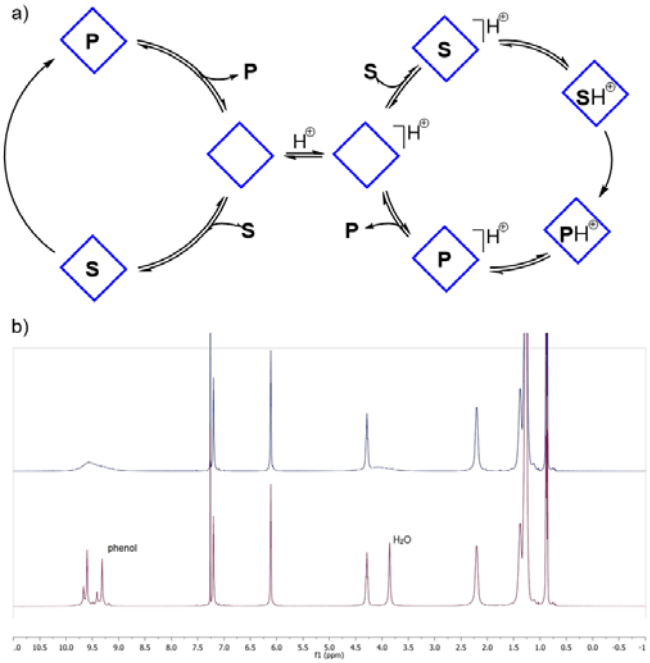

Figure 2. a) Possible reaction pathways for reactions catalyzed inside capsule I with and without HCl as cocatalyst b)^{1}H NMR spectra of capsule **I** in $CDCl_3$ (3.3 mM) before and after addition of 0.3 eq. HCl with respect to capsule **I**.

[a] M. Sc. J. M. Köster, Prof. Dr. K. Tiefenbacher
Department of Chemistry, BPR1096
University of Basel
Mattenstrasse 24a, CH-4058 Basel, Switzerland
E-mail: konrad.tiefenbacher@unibas.ch

[b] Prof. Dr. K. Tiefenbacher
Department of Biosystems Science and Engineering
ETH Zürich
Mattenstrasse 24, CH-4058 Basel, Switzerland
E-mail: tkonrad@ethz.ch

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cocatalyst (HCl) is generally required for catalytic activity or if the inherent Brønsted acidity of capsule **I** itself is sufficient for other reactions.

In order to elucidate the importance of HCl, all reaction classes reported were repeated under precisely controlled conditions. One suitable substrate (high-yielding, high selectivity) was chosen for each reaction class and investigated under the conditions published in the absence and presence of defined HCl amounts. To further exclude background reactions outside of capsule **I**, control experiments were performed as described in literature by blocking the cavity of the supramolecular capsule by addition of the high-affinity guests tetrabutylammonium bromide **2** (Fig. 1c) or tetraethylammonium tetrafluoroborate **3** (Fig. 1d). The results from this screening are summarized in Table 1.

For the hydrolysis of acetaldehyde diethyl acetal (**4**) inside container **I**,[5] a clear correlation between HCl added and the formation of the product was revealed.

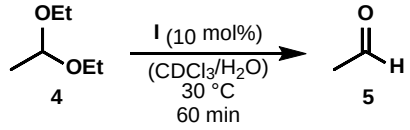
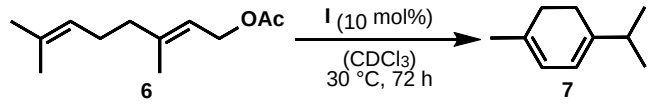
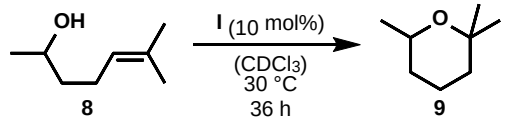
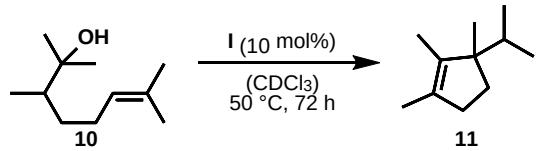
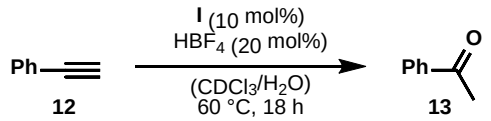
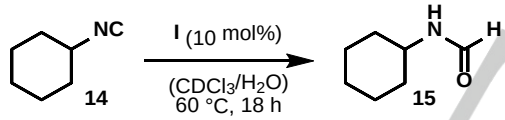
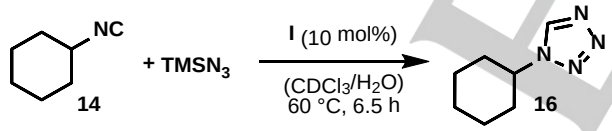
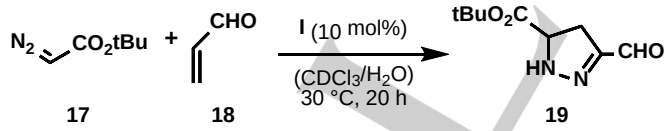
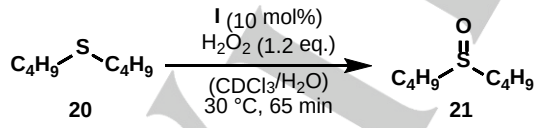
In initial experiments (10 mol% capsule **I**, 3 mol% HCl), almost instantaneous hydrolysis of the acetal was observed. To reproduce the published findings, the HCl content was gradually lowered to 0.1 mol%, which led to a yield of 86 ± 5 % after 60 min of reaction time (entry 1B, Table 1), which is in good agreement with the yield reported in literature. Without the addition of the cocatalyst, no conversion was observed. In this case, the acidity of the hexameric assembly is not sufficient for catalysis inside **I**.[5] Control experiments, where the catalytically active cavity of **I** is blocked by a strong binding guest, tetrabutylammonium bromide (TBAB, **2**, entry 1C),indicate that the reaction is limited to the interior of capsule **I**, even in the presence of 0.1 mol% HCl (entry 1D). Furthermore, very convincing evidence was provided in the original report by size competition experiments.[5]

For the cyclization of geranyl acetate (**6**) the published findings were reproduced,[6] showing conversion only in the presence of HCl as cocatalyst (entry 2B). Control experiments again confirmed that access to the cavity of **I** is required for activity, even in the presence of 3 mol% HCl (entry 2D).

The intramolecular hydroalkoxylation[7] of alkene **8** was also revealed to be highly dependent on the presence of HCl, giving 95 ± 2% yield after 36 h in the presence of 3 mol% of HCl (entry 3B). The requirement of HCl as a cocatalyst for this reaction was overlooked in the original report. Nevertheless, all control experiments performed in the initial report (size competition and blocking experiments) strongly support the fact that the reaction takes place predominantly inside the cavity. The formation of small amounts of product (7 ± 2%) with blocked capsule in the presence of 3 mol% HCl indicates only a slow background reaction outside of capsule **I** (entry 3D).

The cyclodehydration of alkenol **10** takes place under HCl-free conditions inside capsule **I** (entry 4A),[8] but the presence of HCl greatly accelerates the reaction (entry 4B). The acceleration effect on this reaction was not known at the time of the initial report. Negligible amounts of product (3 ± 2%) were formed in the presence of 3 mol% HCl when competitive guest **2** was added (entry 4D). While HCl is not required as cocatalyst for the reaction, addition of catalytic amounts led to a significant acceleration of the reaction.

Table 1. Overview of reactions investigated including yields obtained. Reactions were performed in triplicate and standard deviations were determined; all reactions were performed in $CDCl_3$ filtered through basic Al_2O_3 to remove acid traces and with 10 mol% of capsule **I**; Additives: **A** – no additives; **B** – 3 mol% HCl added; **C** – literature inhibition conditions (ammonium salt **2** or **3**)[b,c]; **D** – literature inhibition conditions (ammonium salt **2** or **3**)[b,c] and 3 mol% HCl added.

#	reaction	A	B	C	D
1		0 ± 1	**86 ± 5**[a]	0[b]	0[a,b]
2		0	**27 ± 3**	0[b]	0[b]
3		0	**95 ± 2**	0[b]	7 ± 2[b]
4		32 ± 1	**65 ± 1**	0[b]	3 ± 2[b]
5		81 ± 3	79 ± 3	2 ± 0[c]	12 ± 5[c]
		acid HBF_4 is present in all cases			
6		95 ± 4	95 ± 1	13 ± 0[c]	14 ± 1[c]
7		90 ± 4	92 ± 5	43 ±1[c]	41 ± 1[c]
8		93 ± 2	90 ± 1	0[c]	0[c]
9		92 ± 1	94 ± 1	70 ±1[c]	70 ± 0[c]

[a] 0.1 mol% HCl added. [b] TBAB (**2**, 1.5 eq.) added. [c] $TEABF_4$ (**3**, 10 eq.) added.

The hydration of alkyne **12** to acetophenone (**13**) was already shown to require the presence of an acid cocatalyst (HBF_4).[12] Supplementing the reaction with additional acid (HCl) led to no significant change in reactivity (entries 5A and 5B). The addition of 10 eq. of **3** efficiently blocked the reactive cavity as evidenced by the drastically lowered yield of acetophenone.

In contrast to the examples discussed so far, the hydration of cyclohexyl isocyanide (**14**) did not depend on an acid cocatalyst (entries 6A and 6B).[9] Control experiments with 10 eq. of the competitive guest **3** led to a significant retardation of the reaction progress, even in the presence of HCl (entries 6C and 6D). This might indicate that protonation of the carbenic-like carbon is not rate-determining in the mechanism.

The [2+3]-cycloaddition of **14** and trimethylsilyl azide is also unaffected by the addition of HCl (entries 7A and 7B).[10a] Employing inhibitor **3** in high excess did not lead to an efficient suppression of the cycloaddition (entries 7C and 7D), which might

indicate a significant background reaction taking place outside of capsule **I**.

Also in the case of the [2+3]-cycloaddition between tert-butyl diazoacetate (**17**) and acrolein (**18**) no significant impact of HCl was observed (entries 8A and 8B).[10b] Blocking of the cavity by addition of 10 eq. of $TEABF_4$ (**3**) completely suppressed product formation.

HCl was also not required for the oxidation of thioether **20** by H_2O_2 (entries 9A and 9B).[13] A very significant background reaction was observed in all control experiments (entries 9C and 9D). This may be explained by the activation of H_2O_2 by replacing water in the hydrogen-bond network of the hexameric assembly, which was already proposed in the original report.[13] The activated peroxide is also accessible from outside of the capsule **I**, leading to oxidation of the thioether upon contact from the bulk solution.

An inspection of table 1 reveals that the experiments performed can be readily divided into two groups: 1) Reactions that are enabled or at least significantly accelerated by an acid cocatalyst (entries 1-5 in Table 1). 2) Reactions which are not accelerated by an acid cocatalyst (entries 6-9).

For reactions in group 1 the acidity of capsule **I** is not sufficient to promote the acid-catalyzed reaction even in the inside of the cavity, where cationic/protonated intermediates and transition states are stabilized. The addition of HCl as cocatalyst in substoichiometric amounts increases the acidity of the capsule and facilitates catalytic turnovers inside the cavity of **I**. Literature control experiments clearly indicate that the reactions take place inside the container and are not catalyzed by HCl alone. In addition, control experiments with HCl were performed (SI chapter 5.5) which also confirmed that HCl alone is not able to catalyze the reactions investigated. Interestingly, one would expect to find the hydration of isonitriles (entry 6) in group 1, since the protonation of the carbenic-like carbon is thought to be crucial in the activation of the isonitrile for a nucleophilic attack of water. The results from table 1, however, indicate that the inherent Brønsted acidity of capsule **I** is sufficient to facilitate the reaction. Reactions in group 2 are accelerated by capsule **I** itself and do not require an external acid for activation. Even the initial rate of the reactions seems not to be influenced by the presence of HCl as experiments with cyclohexyl isocyanide (entry 6) demonstrated (see SI). In two cases (entries 7 and 9) significant background reactions were observed which might indicate that the reactions can also take place outside of capsule **I**.

In conclusion, literature results with capsule **I** as catalysts were reproduced under strictly controlled conditions. Reactions involving cationic intermediates showed a strong dependency upon the presence of HCl resp. HBF_4 as co-catalysts. The transformations of isocyanides to formamides and tetrazoles, which are believed to progress via initial protonation of the carbenic-like carbon, displayed no dependence upon the presence of HCl, which may indicate that the inherent acidity of hexamer **I** is already sufficient for catalysis in these reactions. Oxidation and cycloaddition reactions displayed no dependency on an additional acid cocatalyst. These results clarify the role of HCl as a cocatalyst in the resorcinarene capsule-catalyzed reactions. Since HCl can play a significant role in such reactions we highly encourage scientists to run future studies under strictly controlled conditions only. It is recommended that (1) the solvent is filtered through basic Al_2O_3 directly before the start of the experiment to remove acid traces, and (2) that the calix[4]resorcinarene **1**, which is synthesized under acidic (HCl) conditions is washed with large amounts of water to remove traces of acid (see SI).

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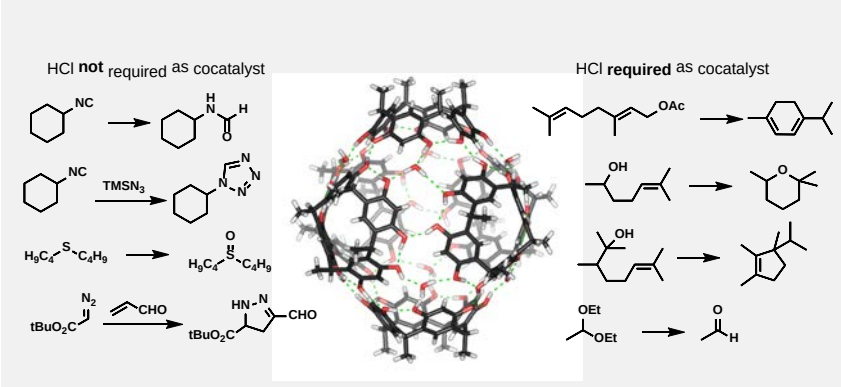

*Jesper M. Köster and Konrad Tiefenbacher**

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Elucidating the importance of HCl as cocatalyst for resorcinarene capsule-catalyzed reactions

Reactivity inspection: Detailed investigations of published resorcinarene capsule-catalyzed reactions reveal a dependency on the presence of HCl, a common photodegradation product of the solvent $CDCl_3$, for some reactions. Other reactions do not depend on an acid cocatalyst.