

Unusual Reaction of Isocyanides with Aromatic Aldehydes Catalyzed by a Supramolecular Capsule

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The supramolecular resorcinarene hexameric capsule efficiently promotes the unprecedented reaction between isocyanides and electron-deficient aromatic aldehydes leading to the formation of imines and carbon monoxide. The mechanism of the reaction was investigated via isotope labelling, kinetic analysis of the

reaction, computational studies and the independent synthesis of a proposed intermediate. Control experiments indicate that the formation of the key aziridinone intermediate is limited to the cavity of the capsule.

Introduction

Supramolecular catalysis, taking inspiration from enzymatic catalysis, is emerging as a powerful cross-discipline that exploits weak non-covalent interactions to accelerate chemical transformations under homogeneous conditions.^[1–9] This cross-discipline is based on unimolecular or self-assembled host structures^[10,11] that, due to nano-confinement effects,^[12] are able to recognize and operate on the substrate with high site and regioselectivity,^[13,14] enabling to achieve unprecedented activities,^[15–17] product,^[18] and substrate^[19–21] and site^[22] selectivities. Among self-assembled supramolecular catalysts, the hexameric capsule^[23–25] **1₆** (Figure 1a) formed by the self-assembly through hydrogen bonding between six resorcin[4]arene **1** and eight water molecules in apolar solvents, is characterized by a large interior cavity of roughly 1400 Å³ that has been investigated as nanometer-sized reaction chamber as well as a supramolecular catalyst. Its catalytic effects are the result of the combination of a weak Brønsted acidity,^[26–28]

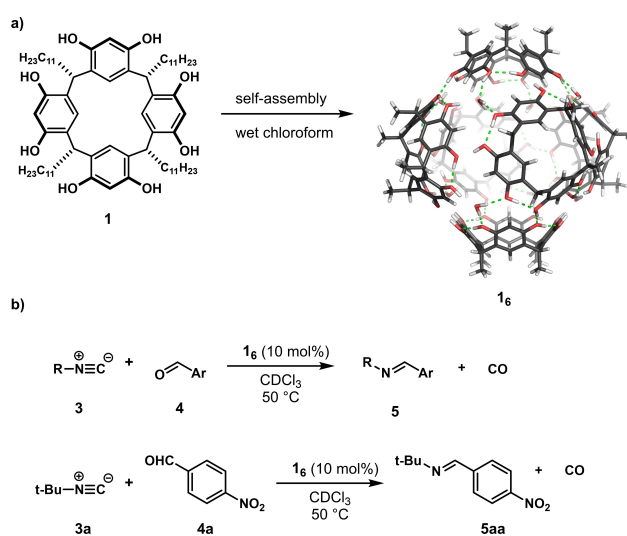


Figure 1. a) Resorcin[4]arene **1** self-assembles in apolar solvents to form hexamer **1₆** (–C₁₁H₂₃ alkyl chains have been omitted for clarity), b) reaction between isocyanides **3** and electron poor aromatic **4** aldehydes leading to imines **5** catalyzed by **1₆**.

internal hydrogen bonding activation of substrates^[29,30] and stabilization of cationic intermediate species.^[31–36] The catalytic activity of **1₆** can be turned off by the addition of competitive cationic guests like tetraethylammonium tetrafluoroborate **2**.^[34] The great potential of this simple and efficient organocatalyst with behavior reminiscent of enzymatic catalysis, enabled for instance the synthesis of terpene and sesquiterpene natural product derivatives,^[37–40] the β -selective *O*-glycosylation exploiting a proton wire mechanism^[41] and the carbonyl olefin metathesis reactions.^[42,43] As a molecular nanoreactor, the capsule was recently exploited for the kinetic and thermodynamic modulation of the imine constituents of the DCLs^[44] or to activate a halogen bonding catalyst^[45] or a carbocation catalyst^[46] once hosted in the cavity.

Isocyanides have been shown to be suitable guests for capsule **1₆**, which are also activated for being attacked by

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nucleophiles such as water,^[47] and azides,^[48] inside the supramolecular assembly.

They are of high synthetic interest due to the unique properties of the carbon atom in the isocyanide moiety, which can function as either an electrophile or a nucleophile.^[49] The probably most well-known reactions involving isocyanides are the Passerini and Ugi multicomponent reactions,^[50] in which these versatile molecules react with carbonyl compounds and carboxylic acids (and amines in the case of the Ugi reaction) to give α -acyloxy amides or di-amides, respectively. These reactions incorporate the full isocyanide moiety into the product structure.

Here we present a novel and highly unusual reaction mode of isocyanides with electron-poor benzaldehydes promoted by capsule **1₆**, leading to the formation of imines and the expulsion of carbon monoxide (Figure 1b). To the best of our knowledge, this reaction is without precedent in literature.

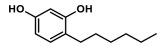
Results and Discussion

Isocyanide Aldehyde Reaction Screening

Based on earlier findings^[47,48] that isocyanides are excellent guests for capsule **1₆** and also displayed good reactivity, the reaction of isocyanide **3 a** with aldehydes was investigated. The reaction with electron-poor benzaldehyde **4 a** under capsule **1₆** catalysis yielded an unexpected product, imine **5 a a** containing one carbon less than the starting materials. This immediately sparked our interest to further investigate this novel reaction, and efforts to optimize the experimental conditions were made. It was found that running the reaction at 50 °C in acid-free chloroform (filtered through basic Al₂O₃) with 10 mol% of capsule **1₆** (13.3 mM) at an isocyanide/aldehyde ratio of 2:1 gave 39% yield of imine **5 a a**. The excess of isocyanide was used after optimization to increase imine product yield (see supporting information chapter 3.1). The identity of imine **5 a a** was confirmed by comparison to an independently synthesized sample of this literature-known compound.^[51]

First, control reactions were performed to identify the role of capsule **1₆** in this reaction (Table 1). In the absence of **1₆**, no reaction was observed (Table 1, entry 2). Substituting the capsule with acetic acid, a Brønsted acid of comparable pK_a (4.7; pK_a(**1₆**) ~5.5)^[26] resulted in no observable conversion (Table 1, entry 3) indicating that the reaction is not solely catalyzed by the inherent Brønsted acidity of **1₆**. Running the reaction with 24 eq. of *n*-hexylresorcinol (comparable amounts of capsule subunits, which may activate the substrates *via* hydrogen bonding) resulted in unselective decomposition of the starting materials, and again no traces of imine were detectable (Table 1, entry 4). The absence of the product in the reaction performed with **1₆** but in the presence of DMSO-*d*₆ that prevents capsule self-assembly, indicated that the assembled capsule is required for **5 a a** formation (Table 1, entry 5). These results pointed towards encapsulation as the possible mode of catalysis for capsule **1₆**. This hypothesis was supported by the addition of 10 eq. of high-affinity guest **2** to the reaction which

Table 1. Control experiments for the reaction between isocyanide **3 a** and aldehyde **4 a** leading to **5 a a**.

#	1₆	Additive	5 a a (%) ^a
1	+	-	39
2	-	-	no conversion
3	-	HOAc (13.3 mM, 10 mol%)	no conversion
4	-		decomposition (5 a a not detected)
5	+	DMSO- <i>d</i> ₆ (10 eq.) ^c	no conversion
6	+	TEABF ₄ (2 , 133 mM) ^d	7

[**3 a**] = 266 mM corresponding to 20 eq. with respect to **1₆**, [**1**] = 80 mM corresponding to 13.3 mM of **16**, [**4 a**] = 133 mM corresponding to 10 eq. with respect to **16**, 0.6 mL de-acidified CDCl₃, 50 °C, 24 h; +: presence; -: absence; a) determined by ¹H NMR spectroscopy; b) 24 eq. with respect to **16**, c) 10 eq. with respect to **1₆**.

occupies the cavity and severely decreased the yield of **5 a a** from 39 to 7% (Table 1, entry 6), highlighting the necessity for an accessible interior of **1₆** for efficient catalysis to occur. A further control experiment was carried out to exclude that the imine was formed by condensation of the aldehyde with free *tert*-butylamine, potentially formed by the hydration of the isocyanide to formylamide^[47] and subsequent hydrolysis. In fact, the reaction of *N-tert*-butyl formamide with aldehyde **4 a** in the presence of capsule did not show any evidence of imine **5 a a** formation even after 24 h at 50 °C (see SI, chapter 6.7).

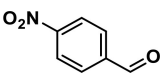
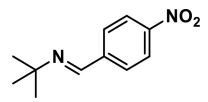
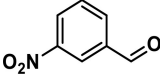
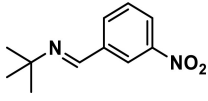
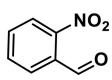
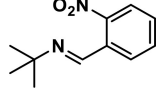
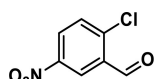
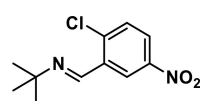
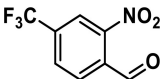
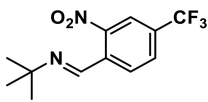
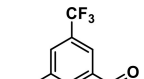
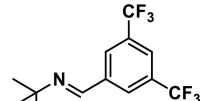
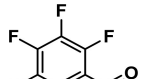
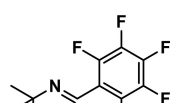
Attempts to further increase the yield were partially fruitful. Running the reaction at a higher temperature (60 °C) and a reduced concentration (54 mM **1₆**), improved the yield of **5 a a** to 49%. As the imine formed is susceptible to hydrolysis under the reaction conditions to furnish *tert*-butyl amine and the starting aldehyde **4 a** (see SI chapter 6.6), our focus shifted towards the scope and the mechanism of this reaction.

Scope of the Reaction

The scope of the reaction was investigated with the newly optimized experimental conditions at 60 °C with **3 a** and a series of electron-deficient benzaldehydes **4 b–g** (Table 2). In all cases, moderate to good yields of the corresponding imines **5** were observed, while the reaction did not proceed in the absence of **1₆**, and a marked decrease in activity was observed when using **2** as a competitive guest for the capsule. Electron-withdrawing substituents turned out to be crucial for reactivity, as the removal of such groups or the installation of an electron-donating group did not lead to imine product formation (see SI, Figure S2). The same was true for aliphatic and unsaturated aldehydes.

The isocyanide scope was explored utilizing isocyanides **3 b–g** with aldehyde **4 d** (Table 3). Besides tertiary isocyanides (**3 a–c**), also a secondary (**3 e**) and a primary derivative (**3 d**) displayed the described reactivity. Also, the aromatic isocyanides (**3 f**, **3 g**) were converted successfully into the correspond-

Table 2. Synthesis of aromatic imines **5** by reaction of **3 a** with a series of electron-poor benzaldehydes **4 a-g** mediated by **1₆**.

#	Aldehyde	Product	Yield (%) ^a
1	 4 a	 5 aa	60 0 ^b 8 ^c
2	 4 b	 5 ab	41 0 ^b 2 ^c
3	 4 c	 5 ac	55 0 ^b 5 ^c
4	 4 d	 5 ad	77 0 ^b 8 ^c
5	 4 e	 5 ae	85 0 ^b 25 ^c
6	 4 f	 5 af	33 0 ^b 1 ^c
7	 4 g	 5 ag	89

[**4 a-g**] = 90 mM, [**3 a**] = 180 mM, [**1**] = 54 mM, 0.6 mL water-saturated CDCl₃, 60 °C, 24 h. a) Determined by ¹H NMR. b) no **1** added; c) [**2**] = 90 mM (10 eq. with respect to the capsule).

ing imines. In all cases, the addition of the high-affinity competitive guest **2** significantly impaired the formation of the respective imine products (Table 3).

To further explore the general applicability of the reaction, we investigated the reaction between adamantyl isocyanide **3 c** and the series of electron-poor aromatic aldehydes (Table 3, entries 7–12). In all cases, the corresponding imines were obtained in good yields with respect to the analogous derivatives using isocyanide **3 a**.

Investigation of the Reaction Mechanism

To learn more about the reaction mechanism, we first decided to elucidate the fate of the isocyanide carbon by utilizing the ¹³C-labelled derivative **3 c***. The isotopically labeled compound was prepared^[52] and reacted with aldehyde **4 d** in the presence of **1₆**. The imine product **5 cd** resulting from this reaction was found to be unlabeled, lacking the ¹³C atom (Figure 2, see SI chapter 6.4). A similar experiment with the ¹³C-labelled derivative **3 c*** with aldehyde **4 f** led to the formation of the unlabeled imine **5 cf** (see SI chapter 6.4). These results indicated that the

Table 3. Synthesis of aromatic imines **5** by reaction of **3 b-g** with a series of electron-poor benzaldehydes **4 a-g** mediated by **1₆**.


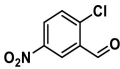
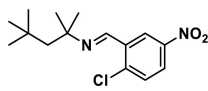

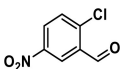
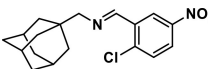
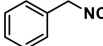
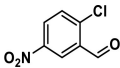
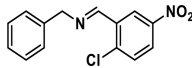

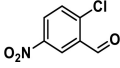
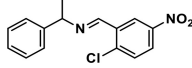
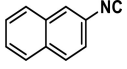
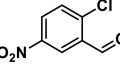
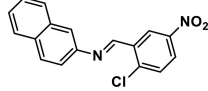

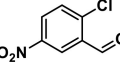
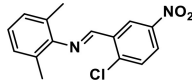

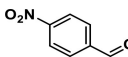
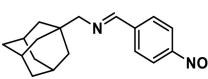

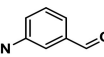
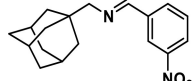

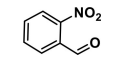
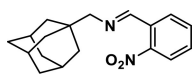

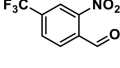
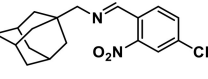

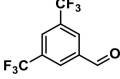
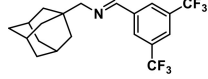


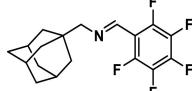
#	Isocyanide	Aldehyde	Product	Yield (%) ^a
1	3 b 	4 d 	5 bd 	94 0 ^b 28 ^c
2	3 c 	4 d 	5 cd 	96 0 ^b
3	3 d 	4 d 	5 dd 	86 0 ^b 19 ^c
4	3 e 	4 d 	5 ed 	90 0 ^b 9 ^c
5	3 f 	4 d 	5 fd 	36 0 ^b
6	3 g 	4 d 	5 gd 	13 0 ^b 1 ^c
7	3 c 	4 a 	5 ca 	91 0 ^b
8	3 c 	4 b 	5 cb 	90 0 ^b
9	3 c 	4 c 	5 cc 	66 0 ^b
10	3 c 	4 e 	5 ce 	83 0 ^b
11	3 c 	4 f 	5 cf 	62 0 ^b

Table 3. continued				
#	Isocyanide	Aldehyde	Product	Yield (%) ^a
12				90 0 ^b
	3 c	4 g	5 cg	

[4 a–g] = 90 mM, [3 b–g] = 180 mM, [1] = 54 mM, 0.6 mL water-saturated CDCl₃, 60 °C, 24 h. a) Determined by ¹H NMR. b) no 1 added; c) [2] = 90 mM (10 eq. with respect to the capsule).

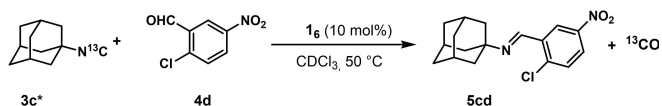


Figure 2. Reaction of ¹³C-labelled isocyanide **3c*** with aldehyde **4d** leading to unlabeled imine **5cd** and carbon monoxide (not monitored in this reaction).

N–C isocyanide bond is cleaved in the process and the respective carbon is potentially released as carbon monoxide. Indeed, carbon monoxide can be detected in the headspace of the reaction mixture (see SI chapter 6.5).

Besides simple hydrolysis, there is very little precedent in the literature covering the cleavage of the N–C bond of isocyanides, with a notable example being the BF₃-mediated reactions of isocyanides and ketones, to produce amide **8** and respective amine **9** that is formed by cleavage of the N–C isocyanide bond of (Figure 3).^[53–55] Under milder conditions, the 2,3-bis(imino)oxetane **10** can be trapped.

Neither amide **8** nor oxetane **10** derivatives were detectable as reaction products in our experiments, further increasing our interest in this puzzling reactivity. We decided to investigate the kinetics of the reaction between isocyanide **3a** and aldehyde **4a** under the experimental conditions described in Table 1. Monitoring the reaction progress is challenging since the isocyanide cannot be observed via NMR due to signal overlaps or GC due to decomposition. The aldehyde concentration is also not a reliable indicator of reaction progress due to its formation during hydrolysis of the imine product. Therefore, the imine formation was monitored. However, the imine product suffers from

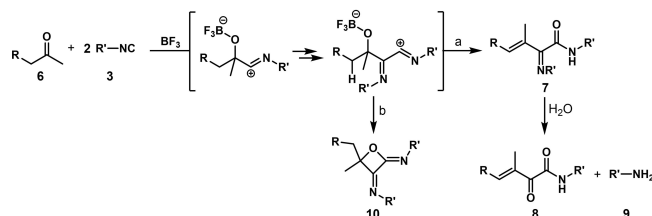


Figure 3. Proposed mechanism for the BF₃-mediated reaction of carbonyl compound **6** with isocyanide **3** by Zeeh *et al.*^[54] (a) at 0 °C and higher concentration of BF₃, hydrolysis releases amide **8** and respective amine **9**; b) Kabbe and Saegusa *et al.* were able to isolate 2,3-bis(imino)oxetanes **10** under milder conditions (–78 °C, lower concentration of BF₃).^[55]

hydrolysis (see discussion above), complicating the kinetic analysis. Nevertheless, the experiments revealed a positive order for all components (aldehyde, isocyanide, and capsule, see SI chapter 6.6). Based on this data, we initially hypothesized a potential formal [2 + 2] cycloaddition/cycloreversion metathesis-like mechanism (red energy profile, Figure 4). According to calculations (see SI chapter 6.9), oxazetidine **11** formation would be formed in a concerted fashion with an extremely high activation barrier of 66.0 kcal/mol. The four-membered intermediate **11** then undergoes a metathesis-like decomposition to imine **5aa** and carbon monoxide with an activation barrier of 27.9 kcal/mol, indicating that the formation of **11** would be rate-determining in this pathway.

However, even assuming a potentially substantial acceleration inside the capsule environment, due to the extremely high gas-phase activation barrier, this pathway seemed not very likely to us. Subsequently, molecular dynamics simulations (see SI chapter 6.9) were performed. These calculations revealed an alternative mechanistic pathway with substantially reduced gas-phase energy barriers (blue energy profile, Figure 4).

The blue pathway proceeds *via* the formation of iminoxirane **12**, which isomerizes to aziridinone **13**. A differently substituted iminoxirane, generated from a carbene and an isocyanate, was shown to isomerize very quickly (10⁴ s^{–1}) to its aziridinone.^[56] The aziridinone **13** then fragments to produce imine **5aa** and carbon

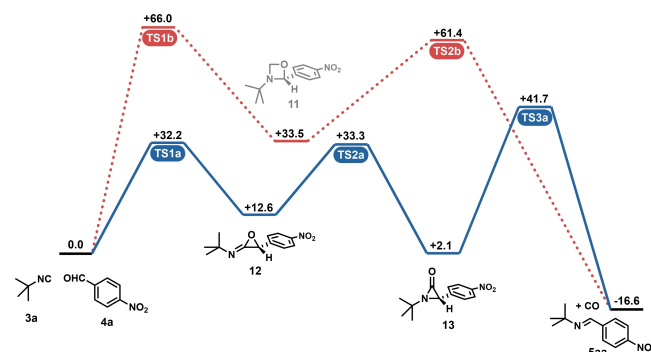


Figure 4. Gas-phase energy profiles for the proposed mechanisms *via* formation of oxazetidine **11** (red pathway) or iminoxirane **12** and aziridinone **13** (blue pathway), relative energies given in kcal/mol, calculated for T = 323 K.

monoxide with a relatively high gas-phase activation barrier of 39.6 kcal/mol.

The chemistry of aziridinones has been studied,^[57] and it was reported that this class of compounds reacts upon heating at 75 °C to deliver a mixture of unsaturated amides, isocyanide, and ketone (see Figure 5). The formation of the latter products was believed to occur via the iminoxirane as an intermediate. The iminoxirane intermediate, suspected to be the missing link in this process, was detected spectroscopically in a later study, lending further credibility to this pathway for the reaction.^[53] For the red pathway (Figure 4), no precedent in the literature was found. The lower gas-phase activation barriers for the blue pathway (32.2 vs. 66.0 kcal/mol for the initial step) and the literature precedence for the formation of aziridinones and iminoxiranes indicated that the reaction is more likely to proceed through this mechanism. To test this hypothesis, we independently synthesized the intermediate aziridinone **13** (see SI chapter 4). Its structure was unambiguously confirmed by X-ray crystallography (see SI chapter 6.10). It was then subjected to standard reaction conditions in the absence and presence of hexamer **1₆**. After 18 h in the presence of hexamer **1₆**, the formation of imine **5aa** (16%) and its hydrolysis product aldehyde **4a** (24% yield) was observed. In the absence of **1₆**, however, the reaction of **13** gave exclusively imine **5aa** in 92% yield. The lower yield and selectivity in the presence of **1₆** may be explained by its Brønsted acidity, which would facilitate the hydrolysis of imine **5aa** upon formation. No further possible decomposition products, *e.g.* amide **15** (Figure 5), were found in these control reactions, indicating that the mechanistic proposal *via* the formation of an intermediate aziridinone and subsequent decomposition to an imine is plausible. We tried to detect the intermediate aziridinone **13** under the reaction conditions by ¹H NMR spectroscopy, however, it was not detectable, likely due to its low concentration.

The relatively high activation barrier for the release of carbon monoxide from intermediate **13** in the blue pathway (39.6 kcal/mol) was calculated in the gas phase and therefore does not take into consideration any stabilizing interactions there may be between the hexameric capsule and the intermediate in the transition state. We therefore propose the following catalytic cycle for the reaction (Figure 6).

Capsule **1₆** binds isocyanide **3a**, leading to the formation of host-guest complex **1₆ ⊃ 3a**. Upon encapsulation of aldehyde **4a** with a much lower affinity to **1₆** than isocyanide **3a** (see SI Chapter 6.3), both components reversibly react to form iminoxirane

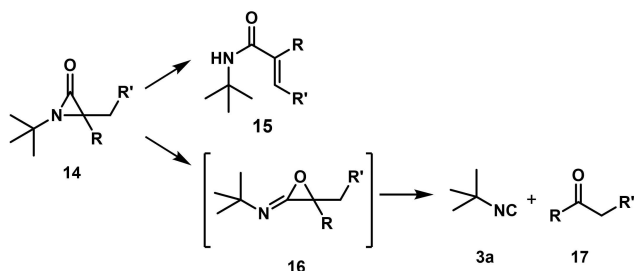


Figure 5. Thermal decomposition pathways for a general aziridinone **14** *via* elimination to unsaturated amide **15** and *via* rearrangement to iminoxirane **16** and subsequent fragmentation to isocyanide **3a** and ketone **17**.

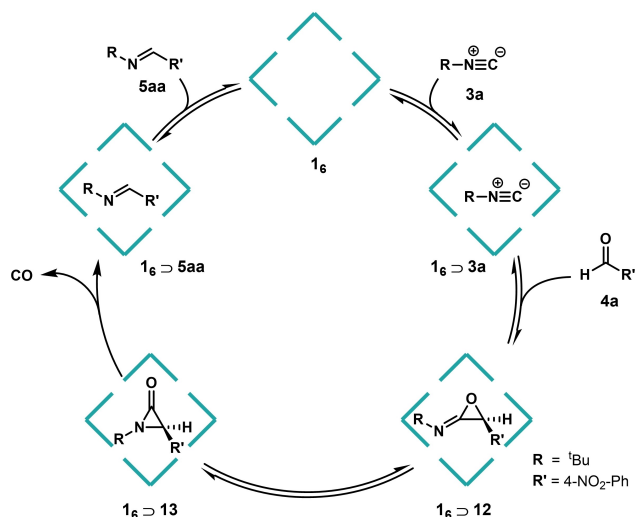


Figure 6. Proposed catalytic cycle for the formation of imine **5aa** from isocyanide **3a** and electron-poor benzaldehyde **4a**, catalyzed by capsule **1₆**.

ane **12**. Isomerization leads to aziridinone **13**, which then decomposes to imine **5aa** and carbon monoxide. The formation of aziridinones **13** from an aldehyde and an isocyanide is unprecedented to the best of our knowledge and was not observed in any control experiment. The decomposition of **13**, however, was also observed in the control experiment without capsule, strongly indicating that the capsule plays only an important role in the first part of the mechanism. Since we observed that the capsule showed a much higher affinity for the isocyanide substrates compared to the electron poor aromatic aldehydes (see SI chapter 6.3), it was not possible to attribute the acceleration of the reaction to an increased local concentration due to co-encapsulation of the reagents.^[9] The role of the capsule could therefore be related to the stabilization of the intermediates of the reaction of the blue pathway in Figure 4, probably by hydrogen bonding with the inwardly oriented OH from the water molecules present in the hydrogen bond seam of the capsule.^[29,30]

Conclusions

In conclusion, we described an unprecedented reaction catalyzed by the hexameric capsule **1₆**, which produces imines from isocyanides and electron-poor benzaldehydes under liberation of carbon monoxide. Interestingly, also the formation of the likely aziridinones intermediate from isocyanides and aldehydes has not been reported before. Inhibition experiments with high-affinity ammonium guests indicate the reaction is catalyzed on the interior of the capsule. Two possible reaction mechanisms were assessed, progressing either through a four-membered, or two three-membered intermediates. Energy calculations indicated the latter pathway, involving the formation of an iminoxirane and an aziridinone intermediate, to be more viable. Synthesis of an aziridinone intermediate and its reaction in the presence of hexamer **1₆** under standard reaction conditions leading to the

imine and carbon monoxide further support this mechanistic proposal.

Experimental Section

Material and Methods: Reactions were carried out under an atmosphere of argon unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ glass-baked plates, which were analyzed under UV light ($\lambda = 254$ nm) or after exposure to standard staining reagents (basic KMnO₄ or CAM: cerium ammonium molybdate). All NMR experiments were performed on a Bruker Avance Neo spectrometer operating at 500 MHz or Bruker Avance operating at 400 MHz. The instrument was equipped with a direct observe 5-mm BBFO FB probe with a self-shielded z-gradient. The experiments were performed at 323 K and the temperature was calibrated using a water standard showing accuracy within ± 0.2 K. Chemical shifts of ¹H NMR and ¹³C NMR are given in ppm. The proton signal of the deuterated solvent was used as reference: CDCl₃ ¹H (δ) = 7.26 ppm, ¹³C(δ) = 77.16 ppm; acetone ¹H (δ) = 2.05 ppm. Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), d (doublet), dd (doublet of doublets), m (multiplet). GC analyses were conducted on a Shimadzu GC-2010 Plus instrument equipped with a FID detector and a Rtx-5 capillary column (length = 30.0 m). Hydrogen was used as carrier gas and constant-pressure mode (pressure = 106.9 kPa) with a split ratio of 1:20 was employed. The following temperature-program was used: 60 °C for 1 min, 15 °C min⁻¹ to 250 °C, and 250 °C for 5 min. GC-MS analyses were performed on a GC Trace GC 2000 equipped with a HP5-MS column (30 m, I.D. 0.25 mm, film 0.25 μ m) using He gas carrier and coupled with a quadrupole MS Thermo Finnigan Trace MS with Full Scan method.

Sources of chemicals: All solvents and reagents used for synthesis were purchased from Sigma-Aldrich and Acros Organics with the highest commercially available purity and employed without further treatment. All isocyanides and aldehydes were purchased from Sigma-Aldrich and Alfa Aesar. CDCl₃ (99.8%, stabilized with silver foil) and acetone-d₆ were purchased from Cambridge Isotope Laboratories. All imine products were identified by ¹H NMR spectroscopy and GC-MS chromatography.

General: Transfer of liquids with a volume ranging from 1 to 10 μ L or from 10 to 100 μ L was performed with a Microman M1 pipette (Gilson, systematic error: 1.40–1.60%) equipped with 10 or 100 μ L pipette tips respectively. The weighing of substrates, catalyst, internal standard, and products was performed using a AB135-S/Fact Mettler Toledo Classic Plus balance.

General procedure (NMR analysis): Reactions in presence of capsule **1₆** were conducted using stock solutions of **1** in CDCl₃. Prior to usage, CDCl₃ was filtered over a basic Al₂O₃ plug (5–6 mL over 2–3 g Al₂O₃) to remove trace amounts of HCl/DCl, potentially generated by photo-degradation of CDCl₃. The stock solution for **1** was prepared by weighing in monomer (440 mg, 0.40 mmol) in a 1 mL volumetric flask, which was then filled to less than full capacity with filtered CDCl₃ and homogenized in an ultrasonic water bath. In case of incomplete dissolution, the flask was heated to approx. 40 °C with a heat gun under agitation. After complete dissolution, the flask was then filled to the calibration mark with filtered CDCl₃ and again agitated to give a clear dark orange solution.

The stock solutions for isocyanides and aldehydes were prepared by weighing the respective starting materials into a GC vial and filling up with calculated amounts of filtered CDCl₃ to reach a final concentration of 1.33 M (isocyanide) and 0.67 M (aldehyde). The small contribution of the starting materials to the total volume of the stock solution was neglected. Isocyanides (100 μ L, 1.33 mol/L, 133 μ mol)

and aldehydes (100 μ L, 0.67 mol/L, 66.7 μ mol) were added as stock solutions in filtered CDCl₃. In all cases the amount of added CDCl₃ was adjusted to maintain an overall volume of 500 μ L.

Stock solutions of isocyanide **3** (100 μ L, 133 μ mol, 20 eq.), aldehyde **4** (100 μ L, 66.7 μ mol, 10 eq.), **1** stock solution (100 μ L, 40 μ mol, 6.0 eq.), and 200 μ L of filtered CDCl₃ were added to a GC vial (1 mL size). Immediately upon mixing a small aliquot (20 μ L) was taken from the reaction mixture and diluted with 0.5 mL of acetone-d₆ and subjected to ¹H NMR spectroscopy. The GC vial was then kept at 50 °C (± 1 °C) using a thermostatted aluminum heating block. The progress of the reaction was monitored via ¹H NMR. For this purpose, the GC vials containing the reaction mixture were removed from the heating block and upon cooling to r.t. a small aliquot (20 μ L) was taken, diluted with 0.5 mL of acetone-d₆ and subjected to NMR spectroscopy. The influence of the temperature drop during removal of aliquots was neglected. Further measurements were taken in the same fashion.

General procedure (GC analysis): Stock solutions of internal standard *n*-decane (100 μ L, 26.7 μ mol, 4.0 eq.), isocyanide (100 μ L, 133 μ mol, 20 eq.), aldehyde (100 μ L, 66.7 μ mol, 10 eq.), *C*-undecylcalixresorcin[4]arene (100 μ L, 40 μ mol, 6 eq.), and 100 μ L of filtered CDCl₃ were added to a GC vial (1 mL) and a small aliquot (10–15 μ L) was taken from the reaction mixture, diluted with heptane (900 μ L, contains 0.08% vol. DMSO) and cooled to –20 °C for 20 minutes. Upon cooling and centrifugation, the catalyst precipitated and was removed. The samples were then subjected to GC analysis. This process was repeated for further measuring points. In order to precisely calculate the conversion and yield, response factors to *n*-decane as internal standard (IS) were determined for the investigated substrates and their corresponding products. Stock solutions of *n*-decane, substrates and products were prepared as described in Table S3, utilizing filtered CDCl₃ as solvent. 40 μ L aliquots of *n*-decane stock solution (242 mmol/L) were added to 16 μ L, 32 μ L or 64 μ L aliquots of analyte (302 mmol/L) for 4-nitrobenzaldehyde (**4a**). For imine **5aa**, 40 μ L aliquots of *n*-decane stock solution were added to 8 μ L, 16 μ L, and 32 μ L aliquots of analyte (301 mmol/L). After dilution with CDCl₃ to a total volume of 500 μ L, analyte to *n*-decane ratios of 0.5, 1, 2 were obtained for **4a** and 0.25, 0.5, 1 were obtained for **5aa**.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Isocyanide · Resorcinarene capsule · Supramolecular catalysis · Enzyme-mimicking systems · Host–guest systems

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