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The Hexameric Resorcinarene Capsule as a Hydrogen Bonding Catalyst in the Conjugate Addition of Pyrroles and Indoles to Nitroalkenes

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The hexameric resorcinarene capsule acts as a hydrogen bonding catalyst for the activation of encapsulated nitroalkenes toward the addition of pyrroles and indoles. Once inside the capsule **C**, β-nitrostyrene **3a** establishes H-bonding interactions with the bridged water molecules having an H-bond-donating free valence. Thus, the activation of nitroalkene favors the conjugate addition of pyrroles and indoles. It is demonstrated that the inherent acidity of the capsule **C** is sufficient to promote the Michael-type Friedel Crafts (MTFC) reaction under the mild reaction conditions here described. *In silico* calculations point out the catalytically relevant role of the bridged water molecules of **C** and confirm the supramolecular control exerted by the capsule, which protects the nitronic acid intermediate with respect to the degradation pathway commonly occurring in the bulk medium.

Introduction

Starting from the basic principles of *Supramolecular Chemistry* and thanks to the imagination of chemists, amazing supramolecular architectures able to mimic the *modus operandi* of natural enzymes have been designed.[1] Among them, the self-assembled capsules have attracted growing attention mainly due to their ease of preparation.[2] In fact, they spontaneously assemble in solution starting from smaller subunits and thus require less synthetic efforts with respect to the classical molecular catalysts. The self-assembled capsules can offer the basic working features of natural enzymes, such as: (i) the presence of a cavity able to confine the reactants; (ii) a substrates and products selectivity; (iii) the stabilization of either the transition states and/or the intermediates of the reaction.[2]

Among the self-assembled systems, the resorcin[4]arene-based hexameric capsule **C** represents one of the most investigated in supramolecular catalysis.[3] Atwood,[3a] for the first time showed that, in the solid state, six resorcinarene **1** molecules and 8 water molecules form a cubic-shaped capsule sealed by 60 (O-H···O) H-bonds (Figure 1a).

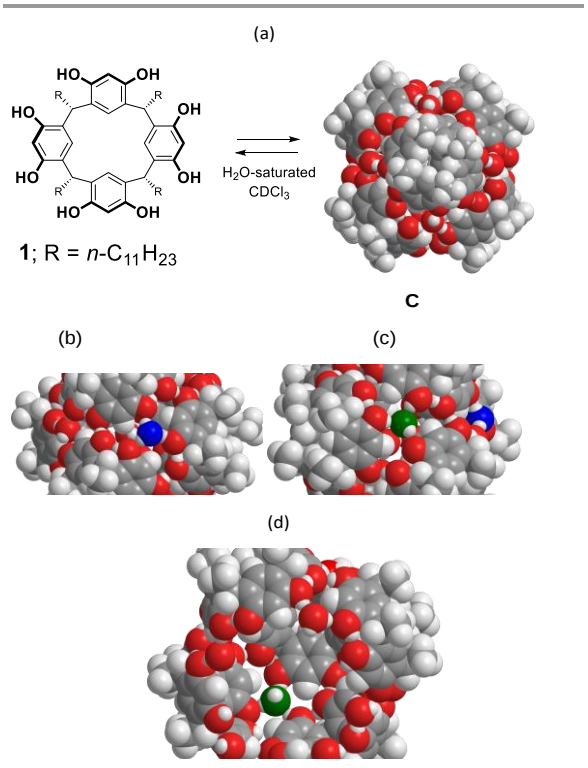

Figure 1. (a) Self-assembly of *C*-undecylresorcin[4]arene **1** into hexameric resorcinarene capsule **C** (in CPK model) in a water-saturated $CDCl_3$ solution. Undecyl chains are removed for clarity. (b) Detailed view (external) of **C** in which one bridging-water molecule (in blue) saturates its H-bond-donating valences. Detailed views, external (c) and internal (d), of another bridging-water molecule (in green) with one H-bond-donating free valence

The X-ray structure of **C** clearly highlights the presence of an H-bond network involving the eight bridged water molecules and

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the six resorcinarene molecules. The bridged-water molecules are located at the corners of a cube (Figure 1b–d) and are involved in three H-bonds each one (Figure 1b–d). Four of these bridging-water molecules complete their H-bond-donating valences with the adjacent resorcinol OH groups (Figure 1b, in blue), while the other four ones can only donate one H-bond[2m] (Figure 1c,d in green) thus leaving one free H-bond-donating valence. Successively, Cohen[3b] and coworkers showed that the hexameric resorcin[4]arene capsule **C** self-assembles also in solution.

To date, many reports in the literature have highlighted the potentialities of the hexameric capsule as a supramolecular catalyst[2] for organic reactions. The capsule **C** is easily formed in wet apolar solvents such as chloroform and benzene and shows[3b] an internal volume of 1375 Å^3 that can host about 6-8 molecules of chloroform or benzene. An examination of the literature data evidence that capsule **C** can work both as a nano-reactor and as a catalyst.[2e,m] In the first nano-reactor case, both catalyst and substrates are recognized and confined inside the nano-container **C**,[2e,m] and an increase of the reaction rate is observed thanks to an overconcentration effect, a substrate preorganization, and a stabilization of intermediates and/or transition states.[2m] In the second case, the capsule **C** can act itself as a catalyst by exploiting its ability to stabilize cationic intermediates and transition states by cation-π interactions, and its mild phenol-based Brønsted acidity with a pK_a value of about 5.5–6.0 (measured in water-saturated $CDCl_3$ relative to the reported aniline pK_a value in water).[4] Very recently, [5] we have shown that the hexameric capsule **C** can promote a Friedel-Crafts benzylation of arenes and heteroarenes through hydrogen-bond catalysis involving the *free H-bond donating valence* of water-bridged molecules (Figures 1c,d, in green).[5] In particular, QM calculations and experimental evidences suggest that an H-bonding interaction polarizes the C–Cl bond of benzyl chloride "C–*Cl*···*H*–OH" with the capsular bridging water molecules that act as H-bond-donating groups (Figures 1c,d, in green).

On the basis of these results[5] we decided to explore other possibilities of H-bonding catalysis in which the hexameric capsule **C** could act as an H-bond catalyst in the activation of confined substrates.

At this regards, the addition of indoles and pyrroles to electron-deficient alkenes may be considered as a Michael-type Friedel-Crafts (MTFC) reaction,[6] and represents one of the most powerful methods to introduce different substituents on these heterocyclic rings. The interest for such compounds is justified by their occurrence as structural motifs in many natural and biologically active products,[7] and their derivatives are widely used as versatile synthetic intermediates for the synthesis of more complex molecules and functional organic materials. [8] Among the electron-poor acceptors, nitroolefins are very attractive electrophilic partners because of the presence of the nitro group which implies a high electrophilicity, due to its strong electron-withdrawing character, and a possible subsequent transformation in different functionalities.[9,10] Numerous procedures have been reported for the Michael addition of pyrroles and indoles to β-nitroolefins in the presence of different catalytic systems, paying attention to the relative instability of the pyrrole nucleus toward acids.[11] However, the questions of regioselectivity, mono- *vs.* polyalkylation, and generality of the procedures for both heterocycles are still significant synthetic challenges which have not yet been adequately addressed. At this regard, one of the most common approaches is the activation of nitro-olefins towards the conjugate addition of heteroaromatics by H-bond organocatalysis or Brønsted acid catalysis.[12]

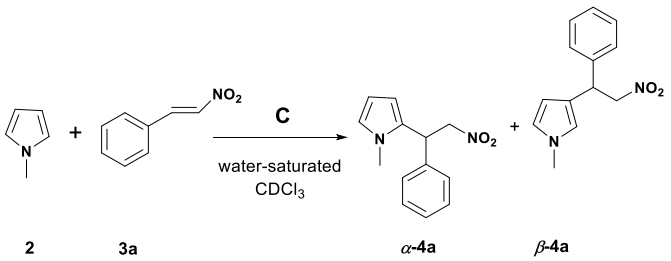
Prompted by our recent results on the catalytic role of the capsule as an H-bond-donor supramolecular organocatalyst,[5] we envisioned that the capsule **C** could catalyze the conjugate addition of heterocyclic aromatic rings to nitroolefins through the H-bond activation of nitrostyrene. Besides, we were intrigued about the possible selectivity (α- *vs.* β-regioselectivity and mono- *vs*. polyalkylation) of the MTFC reaction inside **C**.

Results and Discussion

We started our exploration by keeping in consideration the reaction between N-methylpyrrole 2 and β-nitrostyrene 3a (Scheme 1).

When the reaction was carried out in the presence of 26 mol % of capsule **C** in water-saturated $CDCl_3$ at 30 °C, the adducts **4a** were obtained in 77% overall yield after 4 h (entry 1, Table 1), while no hint of polyalkylated products was detected in the reaction mixture. Under these conditions, the regioisomer α-**4a** was preferentially formed over β-**4a** with an α/β ratio of 86/14 (entry 1, Table 1). In contrast, a control experiment in the absence of capsule **C**, under otherwise identical conditions, did not show any conversion of substrates **2** and **3a** to **4a**, even after prolonged reaction time (entry 2, Table 1). Therefore, these preliminary results supported our assumption that the capsule **C** is able to promote the MTFC reaction between **2** and β-nitrostyrene **3a** and provided the first evidence that the reaction occurred within its cavity.

With these results in hand, a series of experiments were performed in order to investigate the effects of the reaction conditions on the efficiency of the reaction.



Scheme 1. Michael-Type Friedel-Crafts (MTFC) alkylation between *N*-methylpyrrole **2** and β-nitrostyrene **3a**.

Table 1. Optimization of the reaction conditions for the conjugate addition of **2** to **3a**[a]

Entry	solvent	**2:3a**	Capsule (mol%)	T (°C)	t (h)	Yield (%)[b]	α-**4a**/β-**4a**[c]
1	$CDCl_3$	4:1	26	30	4	77	86/14
2[d]	$CDCl_3$	4:1	-	30	16	NR	-
3	$CDCl_3$	4:1	26	50	2	94	80/20
4	$CDCl_3$	4:1	-	50	16	-	-
5	$CHCl_3$	4:1	26	50	2	99	83/17
6	$CHCl_3$	1:1	26	50	2	81[e]	65/35
7	$CHCl_3$	1:4	26	50	2	97[f]	-

[a] 0.16 mmol of **3a**, 1.1 mL of solvent. [b] Yields of the isolated products by chromatography on column. [c] Determined by ^{1}H NMR analysis. See the Supporting Information. [d] Only starting materials were recovered. [e] 9% of disubstituted product was obtained. [f] The reaction gave an inseparable mixture of diastereomers of the disubstituted pyrrole as exclusive products. NR: no reaction.

When the reaction was performed at 50 °C (Table 1, entry 3), then the products **4a** were obtained in 94% yield after 2 h (instead of 77% after 4 h at 30 °C, entry 1), while the regioselectivity was almost unchanged (Table 1, entry 3). In the presence of non-deuterated $CHCl_3$ as solvent, the catalytic efficiency of **C** remains unchanged with respect to $CDCl_3$ (Table 1, entry 5). Interestingly, when the reaction was performed in the presence of **2** and **3a** in 1:1 ratio, then a marked decrease of the regioselectivity α-**4a**/β-**4a** ratio (65/35) was observed, together with the appearance of disubstituted products (Table 1, entry 6). Furthermore, in the presence of a large excess of nitrostyrene **3a** the reaction led to the exclusive formation of disubstituted products (entry 7, Table 1).

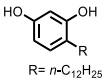
At this point, a series of control experiments were performed in order to clarify the role of capsule **C** in the MTFC catalysis (Table 2). When the reaction between **2** and **3a** in the presence of capsule **C**, was performed in the presence of hexamethonium iodide (HMI), [13] a competitive guest which shows high affinity for the capsule,[13] then no conversion of the reactants to **4a** was observed. This confirmed that the reaction takes place inside the capsule **C**.

As it is known, DMSO is a solvent able to break the hydrogen-bond network of the capsule causing its dissociation. Significantly, when the reaction in Scheme 1 was performed in the presence of 10 equiv. of DMSO then no hint of **4a** was detected in the reaction mixture (Table 2, entry 5). This provided a further evidence on the role played by the entire hexameric capsule in the catalysis of the MTFC in Scheme 1.

The capsule effect is further confirmed by performing the reaction in the absence of the capsule **C** and in the presence of a prototypical monomeric unit of **C**. Thus, in the presence of 4-dodecyl-resorcinol the MTFC reaction between **2** and **3a** in water-saturated $CHCl_3$ led to the formation of traces of **4a** (Table 2, entry 6).

As it is known, the hexameric capsule **C** behaves as a mild Brønsted acid with a pK_a value of about 5.5–6.0.[4] These values have been calculated by evaluating the acid-base equilibria of amines of decreasing basicity with the capsule **C**.[4] The pK_a of

Table 2. MTFC reaction between **2** and **3a**[a] under different reaction conditions. Control experiments.

Entry	Capsule (mol%)	Additive (equiv.)[b]	Yield (%)[c]	α-**4a**/β-**4a**[c]
1[e]	26	HMI (18)[f]	NR	—
2	—	AcOH (1)	NR	—
3	—	$BrCH_2COOH$ (1)	17	59/41
4	—	TFA (1)	34	78/22
5[d,e]	26	DMSO (10)[f]	NR	—
6	—	 R= n-$C_{12}H_{25}$ (**24**)	trace	—

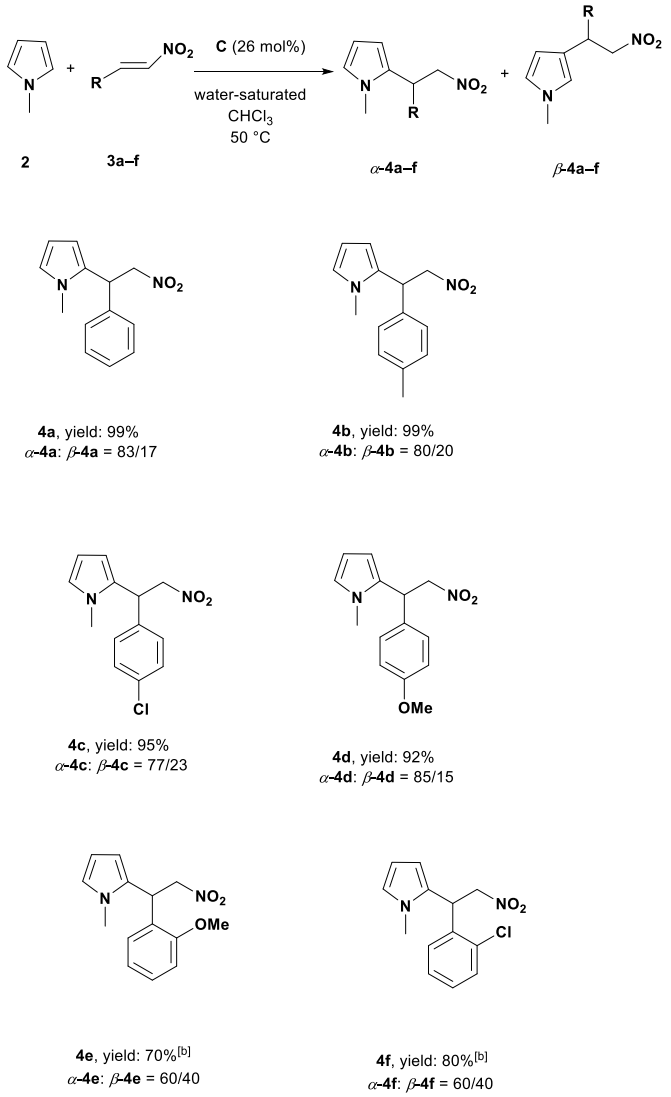
[a] Reaction conditions: **2** (0.59 M), **3** (0.15 M), **C** (0.039 M) in 1.1 mL of water-saturated $CHCl_3$ at 50 °C for 2h. [b] Amount of additive respect to β-nitrostyrene **3a**. [c] Yields of the isolated products by chromatography on column . [d]Determined by ^{1}H NMR analysis. See the Supporting Information. [e] Reaction time = 16 h. [f] Amount of additive respect to the capsule.

the four bridged-water molecules with one free H-bond-donating valence (green in Figures 1c,d) has been recently calculated by our group at the PM6 semi-empirical level of theory, and a value of ≈2.5 has been found.[5] In addition, a mean pK_a value of 6.1 was calculated, at the same level, for all the OH groups of **C**,[5] in excellent agreement with the experimental value.[4]

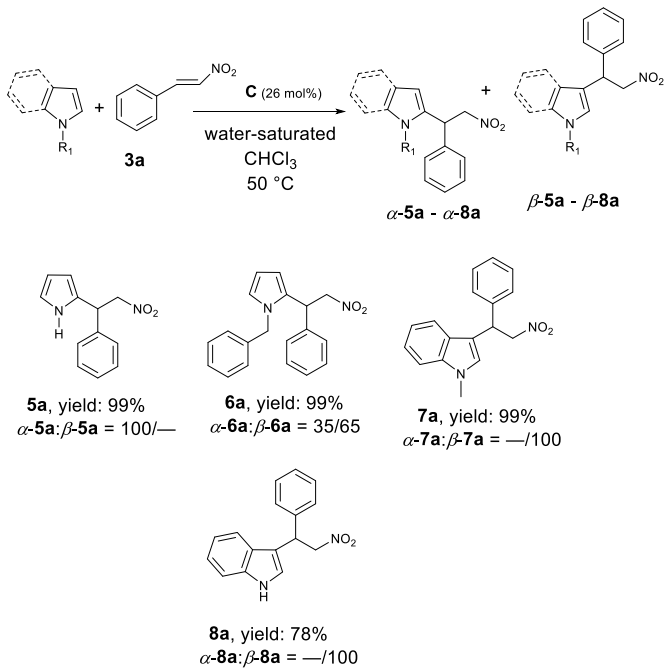
As it is known, a common route for the activation of nitro-olefins towards the conjugate addition of heteroaromatic compounds is the Brønsted acid catalysis.[12e–g] By this consideration, we wondered if the catalytic activity of **C** towards the MTFC reaction in Scheme 1, is due to its inherent acidity. When the reactants **2** and **3a** were mixed in the presence of acetic acid (pK_a = 4.76) and in the absence of **C** in water-saturated $CHCl_3$ at 50 °C (Table 2, entry 2), then no hint of products **4a** was detected. Interestingly, when α-bromoacetic acid (pK_a = 2.86) was used (Table 2, entry 3), in the absence of **C**, then the products **4a** were obtained in 17% yield with a α/β ratio of 59/41. Finally, using the stronger trifluoroacetic acid (TFA, Table 2, entry 4), then the reaction in Scheme 1 was promoted in a non-selective fashion, in the absence of **C**, leading to the formation of **4a** in 34% yield, together with a complex mixture of by-products (Table 2, entry 4). Clearly, these results show that, under the mild conditions reported in the present work, the Brønsted acidity is not sufficient to promote the MTFC reaction in Scheme 1, and that the capsule effect plays a crucial role.

With the optimized reaction conditions in hand, we next focused our attention on the substrate scope to determine the generality of this reaction. As illustrated in Scheme 2, we initially evaluated the Michael acceptor. Under the standard reaction conditions adopted in Table 1, the substrates bearing various substituents on the phenyl ring proved to be all compatible with the method, affording the corresponding products in good or high yields.

Thus, while the nature of the *para*-substituent on the β-nitrostyrene did not affect the reaction efficiency, the α-



Scheme 2. Scope study for the conjugate addition of pyrrole **2** to various nitroolefins **3a–f** [a] . [a] Reaction conditions: **2** (0.59 M), **3** (0.15 M), **C** (0.039 M), $CHCl_3$ (1.1 mL), reaction time 2 h unless otherwise specified. Yields of the isolated products by chromatography on column. [b] Reaction time: 16 h.



Scheme 3. Scope study for the conjugate addition of different heterocyclic rings to **3a** [a] : [a] Reaction conditions: indoles or pyrroles (0.59 M), **3** (0.15 M), **C** (0.039 M), $CHCl_3$ (1.1 mL), reaction time 2 h. Yields of the isolated products by chromatography on column.

regioselectivity was generally favored (Scheme 2). However, when the *ortho*-substituted *β*-nitrostyrenes **3e** and **3f** were used as starting material, then the MTFC reaction with **2** required 16 h for completion, rather than 2 h as in all the other cases reported in Scheme 2. Also, a higher amount of the *β*-regioisomer was obtained when the *ortho*-substituted *β*-nitrostyrene **3e** or **3f** was used (*α*-**4e**/*β*-**4e** and *α*-**4f**/*β*-**4f** ratios: 60/40, Scheme 2). Probably, this result could be attributed to the steric interaction between the substituent in the *ortho*-position of **3e** and **3f** with the methyl group on the nitrogen atom of pyrrole ring.

We successively examined the behavior of the reaction with different heterocyclic rings (Scheme 3). Initially, we investigated the effect of the substitution on the nitrogen atom of pyrrole. The reaction between the unsubstituted NH-bearing pyrrole and **3a** gave the products **5a** in high yield with a complete *α*-regioselectivity.

When the pyrrole ring bears the sterically more hindered *N*-benzyl group, the yield of adducts **6a** remained excellent, and the regioselectivity was reversed in favor of the *β*-**6a** isomer.

When the MTFC reaction was performed using indole as the substrate and **3a**, then the corresponding *β*-adduct **8a** was regioselectively obtained in 78% yield. Similarly, *N*-methylindole selectively gave the *β*-**7a** adduct in 99% yield.

It is evident that the *N*-Me-substituted indole showed a higher efficiency with respect to its unsubstituted counterpart. The presence of the methyl group probably not only increases the electron density of the aromatic ring (thus accelerating the reaction) but also prevents unwanted side reactions such as polymerization. Regarding the proofs of the encapsulation of the reagents **2** and **3a** inside the nanoconfined space of **C**, we have previously reported[5] a detailed 2D NMR study which demonstrated the encapsulation of *N*-methylpyrrole **2** inside **C**. The studies on the encapsulation of *β*-nitrostyrene **3a** inside **C** evidenced a low binding affinity, but sufficient for the activation of substrate **3a**. A DOSY experiment of the mixture **3a**/**C** was performed in which the diffusion coefficient of incapsulated **3a** was aligned with those of the capsule, thus probing its internalization in **C.**

Furthermore, the encapsulation of *β*-nitrostyrene **3a** inside **C** was also proved by a 2D-EXSY experiment of the mixture **3a**/**C** in which the internalization of **3a** was evidenced by the presence of exchange cross-peaks between the vinyl protons of **3a**, respectively outside and inside the capsule (Figures S8,9). In order to gain insights into the reaction mechanism that lead to the formation of products **4** inside the hexameric capsule **C**, we performed a quantum chemical investigation of the effect of the capsule on the course of the MTFC reaction. To this purpose we have chosen, as a representative model, the reaction between

2 and **3a**, using a reduced capsule $\mathbf{C_R}$ with shorter feet and the ONIOM method, in accordance with a previously used approach.[5]

Table 3. Relative enthalpies (ΔH) and Gibbs free energies (ΔG) (in kcal/mol) for all reactants, **4** products, and their combinations within the capsule.

Guest@Host complex	ΔH[a]	ΔG[a]
2@$\mathbf{C_R}$	−8.71	1.13
3a@$\mathbf{C_R}$	−13.81	−0.28
[**2**+**3a**]@$\mathbf{C_R}$	−28.94	−4.14
α-I2@$\mathbf{C_R}$	−19.61	−3.48
β-I2@$\mathbf{C_R}$	−22.42	−3.91
α-**4a**@$\mathbf{C_R}$	−15.12	−1.08
β-**4a**@$\mathbf{C_R}$	−15.75	−0.96

[a] Referred to those of the host and the corresponding non-encapsulated guests

Table 4. Relative enthalpies (ΔH), Gibbs free energies(ΔG), and direct ($\Delta G^{\ddagger}$) and inverse (inv-$\Delta G^{\ddagger}$) activation Gibbs free energies (in kcal/mol) of the stationary (S) and transition state (TS) points involved in the MTFC reaction in the absence and in the presence of the capsule.

S or TS point	ΔH[a]	ΔG[a]	$\Delta G^{\ddagger}$	inv-$\Delta G^{\ddagger}$
MC	0.00	0.00	—	—
α-TS1	23.77	38.32	38.32	n.d.[b]
β-TS1	26.31	39.61	39.61	n.d.
MC-TFA	0.00	0.00	—	—
α-TS1-TFA	19.99	23.84	23.84	n.d.
β-TS1-TFA	22.85	25.34	25.34	n.d.
[**2**+**3a**]@$\mathbf{C_R}$	0.00	0.00	—	—
α-TS1@$\mathbf{C_R}$	27.05	29.93	29.93	1.19
α-I1@$\mathbf{C_R}$	24.41	28.74	—	—
α-TS2@$\mathbf{C_R}$	23.89	28.99	0.20	29.30
α-I2@$\mathbf{C_R}$	−3.75	−0.31	—	—
α-**4a**@$\mathbf{C_R}$	−12.08	−10.46	—	—
β-TS1@$\mathbf{C_R}$	26.04	31.10	31.10	0.62
β-I1@$\mathbf{C_R}$	23.58	30.48	—	—
β-TS2@$\mathbf{C_R}$	24.57	30.75	0.27	30.05
β-I2@$\mathbf{C_R}$	−4.46	0.70	—	—
β-**4a**@$\mathbf{C_R}$	−11.33	−9.95	—	—

[a] Referred to **2**+**3a**, **2**+**3a**+TFA, or [**2**+**3a**]@$\mathbf{C_R}$. [b] Not done.

In accordance with the experimental results, calculations clearly indicated that **C** is capable of hosting nitrostyrene **3a** followed by *N*-methylpyrrole **2**. In fact, an enthalpic stabilization of 13.81 kcal/mol was calculated (Table 3) for the encapsulated reagent **3a** principally due to the formation of an H-bonding interaction between one oxygen atom of the nitro group and a bridged water molecule in $\mathbf{C_R}$ (Scheme 4). In addition, a higher negative complexation enthalpy (28.94 kcal/mol, Table 3) was observed for the direct formation of the hetero-binary molecular complex (MC) [**2**+**3a**]@$\mathbf{C_R}$ (Figure 2). The Gibbs free energies for **3a**@$\mathbf{C_R}$ and [**2**+**3a**]@$\mathbf{C_R}$ complexes were −0.28 and −4.14 kcal/mol, respectively, according to an obvious entropic penalization (Table 3). Contrarily to the FC reaction previously reported,[5] in this case we were not able to isolate the [**2**+**3a**]@$\mathbf{C_R}$ complex in which compounds **2** and **3a** result separated by an adequate distance prior the formation of the effective interacting MC.

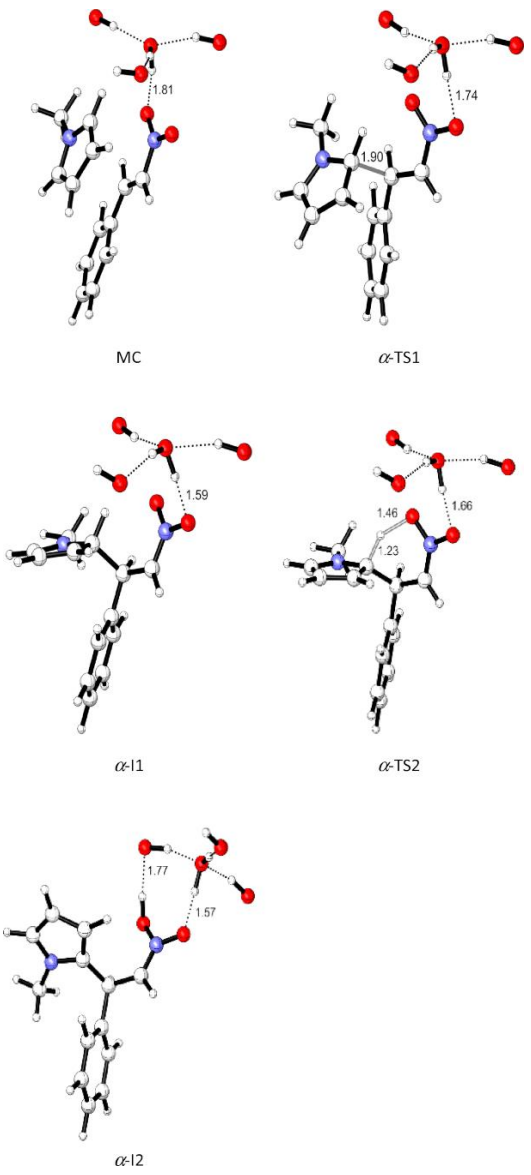
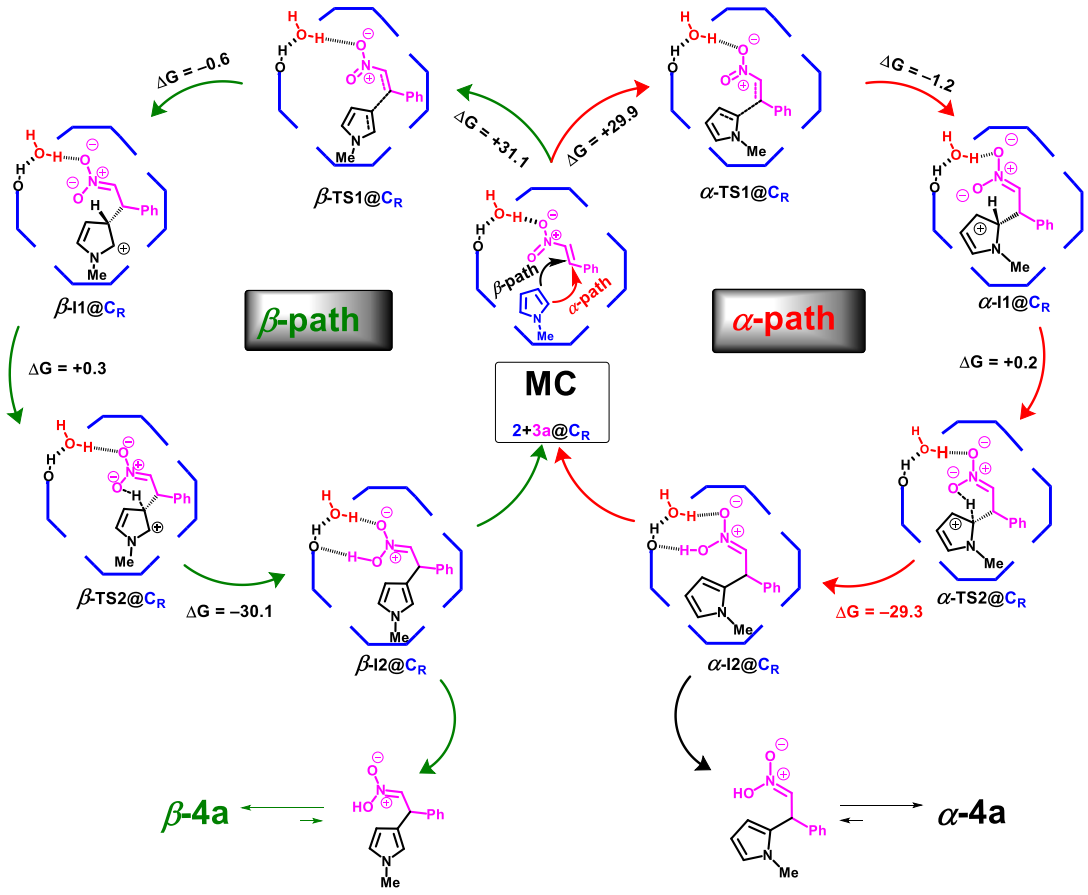


Figure 2. Geometries for all S and TS points associated with the path ongoing to the α-**4a** product for the MTFC reaction. Only the atoms of the ONIOM high layer have been represented; the capsule has been omitted for clarity. Along the path, one oxygen atom of the nitro group present in **3a** is always engaged in a hydrogen bond with a water molecule of $\mathbf{C_R}$. The distances are given in Å. Carried out with CYLview.[15]

The calculation results indicate that the reaction proceeds as depicted in Scheme 4. The energy values and the models of stationary and transition states (TS) point have been reported in Table 4, and Figures 2 and 3. Following the α-path, the MC evolves, through the α-TS1, to the formation of the corresponding Wheland intermediate, α-I1, located 1.2

kcal/mol below α-TS1. Successively, the re-aromatization of the σ-complex α-I1 occurs by transferring the pyrrole α-hydrogen atom to the oxygen atom of the nitro group not H-bonded to water.



Scheme 4. *Alpha* and *beta* channels for the *in silico* studies of the MTFC and nomenclature adopted. The capsule $\mathbf{C_R}$ is always present. For convenience, we adopted the following nomenclature: for the *alpha*-channel, the TSs for the first and the second stepwise mechanism have been named as α-TS1 and α-TS2, respectively, and correspondingly the Is as α-I, and the product as α-**4**; for the beta-channel, in analogy, we have β-TS1–3, β-I1,2, and β-**4**.

This furnishes the intermediate α-I2, located 0.3 kcal/mol below the starting reagents, that correspond to the nitronic acid tautomer of the compound α-**4a**. This rearrangement proceeds very easily thanks to a very low energetic barrier (Figure 3, 0.2 kcal/mol) bringing to a molecular species that is stabilized by two H-bonds. At this point, probably before that α-I2 undergoes the prototropic shift to obtain the most stable nitro tautomer α-**4a**, it is expelled from the capsule to be replaced by **2** and **3a** with the formation of a new MC [**2**+**3a**]@$\mathbf{C_R}$; the Gibbs free energy for this exchange is −0.67 kcal/mol, and this is in accord with the experimental observation that the products do not poison the nanoreactor.

All tentatives to locate a TS for the 1,3-prototropic shift failed probably because the only way to proceed with the tautomerization process should involve the presence of a water molecule inside the capsule.

The route to the formation of the β-**4a** adduct follow the β-path that proceeds in a similar way to the previous one. In this case, the β-TS1 is higher than the corresponding α-TS1 by 1.17 kcal/mol, justifying the preference for the formation of the α-adduct, according to the experimental result (α-**4a**/β-**4a** calculated ratio = 6.18/1, *i.e.*, 86:14).[16]

In summary, the calculations confirm the catalytically relevant role of the capsule and, in particular, they highlight that the capsule exerts a supramolecular control on the reaction stabilizing, all the intermediates and contemporarily activate the whole process, thanks to the formation of H-bonding interactions involving the bridging water molecules with a free H-bond donating valence (green in Figures 1c,d).

An examination of the rate-limiting step for the MTFC reaction between **2** and **3a** in the absence of the hexameric capsule revealed a very high value of the Gibbs free activation energy (α-TS1, $\Delta G^{\ddagger}$ = 38.32 kcal/mol, Table 4) when the reaction takes place without any catalyst. This is in accord with the absence of reaction experimentally observed (Table 1, entries 2 and 4). On the contrary, the presence of TFA (pK_a of 0.23) is sufficient to activate the reaction by lowering the Gibbs free activation energy of α-TS1-TFA by 6.09 kcal/mol with respect to the corresponding α-TS1@$\mathbf{C_R}$ (Table 4). Unfortunately, at the same time, TFA also activates the nitro-aci tautomerism route[14]

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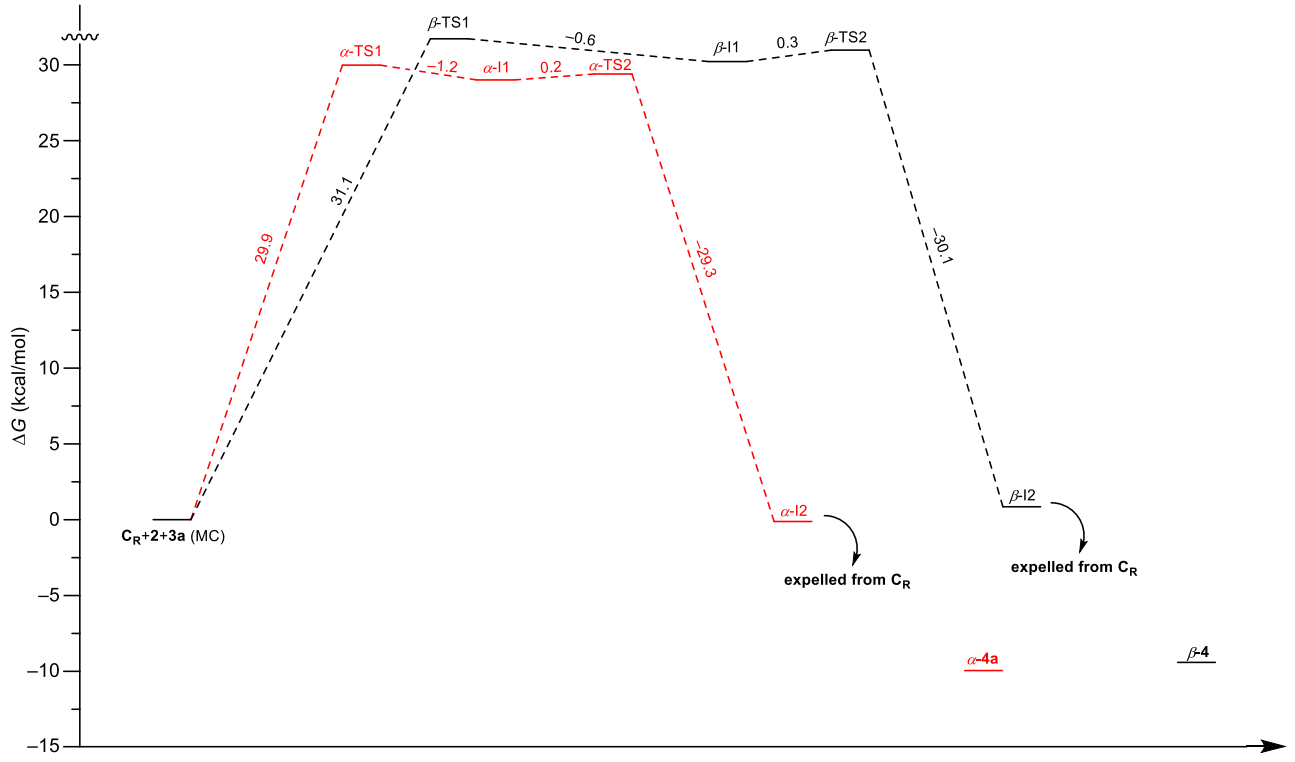

Figure 3. Gibbs free energy profiles for alpha (in red) and beta (in black) paths within $\mathbf{C_R}$; the term @$\mathbf{C_R}$ has been omitted for clarity.

furnishing a discrete quantity of nitronic acid derivative that undergoes degradation to various unidentified products, thus leading to low yield (Table 2, entry 4). The acetic acid acidity (pK_a = 4.76) is not sufficient to activate the MTFC reaction (Table 2, entry 3). Therefore, the presence of the capsule, not only promote the MTFC reaction but also prevents the degradation of the obtained products.

Conclusions

We have herein showed that the hexameric capsule **C** is able to promote the conjugate addition of pyrroles and indoles to nitroalkenes under mild conditions by exploiting the H-bond donor capabilities of the bridging water molecules of **C**. Control experiments provided evidences that the reaction proceeded within the cavity of **C**. The synergistic interplay between the nanoconfined space and the activation of nitrostyrene by H-bonding interactions with the bridging water molecules of the capsule led to a control of the reaction efficiency regarding yield, reaction rate, and selectivity.

Also, *in silico* studies showed that the MTFC reaction proceeds expedite thanks to the intrinsic microenvironmental acidity of the network bridged water molecules that engage an H-bond with the nitro moiety thus activating the MT addition and stabilizing all intermediates. Moreover, the instauration of an additional H-bond favors the formation of nitronic acid intermediates which, after the expulsion from the capsule, tautomerize to the final adducts **4**. Contemporarily, the presence of the capsule and the environment of the reaction protect the final products from tautomerization to nitronic acids thus preventing their subsequent degradation.

Experimental

Preparation of capsule C

Resorcinarene **1** (281.6 mg, 0.25 mmol) was weighed in a vial and water saturated deuterated chloroform (1.1 mL) was added. The mixture was sonicated in an ultrasonic water bath at 40 °C to a clear solution (ca. 10 min).

Typical procedure for the addition of heteroaromatic *N*-containing derivatives to nitroolefins in the presence of C.

To a clear solution of **1** (281.6 mg, 0.25 mmol) in water saturated deuterated chloroform (1.1 mL), the heteroaromatic compound (0.65 mmol) was added and the solution was stirred at the indicated temperature for 10 min. After nitroolefin **3** (0.16 mmol) was added, the reaction mixture was thermostated at the indicated temperature and vigorously stirred for the appropriate time. The reaction progress was followed by ^{1}H-NMR spectroscopy. Then, the reaction mixture was poured into a 50 mL Eppendorf conical tube and diluted with a solution of DMSO in *n*-hexane (0.13% *v*/*v*, 35 mL). Cooling to −20°C, resorcinarene **1** was separated by precipitation. The clear solution was concentrated under vacuum and the crude mixture was purified by column chromatography. Regioisomeric ratios of the title compounds were determined by integration of ^{1}H-NMR signals of the crude reaction mixtures in comparison with the literature values. Spectroscopic data of derivatives α-**4a-e**,[11g] β-**4a**,[11d] α-**5a**,[11b] β-**7a**,[11b] β-**8a**[11b] matched those reported in literature.

Computational details

Due to the high computational cost derived from the large number of atoms involved we choose to conduct an in silico investigation using the ONIOM method upon a reduced model of (**1**)$_6$•8H_2O, namely $\mathbf{C_R}$ substituting the undecylic residues (the so-called "feet") present in the hexameric capsule with the methyl ones.

The calculations have been performed using the ONIOM method incorporated in the Gaussian16 package, for the reaction between the N-methyl pyrrole **2** and the nitrostyrene **3a**. The reactive species (**2** and **3a**) together with one of the four acidic molecules of water directly involved in the supramolecular assembly and the corresponding three phenolic hydroxyl groups surrounding it were modeled using the M06-2X DFT functional, employing the cc-pVDZ basis set, while the semiempirical method PM6 was employed for all the other atoms.

In order to determine the activation energy barrier of each step and the reaction energy profile, reactant complex, transition state and product complex structures were optimized. All transition structures were characterized by only one imaginary frequency in normal mode analysis and further supported by Intrinsic Reaction Coordinate (IRC) calculations. Other stationary points (reactant complex, intermediates, and product complex) were characterized by all real frequencies and by IRC calculations. Thermodynamic corrections were calculated at 298.15 K and 1 atm for the optimized geometries. All the relative energies presented in the manuscript are referred to the sum of electronic and thermal free energies calculated at the ONIOM[M06-2X/cc-pVDZ:PM6] level (zero-point energy-corrected ONIOM values). The optimizations were carried out using the Berny analytical gradient optimization method. All calculations were carried out with the Gaussian 16 suite of programs.

Conflicts of interest

There are no conflicts to declare.

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16 Conversely, in the FC benzylation of the pyrrole previously reported[5] the β-regioisomer is favored because the α-TS1 undergoes a 1,2-benzyl shift followed by a 1,2-H shift which rearranges the α-adduct into a more stable β-adduct. Furthermore, the encapsulated product β-adduct@C_R is thermodynamically more stable than the α-adduct@C_R by 2.8 kcal/mol.