MASSA 2020 – VIRTUAL INTERNATIONAL PRE-CONGRESS

Detection of a Catalytically Active Self-Assembled Resorcinarene Capsule by Mass Spectrometry

Pellegrino La Manna[a], Margherita De Rosa[a], Carmen Talotta[a], Giuseppina Ferrino[a], Antonio Rescifina[b], Giuseppe Floresta[b], Annunziata Soriente[a], Carmine Gaeta[a], Placido Neri[a]

[a]Dipartimento di Chimica e Biologia "A. Zambelli", Università degli Studi di Salerno

[b]Dipartimento di Science del Farmaco, Università degli Studi di Catania

email: plamanna@unisa.it

Università degli Studi di Salerno

Società Chimica Italiana
Divisione di Spettrometria di Massa

INTRODUCTION

In the last decades, many efforts have been devoted to the study of reactions catalyzed in nanoconfined spaces for the synthesis of drug candidates.[1] In particular, pyrrole and *C*-alkylated pyrroles are among the most important fundamental constituents of biologically and physiologically active molecules, such as chlorophyll, porphyrin, hemoglobin, Vitamin B12 and bile pigments.[2] In addition *C*-alkylated pyrroles play important roles in medicinal chemistry, where they act as anticancer agents.[2]

Halogen-bonding (XB)[3] is a secondary interaction between a covalently bound halogen atom in a R–X compound (the "XB donor", where X = I, Br, Cl, F, and R = C or any other atom including even I, for example) and a Lewis base (the "XB acceptor").[3] Recently, increasing attention has been devoted to exploiting the XB interaction in organocatalysis.[4] Catalysis in nanoconfined environments has been object of many efforts.[1,5] Particularly, hexameric resorcinarene capsule **C**[6] (Figure 1) has been well exploited as nanoreactor for several chemical reaction.[1,5]

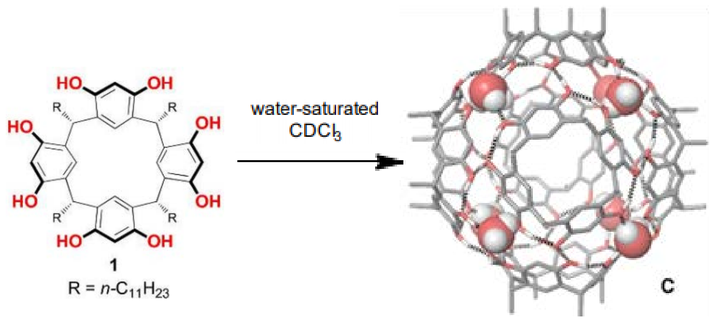


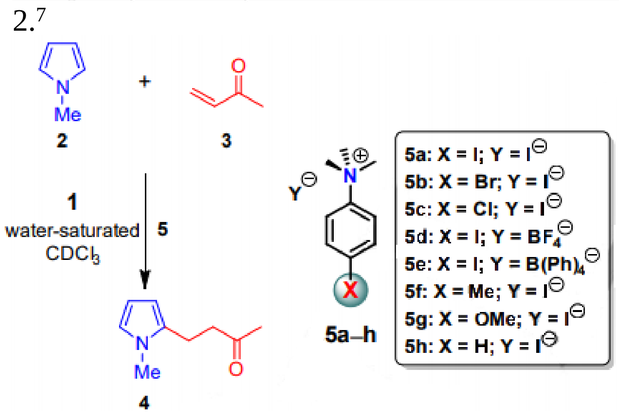
Figure 1:. Capsule **C** formed by 6 resorcinarene **1** units and 8 water molecules.

On the basis of these considerations, we investigated the Michael reaction between substrates **2** and **3** to give the *C*-alkylated pyrrole **4** in the presence of the catalyst **5a** inside a resorcinarene capsule (Figure 1).[7] In details, under the conditions reported in Scheme 1, a catalytically active open-capsule is formed which shows a pentameric structure (Figure 2).[7]

Evidences of the formation of the pentameric resorcinarene capsule were obtained by HR FT ICR ESI mass spectra.[7]

RESULTS AND DISCUSSION[7]

Initially, we investigated the reaction between *N*-methylpyrrole **2** and methyl vinyl ketone **3** in the presence of resorcinarene **1** (Scheme 1), in water-saturated $CDCl_3$ as solvent, under the standard conditions of formation of the capsule **C**[1,5,7]. When the reaction mixture (Table 1, entry 3) was stirred in absence of XB catalyst **5a** and in presence of **1**, then the product **4** was obtained in 12% of yield, differently no hint of **4** was detected in absence of **1** and in presence of **5a** (entry 4). Interestingly, when both, the XB catalyst **5a** and resorcinarene **1** were added to the reaction mixture of **2**, and **3** in water-saturated $CDCl_3$, a 98% of yield of product **4** was obtained after 16 h at 50 °C (Table 1, entry 2). These results confirm the crucial role played by the *p*-iodophenyltrimethylammonium iodide in the catalysis of the Michael reaction reported in Figure 2.[7]



Scheme 1. Halogen bonding catalyzed Michael reaction between *N*-methylpyrrole **2** and methyl vinyl ketone **3** in the presence of **1**.

To corroborate the catalytic role of the halogen bonding interaction (Figure 2), we studied the reaction reported in Scheme 1 using *p*-X-phenyltrimethylammonium salts **5b–d** (Table 1, entries 8, 10 and 12). As is known[3,4], the XB strength increase with the polarizability of the XB donor atom, F < Cl < Br < I. Thus, when *N*-methylpyrrole **2** was reacted with **3**, in the presence of **1**, and *p*-bromophenyltrimethylammonium iodide **5b**, then the product **4** was obtained in 45% yield (Table 1, entry 8), while a 53% of **4** was obtained using *p*-chlorophenyltrimethylammonium iodide **5c** (Table 1, entry 10).

Table 1. Halogen bonding catalyzed Michael reaction between N-methylpyrrole **2** and methylvinylketone **3** in the presence of **1**.

Entry[a]	T (°C)	Halogen bonding catalyst (20%)	Capsule amount (mol%)	Yield of 4 (%)[b]
1	30	**5a**	26	82
2	50	**5a**	26	98
3	50	—	26	12
4	50	**5a**	—	—
5[c]	50	**5a**	26	88
6[d]	50	**5a**	26	1
7[e]	50	**5a**	26	—
8	50	**5b**	26	45
9	50	**5b**	—	—
10	50	**5c**	26	53
11	50	**5c**	—	—
12	50	**5d**	26	5
13	50	**5d**	—	—
14	50	**5e**	26	50
15	50	**5e**	—	—
16	50	**5f**	26	24[f]
17	50	**5g**	26	8[g]
18	50	**5h**	26	33

[a] Reaction conditions: **2** (0.59 M), **3** (0.15 M), **1** (0.0063 M) in 1.1 mL of watersaturated $CDCl_3$, 16 h. [b] Isolated yield. [c] Reaction time: 4 h. [d] The reaction was performed in the presence of hexamethonium bromide (0.76 M). [e] The reaction was carried out in the presence of DMSO. [f,g] The 25% [f] and 18% [g] of 2,5-disubstituted product was obtained.

These results confirm that the Michael reaction between *N*-methylpyrrole **2** and methyl vinyl ketone **3** is catalysed in the confined space of a resorcinarene capsule (Figure 2) by activation of the carbonyl of **3** by halogen bonding interaction with the co-catalyst **5a** (see Figure 2).[7]

Quantum-mechanical investigations highlighted that the Michael reaction proceeds through the activation of the carbonyl by synergistically enhanced halogen/hydrogen bonding interactions, and takes place in an open pentameric capsule (Figure 2). Experimental evidences of the presence of a pentameric resorcinarene capsule ***C*** *under the catalytic reaction conditions were obtained by HR FT-ICR ESI MS (Figure 3).*

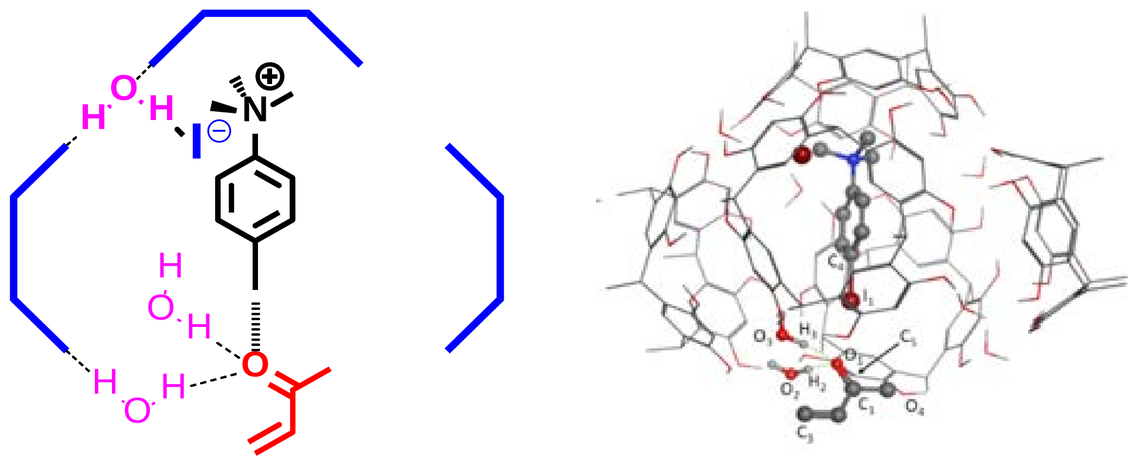


Figure 2. (Left) Schematic representation of the pentameric capsule hosting **2** and **3**. In dashed line, the halogen bonding interaction between iodine atom of **5a** and carbonyl of **3** that plays a crucial role in the activation of the unsaturated ketone. (Right) Full optimized geometry of the supramolecular complex [**5a**+**3**]@$\mathbf{1}_5$ (pentameric capsule)

Experimental evidences of the presence of a pentameric resorcinarene capsule **C** under the catalytic reaction conditions reported in Scheme 1 were collected by DOSY studies and HR FT-ICR ESI MS (Figures 2 and 3).

When resorcinarene **1** was ionized with an ESI source in the absence of catalyst **5a**, then only the molecular peak of **1** at 1104.835 *m/z* was detected (Figure 3a). Differently, when an equimolar mixture of resorcinarene **1** and catalyst **5a** was ionized with an ESI source according to the conditions reported previously by Schalley and coworkers,[8] then the mass spectrum reported in Figure 3b was obtained. The results in Figure 3b suggested that the organic cation of **5a** templates the formation of pentameric $(\mathbf{5a})_2@\mathbf{1}_{5a}$ and hexameric $(\mathbf{5a})_2@\mathbf{1}_6$ aggregate, which were detected at 3024.613 *m/z* and 3579.024 *m/z*, respectively, and in which two units of **5a** were present inside the capsules.

Significantly, when the reactants **2** and **3** were added to the reaction mixture then the mass spectrum in Figure 3c was obtained, in which a peak at 5787.241 *m/z* was revealed attributable to the pentameric aggregate containing a single unit of catalyst **5a**, ($\mathbf{5a}@\mathbf{1}_a$). Under these conditions, no hexameric capsule was detected.

In conclusion, HR MS studies confirm the presence of the pentameric capsule postulated by DFT calculations.

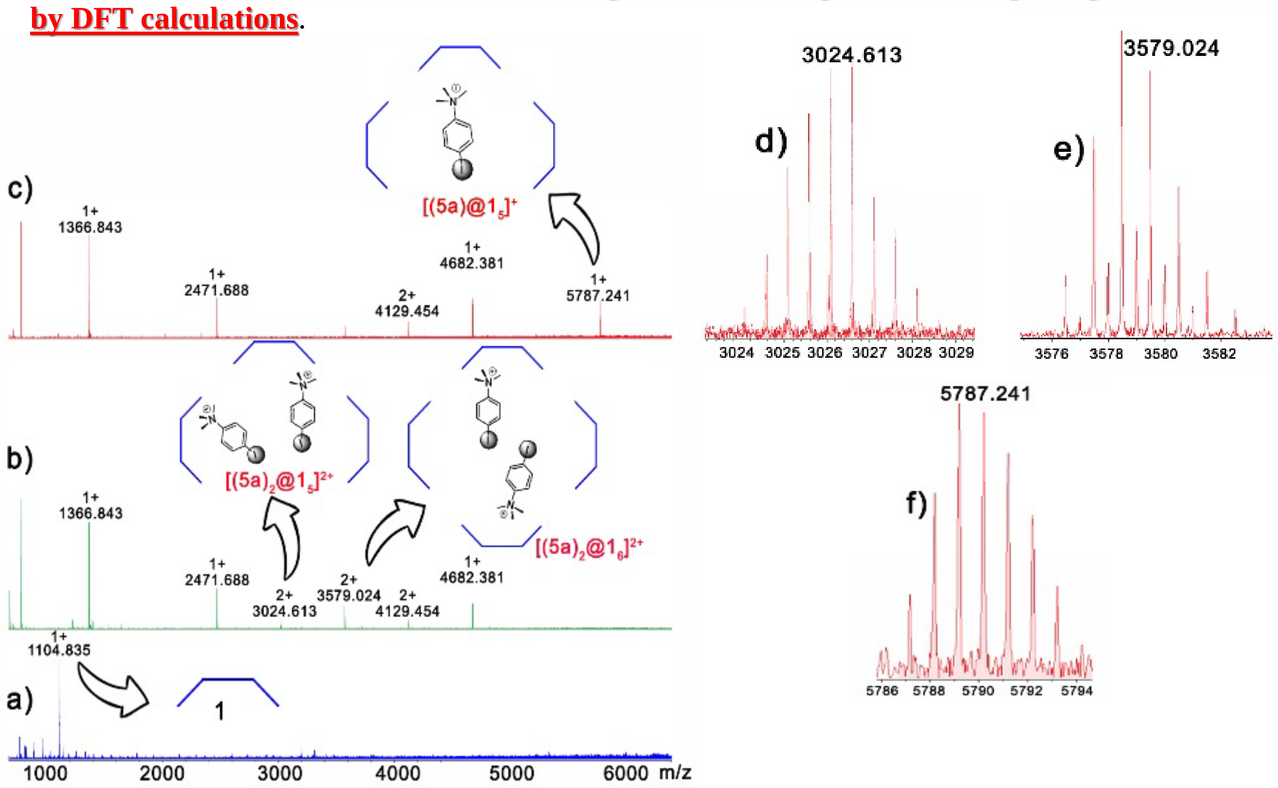


Figure 3. ESI-FT ICR mass spectra of: a) 250 μM solution of **1** in water-saturated $CHCl_3$, b) after addition of a stoichiometric amounts of **5a**, c) mixture in (b) in the presence of **2** and **3** (same reaction conditions), Experimental patterns of d) $\mathbf{[(5a)_2@1_5]^{2+}}$, e) $\mathbf{[(5a)_2@1_6]^{2+}}$, and f) $\mathbf{[5a@1_5]^{2+}}$.[6]

CONCLUSIONS

The results here reported show that the Michael reaction proceeds through the activation of the carbonyl of **3** by synergistically enhanced halogen/hydrogen bonding interactions, and takes place in an open pentameric capsule (Figure 3). Experimental evidences of the presence of a pentameric resorcinarene capsule C under the catalytic reaction conditions were obtained by HR FT-ICR ESI MS (Figure 3).

REFERENCES

1. C. Gaeta, C. Talotta, M. De Rosa, P. La Manna, A. Soriente, P. Neri, *Chem. Eur. J.* **2019**, *25* , 4899-4913.
2. A. Joule, K. Mills, G.F. Smith Heterocyclic Chemistry (4th ed.), Blackwell Science, Oxford (2000)
3. G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Soc. Rev.*, **2016**, *116*, 2478-2601.
4. D. Bulfield, S. M. Huber *Chem. Eur. J.* **2016**, *22*, 14434–14450.
5. Q. Zhang, L. Catti, K. Tiefenbacher, *Acc. Chem. Res.* **2018**, *51*, 2107−2114
6. L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469-472.
7. P. La Manna, M. De Rosa, C. Talotta, A. Rescifina, G. Floresta, A. Soriente, C. Gaeta, P. Neri, *Angew. Chem., Int. Ed.* **2020**, *59*, 811-818.
8. N. K. Beyeh, M. Kogej, A. Ahman, K. Rissanen, C. A. Schalley, *Angew. Chem. Int. Ed*. **2006**, *45*, 5214–5218