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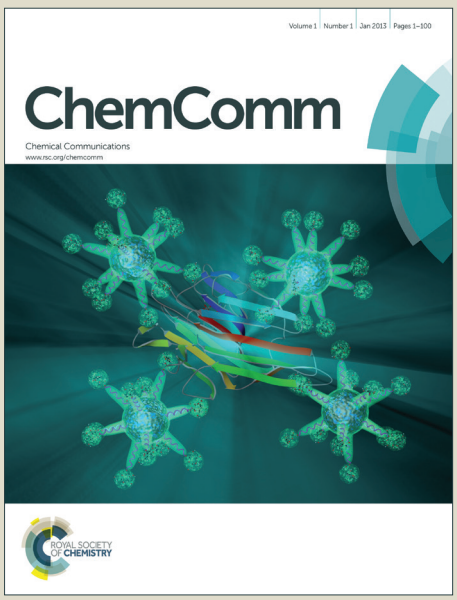

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Substrate Selective Amide Coupling Driven by Encapsulation of a Coupling Agent within a Self-Assembled Hexameric Capsule

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Sonia Giust,[a] Giorgio La Sorella,[a] Laura Sperni,[a] Giorgio Strukul,[a] Alessandro Scarso[a,*]

Encapsulation of a cationic carbodiimide condensing agent within a self-assembled hexameric capsule made of resorcin[4]arene units provide a nano-environment that efficiently steers the substrate selectivity in the amide synthesis reaction between carboxylic acids and primary amines. While in solution pairs of acids react similarly with a given amine, in the presence of the capsule the formation of the shorter amide is greatly favored

Among the several impressive properties of enzymes, their high substrate selectivity[1] is a feature that traditional homogeneous catalysts still cannot rival. This is basically due to the high ability of enzymes to bind selectively the substrate that better fits the geometric and electronic properties of the active site. This occurs thanks to proper matching of size, shape and charge of the substrate with the active site of the enzyme. This recognition event is driven by the formation of several weak intermolecular forces that enable to select one substrate out of several, often very similar, other ones.

Aiming at bridging the gap between traditional homogeneous catalysis and enzymatic catalysis, it is important to increase the surface interactions between catalyst and substrates. Supramolecular catalysis is growing as a new cross-discipline that points at implementing weak intermolecular forces in artificial catalysts to achieve high activity, product and substrate selectivity.[2] To improve the surface interaction between substrates and catalyst and impart substrate selectivity an alternative approach consists in wrapping both within a solvation sphere with a lifetime long enough to impart steric effects.

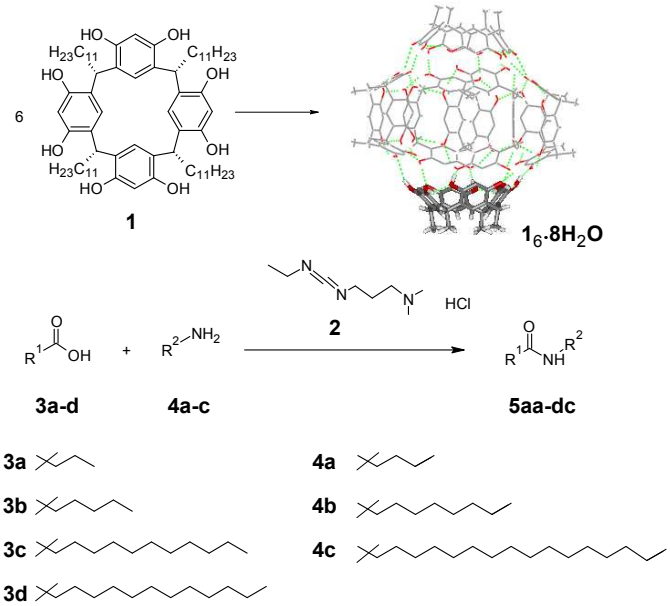
Except for the kinetic resolution of racemates,[3] examples of substrate selectivity showed by artificial supramolecular catalysts are basically divided into three groups: i) those involving substrates bearing extra functionalities such as e.g. hydrogen bonding or ionic moieties[4] that enable secondary interactions with the catalyst thus favouring their selective recognition; ii) those related to reactions in water where the hydrophobic effect is the driving force for recognition in micelles[5] and in well defined organic or metal-ligand based capsules and cavitands[6] and ii) those working in organic solvents where steric interactions and size and shape selectivity is the selection rule. Recently we reported that a hexameric self-assembled capsule based on resorcin[4]arene **1**[7] can efficiently bind a Au(I) catalyst and impart unique product[8] as well as substrate[9] selectivity properties in chloroform due to the size and shape of the capsule that operates as a rigid solvation sphere for the reaction. An example of substrate selectivity based on the hexamer of resorcin[4]arene was also reported for the hydrolysis of acetals.[10]

Typically, the large cavity of about 1375 Å^3 [11] is suitable to bind quaternary ammonium compounds[12] thanks to extended cation-π interactions.[13] Among neutral guests the stabilization of electron poor molecules like isonitriles has been reported,[14] as well as examples of encapsulation of carboxylic acids, aminoacids and polyols through hydrogen bonding, especially when they are present in a large excess with respect to the host.[15]

Herein we present an example of efficient supramolecular substrate selectivity in amide coupling driven by encapsulation of the coupling agent **2** within the hexameric capsule $\mathbf{1}_6 \cdot 8H_2O$ (Scheme 1). The capsule accommodates the cationic carbodiimide **2** and selects preferentially the shorter carboxylic acids **3** and the shorter primary amines **4** present in the system, leading to preferential formation of the shorter amides **5**, while in the absence of the capsule the reaction is much less substrate selective and similar amounts for all possible amides are observed. It is worth to note that a similar coupling agent encapsulated in a cylindrical capsule of comparable size turned out to be initially inactive in the amide coupling, giving rise to chemical amplification during the course of the amide coupling reaction.[16] In the present work, the self-assembled host $\mathbf{1}_6 \cdot 8H_2O$ does not substantially catalyze the reaction

but acts as a nano-reactor that imparts steric restrictions to the encapsulated reagents.

The reaction we initially tested with a series of cationic coupling agents and found that 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride **2** provided quantitative encapsulation when added in stoichiometric amount with respect to the capsule $\mathbf{1}_6{\cdot}8H_2O$ (Figure 1). Such condensing agent exists in chloroform-d solution as a ~ 5:1 mixture of both the open and six-membered closed form derived by intramolecular attack by the dimethylamino terminal moiety on the carbodiimide C atom.



Scheme 1. Amide **5** synthesis through coupling reaction between carboxylic acids **3** and primary amines **4** mediated by the cationic carbodiimide **2** in the presence of the self-assembled capsule $\mathbf{1}_6.(H_2O)_8$ as substrate selective nano-reactor.

All the resonances of the coupling agent **2** completely disappeared upon addition of 1.1 equivalents of the capsule $\mathbf{1}_6{\cdot}8H_2O$ due to the shielding effect imparted by the aromatic surfaces of the cavity. Once encapsulated, the carbodiimide **2** remained stable for several days without formation of the corresponding urea derivative by reaction with water, while addition of ten equivalents of tetraethylammonium tetrafluoroborate as a competitive cationic guest led to the release of **2** from the capsule (see supporting information). Similarly, we investigated the interaction of the capsule with hexanoic acid **3a** recording several ^{1}H NMR spectra in the presence of variable amounts of the substrate up to two equivalents observing no substantial variation of the resonances of both capsule and carboxylic acid, indicating that no particularly strong mutual attractive forces are present even though it is likely that some hydrogen bonding interactions could exist (see supporting information). The same experiment was also carried out with butylamine **4a** observing the formation of encapsulated ammonium species (see supporting information) due to deprotonation of the hydrogen bond seam of the capsule as recently disclosed by Tiefenbacher.[10] At last, titration of the capsule with increasing amounts of a 1:1 mixture of butylamine **4a** and hexanoic acid **3a** showed the presence of extra resonances in the region < 0 ppm which differ from those of the encapsulated butylammonium cation and therefore could be attributed to the possible co-encapsulation of **3a** (see supporting information).

Subsequently, we investigated the competitive condensation reaction between two aliphatic amines butylamine **4a** and octylamine **4b** in combination with butyric acid **3a** mediated by carbodiimide **2** both in the presence and in the absence of the capsule $\mathbf{1}_6{\cdot}8H_2O$ at 60°C for 18 h (Table 1).

Table 1. Catalytic tests for the competitive coupling of butylamine **4a** and octylamine **4b** with carboxylic acids **3** in the presence of cationic carbodiimide **2** with or without $\mathbf{1}_6{\cdot}8H_2O$ capsule.

#	Acid	Amine	Capsule $\mathbf{1}_6{\cdot}8H_2O$	Amide (%)[a]	Short 5/Long 5 Amide Ratio
1	**3a** C_4	**4a** C_4 **4b** C_8	-	**5aa** (C_4+C_4) 25 **5ab** (C_4+C_8) 15	1.7
2	**3a** C_4	**4a** C_4 **4b** C_8	+	**5aa** (C_4+C_4) 32 **5ab** (C_4+C_8) 15	2.2
3	**3b** C_6	**4a** C_4 **4b** C_8	-	**5ba** (C_6+C_4) 50 **5bb** (C_6+C_8) 20	2.5
4	**3b** C_6	**4a** C_4 **4b** C_8	+	**5ba** (C_6+C_4) 57 **5bb** (C_6+C_8) 11	5.1
5	**3c** C_{12}	**4a** C_4 **4b** C_8	-	**5ca** (C_{12}+C_4) 27 **5cb** (C_{12}+C_8) 23	1.2
6	**3c** C_{12}	**4a** C_4 **4b** C_8	+	**5ca** (C_{12}+C_4) 19 **5cb** (C_{12}+C_8) 10	2.0

[**1**]= 81.4 mM, [**2**]= 13.2 mM, [**3**]= 6.7 mM, [**4**]= 6.7 mM, water saturated chloroform-d 1 mL, 60°C, time 18 h. +: presence; -: absence; a) Determined by GC-MS analysis with an alkane standard.

In this case using half equivalent of each amine with respect to **2** and half equivalent of the acid, we observed only a slightly better ratio between the shorter **5aa** with respect to the longer **5ab** amide product in the presence of the capsule with respect to the same reaction in the absence of the capsule. The same general result was observed when comparing butylamine **4a** and octylamine **4b** in combination with hexanoic acid **3b** or dodecanoic acid **3c**. The small effect on the substrate selectivity imparted by the capsule in the amide coupling when comparing two amines with one acid is likely to be ascribed to the mechanism of carbodiimide coupling. In fact, the rate determining step of the reaction has been proposed to be the attack of the acid to the coupling agent to form the O-acylisourea, followed by a faster attack of the amine to the intermediate.[17]

Table 2. Catalytic tests for the competitive coupling of hexanoic **3b** and dodecanoic acid **3c** with amines **4** in the presence of cationic carbodiimide **2** mediated or not by capsule $\mathbf{1}_6{\cdot}8H_2O$.

#	Acid	Amine	Capsule $\mathbf{1}_6{\cdot}8H_2O$	Amide (%)[a]	Short 5/Long 5 Amide Ratio
1	**3b** C_6 **3c** C_{12}	**4a** C_4	-	**5ba** (C_6+C_4) 15 **5ca** (C_{12}+C_4) 30	0.5
2	**3b** C_6 **3c** C_{12}	**4a** C_4	+	**5ba** (C_6+C_4) 22 **5ca** (C_{12}+C_4) 3	8.1
3	**3b** C_6 **3c** C_{12}	**4b** C_8	-	**5bb** (C_6+C_8) 28 **5cb** (C_{12}+C_8) 25	1.1
4	**3b** C_6 **3c** C_{12}	**4b** C_8	+	**5bb** (C_6+C_8) 39 **5cb** (C_{12}+C_8) 5	7.9
5	**3b** C_6 **3c** C_{12}	**4c** C_{16}	-	**5bc** (C_6+C_{16}) 24 **5cc** (C_{12}+C_{16}) 19	1.2
6	**3b** C_6 **3c** C_{12}	**4c** C_{16}	+	**5bc** (C_6+C_{16}) 22 **5cc** (C_{12}+C_{16}) 0.8	28

[**1**]= 81.4 mM, [**2**]= 13.2 mM, [**3**]= 6.7 mM, [**4**]= 6.7 mM, water saturated chloroform-d 1 mL, 60°C, time 18 h. +: presence; -: absence; a) Determined by GC-MS analysis with an alkane standard.

Therefore we inverted the reagents and investigated the competition between two aliphatic carboxylic acids like hexanoic **3b** and dodecanoic **3c** acid towards one aliphatic amine either with or without capsule (Table 2). Under these conditions for all amines

tested we observed a marked increase of selectivity towards the shorter amide product when performing the coupling reaction in the presence of $\mathbf{1}_6 \cdot 8H_2O$. While the reactions with free condensing agent **2** in solution led to ratios of amide products in the range 0.5-1.2, the same coupling with the encapsulated **2** showed shorter/longer amide ratios between 8 up to 28 in the case of hexadecylamine **4c**.

The study was extended to the reaction between octylamine **4b** and pairs of acids in the presence and absence of the capsule. In Figure 1A are reported the ratios between the shorter and the longer amide product for each combination of acids tested, both in the presence and in the absence of capsule. It is evident that the nano-environment of the capsule is sensitive to the difference in length between the acids tested with negligible effects when the acids differ for only one methylene unit. On the other hand when increasing the difference in length from two, to six to eight methylene units the substrate selectivity greatly increased. It is noteworthy that while butyric acid **3a** and dodecanoic acid **3c** react almost identically with **2** in the absence of capsule, the same reaction mediated by $\mathbf{1}_6 \cdot 8H_2O$ led to a more than ten times preference for the shorter acid **3a** with respect to the longer **3c**, with 45 and 4% of the corresponding amides formed after 18 h, respectively.

The trend observed can be better understood plotting the ratio between the amounts of short and long amide with respect to the ratio between the number of C atoms of the amide products (Figure 1B). It is evident that a linear trend with approximately zero slope is present in the absence of the capsule indicating that no discrimination on the basis of acid length difference can be observed in a regular solution. Differently, in the presence of the capsule an approximately sigmoidal trend is observed indicating that much better substrate selectivity is possible increasing the difference in length between pairs of competing acids.

Finally, a competitive experiment between two acids (hexanoic **3b** and dodecanoic **3c**) and two amines (butylamine **4a** and octylamine **4b**) yielding a total of four possible amides was carried out (Figure 2).

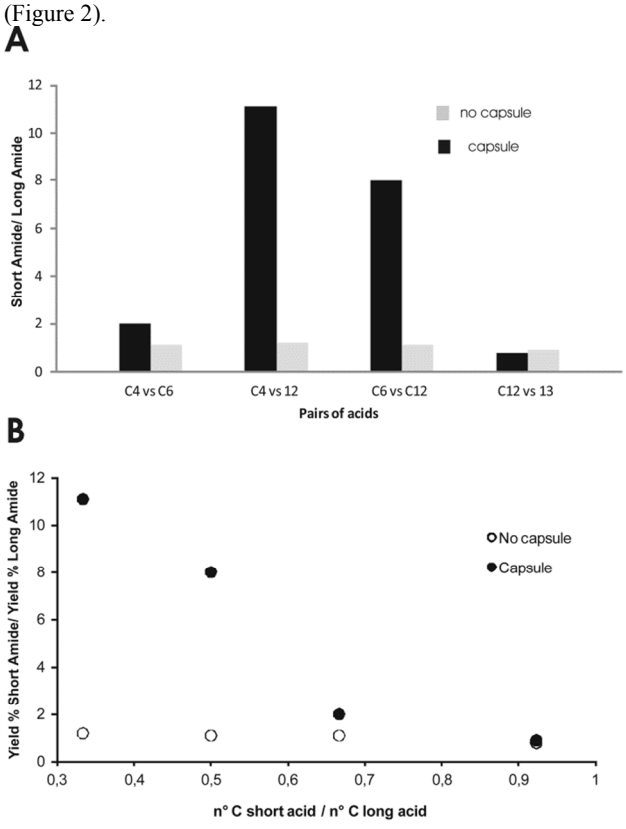


Figure 1. A) Catalytic tests for the competitive coupling of pairs of carboxylic acids **3** with octylamine **4b** in the presence of carbodiimide **2** mediated or not by capsule $\mathbf{1}_6 \cdot 8H_2O$. Experimental conditions: [**1**]= 81.4 mM, [**2**]= 13.2 mM, [**3**]= 6.7 mM, [**4**]= 6.7 mM, 60°C, 18 h. B) Plot of the ratio between the yields of the short and long amides for the reaction of **4b** and pairs of acids *vs.* the ratio between the number of carbon atoms of the competing carboxylic acids.

As shown in the absence of capsule the reaction provided all four possible amides in similar amounts (yields 28-12%) while in the presence of the capsule, the combination between the shorter acid **3b** and the shorter amine **4a** was greatly preferred over the others. The shorter amide **5ba** was obtained in 50% yield while the longer **5cb** was formed with only 4% yield. The capsule was also able to select between two amides characterized by very similar overall length but starting from different combination of substrates. In particular the product **5bb** derived by the shorter acid was formed in almost double amount with respect to **5ca** when using the capsule. Conversely, the two amides were obtained in 17 and 18% yield respectively in the absence of the nano-reactor.

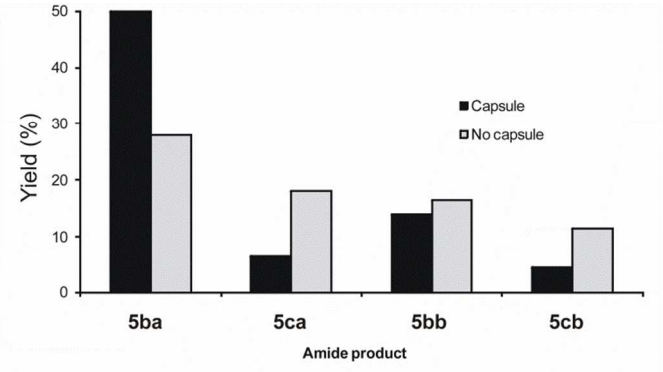


Figure 2. Catalytic tests for the competitive coupling of pairs of carboxylic acids **3b** and **3c** with pairs of amine **4a** and **4b** in the presence of carbodiimide **2** mediated or not by capsule $\mathbf{1}_6 \cdot 8H_2O$. Experimental conditions: [**1**]= 81.4 mM, [**2**]= 13.2 mM, [**3**]= 6.7 mM, [**4**]= 6.7 mM, 60°C, 18 h.

Conclusions

In conclusion, we described an example of supramolecular catalysis where the hexameric capsule $\mathbf{1}_6 \cdot 8H_2O$ hosted the cationic carbodiimide condensing agent **2** and in the presence of a series of acids **3** and amines **4** characterized by different length, selected the shorter ones because of better co-encapsulation leading to the formation of the shorter amides **5**. Conversely, in the absence of the self-assembled capsule, the coupling reaction was much less substrate selective leading to very similar distributions of the possible amides **5**. This indicates that the driving force for substrate selectivity is the selective binding of the carboxylic acid on the basis of its length. The results observed opens the way to the employment of the self-assembly capsule $\mathbf{1}_6 \cdot 8H_2O$ as a nanometric reactor sufficiently large to possibly steer substrate and product selectivity of other reactions that involve cationic reagents and intermediate species.

Notes and references

a) Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari di Venezia, Calle Larga S. Marta 2137, 30123, Venezia (ITALY). Fax: +39-041-2340517; Tel:+39-041-2348569

† Electronic Supplementary Information (ESI) available: experimental details and encapsulation spectra. See DOI: 10.1039/b000000x/

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