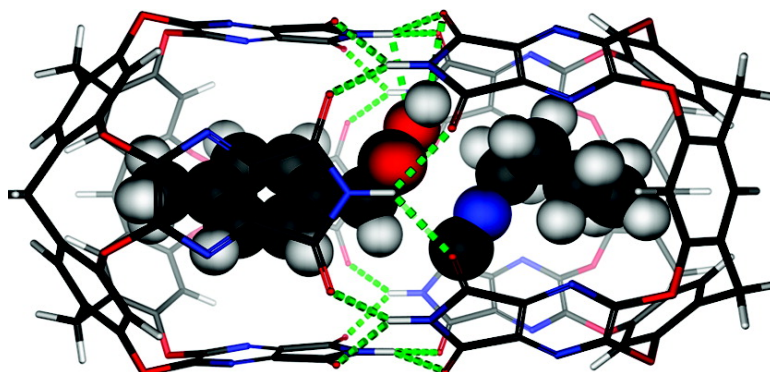Communication

Reaction of Carboxylic Acids and Isonitriles in Small Spaces

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Reaction of Carboxylic Acids and Isonitriles in Small Spaces

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Reversible encapsulation is an ultimate form of molecular recognition in which a self-assembled host completely surrounds the guest. The process temporarily isolates the guest from bulk solution and can provide a safe haven for otherwise labile species.[1] When two different guests are coencapsulated, reactions between them can be accelerated[2] and even catalyzed.[3] The shape of the inner space can channel the reaction along one stream rather than another.[4] Here, we apply encapsulation to the reaction of isonitriles with carboxylic acids and give evidence for the detection of an elusive intermediate along the pathway.

The reaction of carboxylates with nitrilium ions glows at the core of the Passerini[5] and Ugi[6] reactions, much-admired in combinatorial chemistry. In contrast, the prototypical combination of acid with isonitrile is a relatively obscure reaction and practically unknown under ambient conditions.[7] Danishefsky[8] has recently applied the reaction in nonprotic solvents ($CHCl_3$) with microwave heating at 150 °C for 30 min. These conditions lead to formylated secondary amides in admirable yields (Scheme 1).

The pathway undoubtedly involves the intermediate *O*-acyl isoamide (the acyclic version of an azlactone) followed by the Mumm rearrangement[9] of the acyl from O to N. To our knowledge, no observations of this intermediate from isonitriles and acids are consistent with spectroscopic data,[7b] but the analogous intermediate from substituted nitrilium ions and carboxylates is known[9] and can be intercepted with external nucleophiles such as amines to give amides or react with another molecule of carboxylic acid to give a symmetric anhydride. The overall reaction of Scheme 1 is known to be reversible at high temperatures.[9d]

We studied this reaction in the cylindrical host **1.1**[10] (Figure 1) by NMR methods. This structure self-assembles only in the presence of a suitable guest or combinations of different guests[11] that properly fill the space. The aromatic environment in **1.1** causes characteristic upfield shifts in the NMR spectra, and hydrogens near the ends of the capsule appear at 0 to −4 ppm.

The combination of *p*-tolylacetic acid **2** and *n*-butyl isonitrile **3** provides a single[12] encapsulation complex with **1** in which the isonitrile and the acid groups are located near one another in the polar middle of the capsule (Figure 2). The ^{1}H NMR spectra show that the initial coencapsulation complex is replaced by the rearrangement product **4** even at room temperature. The intermediate is not observed to build up in concentration. A small amount of formamide **5** coencapsulated with acid **2** is also observed on completion of the reaction. Under mildly elevated temperatures (40 °C), the reaction was complete over the course of 20 h. Control experiments at millimolar concentrations at the same temperature and solvent showed that no reaction could be detected in the absence of the capsule. However, the same reagents at 4.0 M concentration and 40 °C result in the formamide **5** and the anhydride **6** after 2 days. No rearrangement product **4** was observed under these conditions. Accordingly, *the reaction takes a different and accelerated course inside the capsule.*

Scheme 1
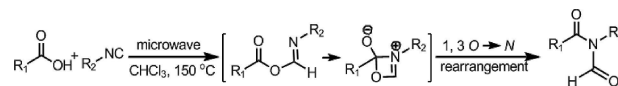
How does the capsule **1.1** facilitate this reaction? First, the capsule amplifies the concentration of reactants since each component exists at a 4 M concentration inside the capsule. Second, the capsule arranges the acid and isonitrile in the appropriate orientation. The long butyl group of the isonitrile pushes the reactive centers toward the middle of the capsule where the seam of hydrogen bond donor and acceptor can stabilize polar transition states.[9] The acyl rearrangement involves a four-membered ring which creates a great deal of strain, but the *n*-butyl group is apparently flexible enough to accommodate the necessary motions inside.

We next studied the reaction with a bulkier group on the isonitrile. Treatment of acid **2** with isopropyl isonitrile **7** at 4.0 M concentration in mesitylene-d_{12} at 40 °C results in a 40% yield of formamide **10** after 2 days. Only 1% of the rearrangement product **9** was observed. In the presence of the capsule **1.1**, *at millimolar concentrations*, immediate formation of a coencapsulation complex takes place, as shown by the NMR spectra (Figure 3a).

The initial complex is gradually replaced by another one—a complex that builds up then disappears (Figure 3b−d). It has the spectroscopic earmarks expected for the elusive intermediate **8**; the signal for the isopropyl group is the furthest upfield shifted, indicating it is the longest occupant of the capsule. Its rearrangement appears to be thwarted within the capsule since none of the formylated secondary amide **9** is produced. Instead, the intermediate is released to the bulk solution where it reacts with the carboxylic acid **2** to give **10** and the symmetrical anhydride **6**. Together, **10**
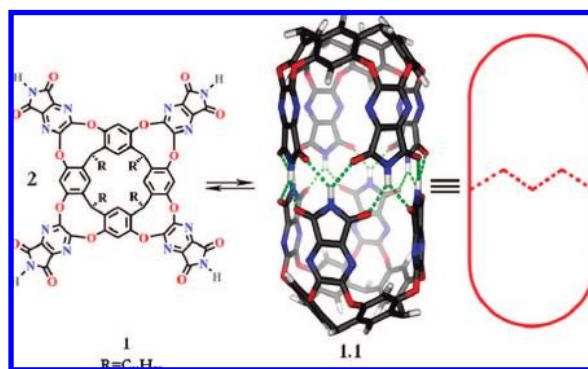

Figure 1. Two cavitands self-assemble through hydrogen bonding into a cylindrical capsule **1.1**. Two representations of the capsule are shown. In the center is the energy-minimized (semiempirical AM1, HyperChem 7) structure **1.1**; the long alkyl chains and CH hydrogen atoms are omitted for viewing clarity. Right: the cartoon representation.
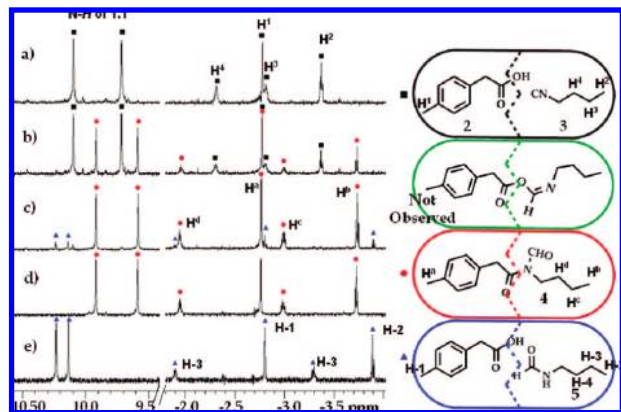
Figure 2. Partial ¹H NMR spectra show the transformation of acid **2** (20 mM) and isonitrile **3** (6.0 mM) in the presence of capsule **1.1** (2.0 mM) at 300 K. Cartoon representations show the complexes involved in the transformation. The intermediate within capsule (green) is undetectable in ¹H NMR spectrum: (a) $t = 0$ h; (b) $t = 7$ h; (c) $t = 20$ h; (d) **4** (authentic sample) within capsule **1.1**; (e) **5** (authentic sample) and acid **2** within capsule **1.1**.
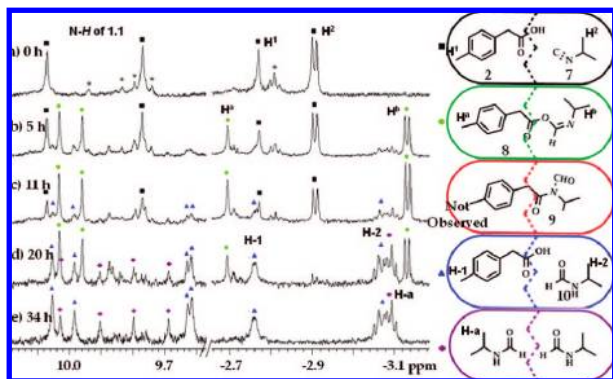

Figure 3. Partial ¹H NMR spectra show the transformation of acid **2** (20 mM) and isonitrile **7** (2.0 mM) in the presence of capsule **1.1** (2.0 mM) at 300 K (∗ = impurities). Cartoon representations show the complexes involved in the transformation: (a) $t = 0$ h; (b) $t = 5$ h; (c) $t = 11$ h; (d) $t = 20$ h; (e) $t = 34$ h.

and the acid **2** gradually fill the capsule. This combination was identified by comparison with an independently synthesized sample of **10** (Figure 3).

Ironically, the expected but absent rearrangement product **9** is a better guest (nearly ideal occupancy[12]) than any of the other products observed from the reaction in the presence of the capsule, as revealed by competitive binding experiments. The formation of **8** in the capsule is irreversible since the ratio of the starting coencapsulation complex to **8** changes (decreases) with time. At any rate, this capsule prevents the rearrangement, yet provides a source of reactive **8** that leaks out of the capsule to react with the acid in bulk solution. The capsule could be regarded as a catalyst for the formation of the symmetrical anhydride **6** since it is too large to fit inside the capsule. However, the other product, **10**, does eventually occupy the capsule so classic product inhibition is the

result. The complexity of the spectrum for encapsulated **10** reflects its existence as a mixture of rotamers[13] and social isomers.[14]

Elsewhere, we have described the principles of coencapsulation of two guests within a host: the congruence of shapes, the compatibility with lengths, the conformity with volumes, and the complementarity of surfaces. These features manipulate reactivity within the rigid capsules[15] and contrast with flexible receptors with more functionality[16] or other unimolecular cages.[17] The surroundings may also be thought of as a solvent cage fixed in place through synthesis. The adaptation of solvent to the transition state during a reaction inside a capsule does not incur an entropic price. Some reactions do not—perhaps cannot—occur inside the confined environment. In the cases at hand, encapsulation does provide an alternative to reactions at high temperatures in bulk solution.

References

(1) (a) Yoshizawa, M.; Kuskawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *122*, 6311–6312. (b) Ziegler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4119–4121. (c) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464–1465.
(2) (a) Kang, J.; Rebek, J., Jr *Nature* **1997**, *385*, 50–52. (b) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85–88. (c) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 7000–7001. (d) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 14366–14367.
(3) Kang, J.; Santamaria, J.; Hilmersson, G.; Rebek, J., Jr *J. Am. Chem. Soc.* **1998**, *120*, 7389–7390.
(4) (a) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251–254. (b) Chen, J.; Rebek, J., Jr *Org. Lett.* **2002**, *4*, 327–329.
(5) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.
(6) (a) Ugi, I.; Meyr, R. *Angew. Chem.* **1958**, *70*, 702–703. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
(7) (a) Gautier, A. *Liebigs Ann.* **1896**, *151*, 240–243. (b) Shaabani, A.; Soleimani, E.; Rezayan, A. H. *Tetrahedron Lett.* **2007**, *48*, 6137–6141.
(8) Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448.
(9) (a) Schwarz, J. S. P. *J. Org. Chem.* **1972**, *37*, 2906–2908. (b) Brady, K.; Hegarty, A. F. *J. Chem. Soc., Prekin Trans. 2* **1980**, 121–126. (c) Hegarty, A. F. *Acc. Chem. Res.* **1980**, *13*, 448–454. (d) Hoy, D. J.; Poziomek, E. J. *J. Org. Chem.* **1968**, *33*, 4050–4054.
(10) (a) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr *Nature* **1998**, *394*, 764–766. (b) Heinz, T.; Rudkevich, D. M.; Rebek, J., Jr *Angew. Chem., Int. Ed.* **1999**, *38*, 1136–1139. (c) Körner, S. K.; Tucci, F. C.; Rudkevich, D. M.; Heinz, T.; Rebek, J., Jr *Chem.—Eur. J.* **2000**, *6*, 187–195.
(11) Rebek, J., Jr *Angew. Chem., Int. Ed.* **2005**, *44*, 2068–2078.
(12) Mecozzi, S.; Rebek, J., Jr *Chem.—Eur. J.* **1998**, *4*, 1016–1022.
(13) Avalos, M.; Babiano, R.; Barneto, J. L.; Cintas, P.; Clemente, F. R.; Jimenez, J. L.; Palacios, J. C. *J. Org. Chem.* **2003**, *68*, 1834–1842.
(14) Shivanyuk, A.; Rebek, J., Jr *J. Am. Chem. Soc.* **2002**, *124*, 12074–12075.
(15) For reviews, see: (a) Fiedler, D.; Leung, D. H.; Bergman, R. G.; Raymond, K. N. *Acc. Chem. Res.* **2005**, *38*, 349–358. (b) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, M.; Kusakawa, T.; Birhada, K. *Chem. Commun.* **2001**, 509–518. (c) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr *Angew. Chem., Int. Ed.* **2002**, *41*, 1488–1508.
(16) Galán, A.; de Mendoza, J.; Toiron, C.; Bruix, M.; Deslongchamps, G.; Rebek, J., Jr *J. Am. Chem. Soc.* **1991**, *113*, 9424–9425.
(17) Brody, M.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr *Angew. Chem., Int. Ed.* **1999**, *38*, 1640–1644.

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