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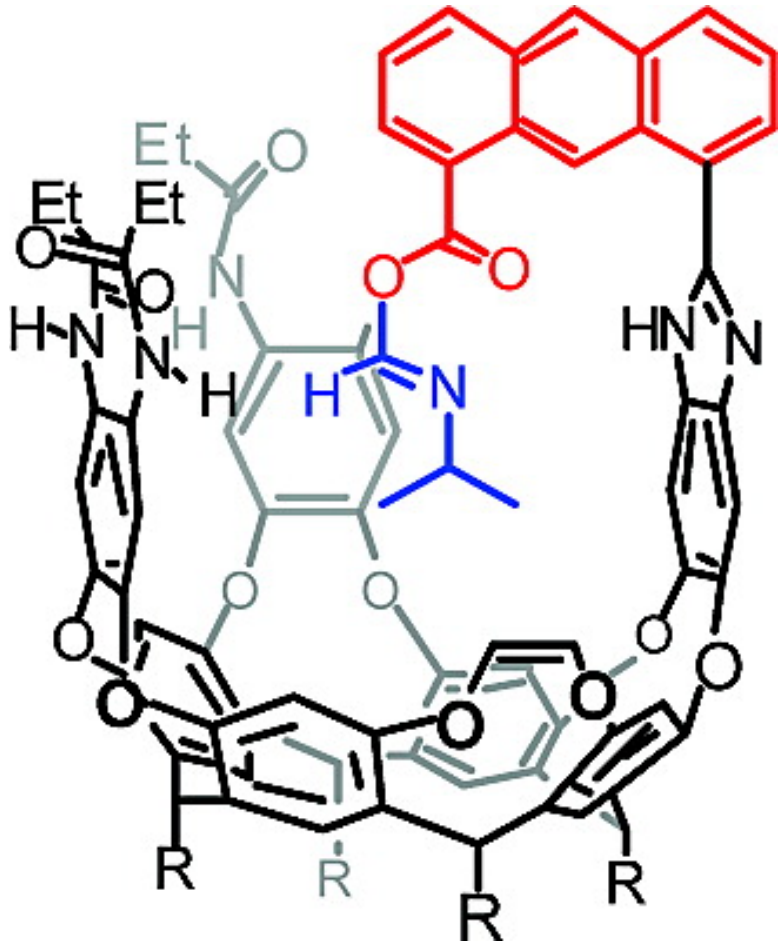

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Reaction of Isonitriles with Carboxylic Acids in a Cavitand: Observation of Elusive Isoimide Intermediates

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Cavitands are vase-shaped structures that have been widely used in studies of molecular recognition.[1] While it is generally difficult to derivatize their (internal) concave surfaces, the upper rims are readily functionalized. Unconventional reagents such as Kemp's triacid[2] attached there can lead to receptor molecules that fold around small molecules, isolate them from bulk solution, and present them with functional groups directed into the cavity.[3,4] A range of chemical transformations can be promoted within the structured environment of the cavitands, including stabilization of labile carbonyl addition intermediates[5] and acceleration of organic reactions.[6] Here, we introduce cavitand **1** (Scheme 1) containing an "introverted" acid functionality on an anthracene skeleton. Its reaction with small, aliphatic isonitrile molecules bound inside the cavity gives elusive intermediates that are observed by conventional spectroscopic methods.

The reaction of carboxylates with nitrilium ions is well-known and is the key step in the Ugi and Passerini multicomponent condensations.[7] In contrast, the reaction of carboxylic acids and aliphatic isonitriles is rare.[8] Recently, Danishefsky and Li[9] showed that this reaction occurs under microwave heating at 150 °C for 30 min in $CHCl_3$ and provides an efficient synthesis of diverse imides. The reaction proceeds via the *O*-acyl isoimide intermediate **A** followed by a *1,3-O→N* acyl transfer (Mumm rearrangement)[7a−d] to form *N*-acylformamide **B**. In a recent departure, we investigated this process with the reactants in a cylindrical capsule and showed that the reaction inside occurs at significantly lower temperatures.[10] In addition, the formation of a transient intermediate could be detected by ^{1}H NMR spectroscopy, but we were unable to further characterize it. The covalent attachment of the acid and its isolation inside cavitand **1** now allow the corresponding intermediate **A** to be characterized by NMR and IR methods.

We prepared cavitand **1** by oxidation of the previously described "introverted" aldehyde cavitand.[5a] Cavitand **1** folds in competitive solvents such as THF-d_8, but in mesitylene-d_{12} that does not fit inside the cavity, the peaks in the ^{1}H NMR spectrum are broad and undefined. Upon addition of a small isonitrile molecule such as ^{i}PrNC the peaks sharpen considerably and show characteristic signals for the bound guest.[11] These signals appear shifted far upfield due to the magnetically shielded environment inside the cavity of **1** created by the aromatic walls (Figure 1).

After addition of ^{i}PrNC to **1** in mesitylene-d_{12}, two sets of doublets were observed in the ^{1}H NMR spectra arising from the terminal methyl groups of **A** and **B**, respectively, buried deep inside the cavity of **1**. The nearby chiral environment of cavitand **1** renders the two isopropyl methyl groups diastereotopic, and they are observed as separate signals. The cyclic seam of intramolecular hydrogen bonds that stabilize the vase-like conformation of **1** can be oriented either clockwise or counterclockwise, and interconversion is slow on the NMR chemical shift time scale.[12] Over the course of a few hours the doublets arising from intermediate **A**

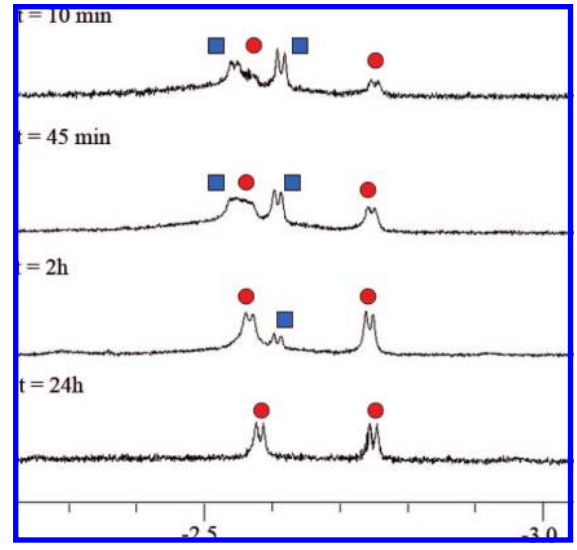
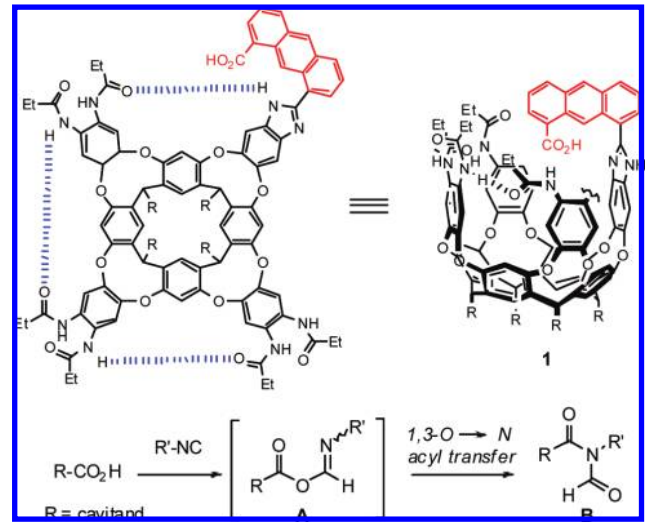


Figure 1. ^{1}H NMR spectra of cavitand **1** and ^{i}PrNC. Blue square shows intermediate **A** and red circle product **B**.

Scheme 1. Reaction of Cavitand **1** with Aliphatic Isonitriles



disappeared and were replaced by signals from the rearranged product **B**. The formation of **B** was confirmed by ESI-HRMS which gave a mass of 2157.2520 [$M + H^+$].

The reaction was also monitored by IR spectroscopy (Figure 2). Immediately after addition of ^{i}PrNC to **1** the IR spectrum showed only one carbonyl (C═O) band ($\nu = 1667$ cm^{-1}) which arises from the amide carbonyls on the brim of **1**.[13] After 10 min the appearance of another carbonyl (C═O) band at 1771 cm^{-1} appeared. This value

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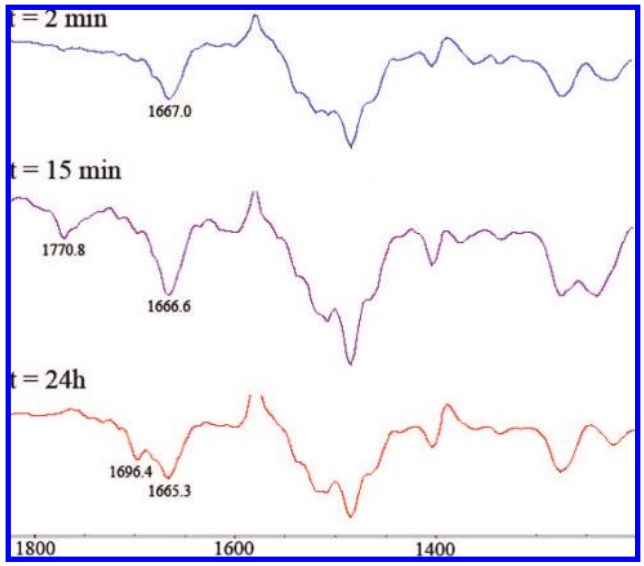

Figure 2. IR spectra of cavitand **1** and ^{i}PrNC.

is consistent with previously reported data for structurally related α-amino isobenzimides generated from iminoaziridines ($\nu = 1747$ cm^{-1}).[14] After 24 h, the absorption at 1771 cm^{-1} had disappeared and was replaced by a carbonyl C═O band at 1696 cm^{-1}, a value in good agreement with reported data for *N*-acyl formamides.[15]

Similar results were obtained using ^{t}BuNC as the reagent in cavitand **1**.[16] In this case, the ^{1}H NMR spectra showed upfield signals for the noncovalently bound guest along with *O*-acyl isoimide intermediate **A** and rearranged product **B**. After 24 h only the signal from product **B** remained. IR spectroscopic analysis showed a C═O absorption at 1766 cm^{-1} for intermediate **A** and 1698 cm^{-1} for product **B** as before.

How does the cavitand facilitate the reaction between the carboxylic acid moiety and the isonitriles? First, the cavitand amplifies the concentrations of the reacting species by binding the guest: the reaction is effectively promoted from a bimolecular to a unimolecular one inside the cavity. Second, the cavitand can be thought of as a solvent cage fixed in time through synthesis. The cavitand's aromatic walls offer an electron-rich π-surface that can interact with the bound substrate whereas the secondary amide bonds in the rim make up a polar region rich in hydrogen-bond donors. Third, the confined space can provide steric barriers that slow the rearrangement of intermediate **A** (Scheme 1). These features create a unique environment in the cavity not possible in bulk solution which isolates and stabilizes labile and otherwise unobservable reaction intermediates. No reaction was observed between the isonitriles and typical acids under these conditions in the absence of cavitand **1**.[10] Cavitands have previously shown rate accelerations and catalysis of reactions even without functional groups attached.[17] In conclusion, cavitand **1** possessing an inwardly directed carboxylic acid function binds and reacts with small isonitrile guests held inside its cavity at *ambient temperature* and *millimolar concentrations*.[11] It was also possible to observe the labile *O*-acyl isoimide intermediate **A** by ^{1}H NMR and IR spectroscopy. Elsewhere, complete encapsulation was shown to alter the reactivity of bound species and prolong the lifetimes of otherwise unstable molecules.[18] Examples include isolation of iminium ions[18a] and siloxanes[18c] from aqueous media, detection of unfavored conformations,[19] and appearance of unknown reaction courses[20] channeled by the size and shape of the host. Cavitands and capsules provide versatile, modern complements to classical kinetics and nonkinetic[21] methods for the study of reaction intermediates and offer promise as models for enzyme catalysis.

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Supporting Information Available: Synthesis of cavitand **1** and spectral data characterization of **1** and the reaction intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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