JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Bimolecular Reaction via the Successive Introduction of Two Substrates into the Crystals of Networked Molecular Cages

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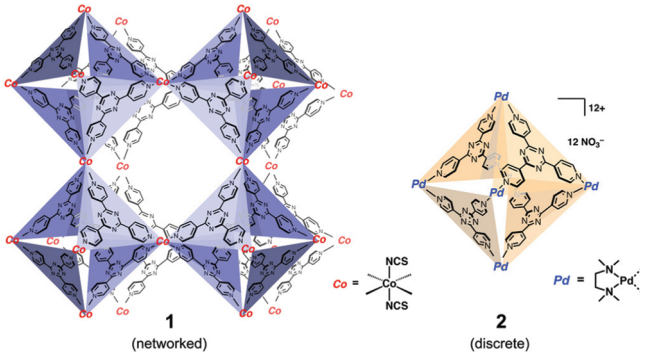
Supporting Information

ABSTRACT: Two substrates, 4-hydroxydiphenylamine (**3**) and ethyl isocyanate (**4**), were successively introduced into the crystals of networked M_6L_4 cages **1**. Because of the encapsulation effect, most of the initially introduced substrate **3** remained within the crystals during immersion in a solution of **4**. X-ray analysis revealed that before the reaction, the nucleophilic NH group of **3** is effectively protected by tight packing within the cage units while the OH group is exposed to the incoming second substrate. Successive introduction of **4** into the crystal results in the chemoselective acylation of **3** at the less nucleophilic OH group. The observed chemoselectivity is consistent with that exhibited by discrete M_6L_4 cage **2** in solution.

Tremendous effort has been devoted to the design and utilization of porous coordination networks[1] as solid-state reaction containers.[2,3] Unlike solution reactions, however, the successive introduction of two substrates into crystals is a seemingly simple yet unexpectedly difficult task and has rarely been examined because the in-diffusion of the second substrate often induces out-diffusion of the first.[4] Crystalline-state reactions in the pores have therefore been typically examined by covalently or noncovalently installing the first substrate on the network framework and then introducing the second substrate (reagent) by diffusion.[5] We recently synthesized coordination network **1** consisting of two structurally unique compartments: infinitely arrayed octahedral M_6L_4 cages and the remaining interstitial pores.[6] Like their counterpart Pd_6L_4 discrete cages (**2**),[7] the M_6L_4 cage units of **1** strongly bind incoming substrates, whereas the interstitial pores do not; in contrast, however, the substrates have fluidity in the networked M_6L_4 crystal.



The distinct features of the two compartments prompted us to design a bimolecular reaction via the successive introduction of two substrates into the crystal. Our idea was to firmly entrap the first substrate in the M_6L_4 cages and subsequently introduce the second substrate into the interstitial pores without leaching of the first substrate from the cages. Accordingly, we examined the acylation of 4-hydroxydiphenylamine (**3**) with ethyl isocyanate (**4**) in the cavities of **1**. We report that the bimolecular reaction was successfully promoted by our strategy, and we unexpectedly observed unusual chemoselective O-acylation in this reaction.

Network **1** was prepared from tris(4-pyridyl)triazine (TPT) and $Co(NCS)_2$ in a MeOH/*o*-dichlorobenzene mixture according to the procedure reported previously.[6] The introduction of the first substrate **3** was easily accomplished simply by soaking the crystals of **1** in a saturated toluene solution of **3**, wherein the orange crystals of **1** immediately turned reddish-black and revealed broad charge-transfer (CT) bands at 500−700 nm in the diffuse reflectance spectra [Figure S1 in the Supporting Information (SI)]. The thermogravimetric analysis and extraction experiment showed that included guest **3** amounted to ∼35 wt %. On the basis of the elemental analysis, the inclusion complex (hereafter denoted as **1**⊃**3**) was best formulated as $[(Co(NCS)_2)_3(TPT)_4(\mathbf{3})_m\cdot(\text{solvent})]_n$ (m = 8−9).

The guest inclusion occurred in a single-crystal-to-single-crystal fashion, and because of the strong host−guest binding in the cage, the guests were not disordered. The inclusion geometry of **3** within the cage was clearly displayed by crystallographic analysis (Figure 1).[8] The X-ray structure revealed that four guests **3** are fixed in the M_6L_4 cage unit along the cage's S_4 symmetry axis. The OH groups of the molecules of **3** are exposed toward the interstitial pores at every portal of the cage, while the NH groups are fully shielded by the TPT ligands (Figure 1b). The large interstitial pores also included guests **3**, which were crystallographically located at two different positions. The larger thermal ellipsoids and lower occupancies suggested weak binding of the guest molecules in the pores. Importantly, the environment of **3** in the M_6L_4 cages differs considerably from that in the interstitial pores.

Subsequently, the second substrate **4** was introduced into the crystal by immersing the crystals of **1**⊃**3** in a decane solution containing a large excess of **4**. After 12 h, the crystals were filtered and decomposed using HCl. The products formed in the crystal were then extracted with CH_2Cl_2 and analyzed by NMR spectroscopy, which showed the formation of the O-acylated

Received: October 2, 2011
Published: November 09, 2011

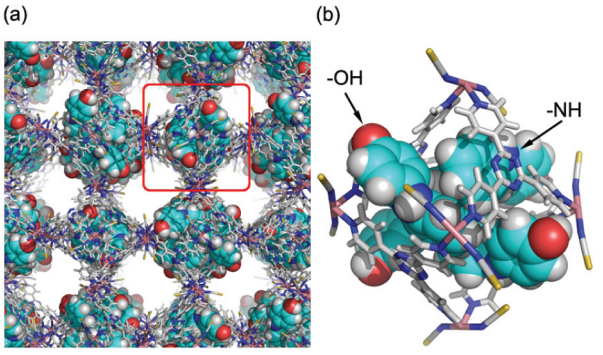
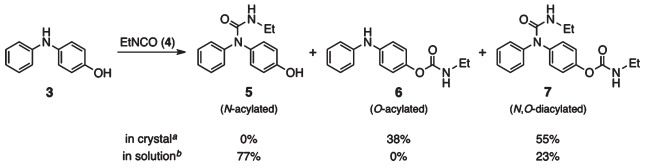


Figure 1. X-ray crystal structures of the inclusion complex **1**⊃**3**: (a) network structure; (b) one M_6L_4 cage. Guests **3** are represented as CPK models. Other guests **3** in the interstitial pores have been omitted for clarity.

Scheme 1. Acylation of 4-Hydroxydiphenylamine (3) with Ethyl Isocyanate (4) in Crystals of 1⊃3 and in Toluene Solution



[a] Inclusion complex **1**⊃**3** was soaked in a decane solution containing a large excess of **4** for 12 h. [b] A toluene solution of **3** was treated with excess **4** (added using a syringe pump) for 12 h.

and N,O-diacylated compounds **6** and **7** in yields of 38 and 55%, respectively (Scheme 1).[9] It is worthy of note that a total of 93% of the originally introduced substrate **3** was acylated in the crystal without leaching out. Analysis of the supernatant consistently showed the leaching of only a small amount of the products (7%). Practically, this small amount of product leaching was completely avoided by introducing **4** into the crystals using a vapor diffusion method. The crystallinity of network **1** remained intact throughout the reaction, and leaching of free TPT ligand or Co(II) ions was not detected by an elution test.

In this reaction, we unexpectedly observed unusual chemoselectivity. As mentioned above, only O-acylated product **6** and N,O-diacylated product **7** were formed, and *N*-acylated product **5** was not detected in the reaction mixture. In other words, the acylation predominantly occurred at the less nucleophilic O site, in striking contrast to the selective N-acylation of free **3** in solution under standard conditions (Scheme 1). Despite the presence of the unreacted amino group in **6**, prolonged treatment with **4** for 24 h did not cause any change in the product ratio. Thus, the chemoselective formation of **6** is ascribed to the protection of the N site by the cage, as clearly revealed by X-ray structure.

To understand the unusual chemoselectivity, we traced the product ratio during the reaction (Figure 2) by quenching the reaction at various points and analyzing the products by NMR spectroscopy. The product distribution at 0−4 h clearly revealed that N-acylated product **5** was involved at the early stage of the reaction and clearly served as an intermediate for the N,O-diacylated product **7**. Interestingly, the yield of **6** slowly but monotonically increased over 8 h. Even in the presence of excess

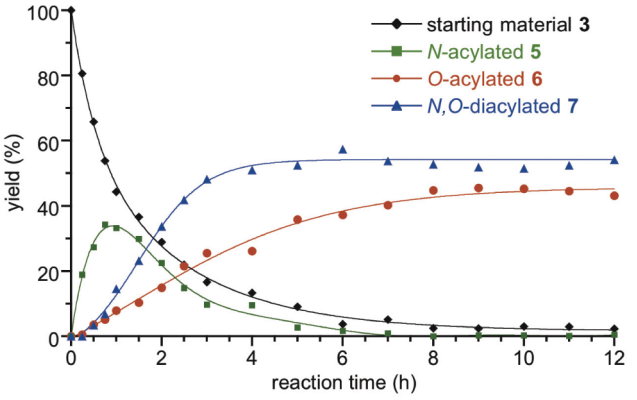
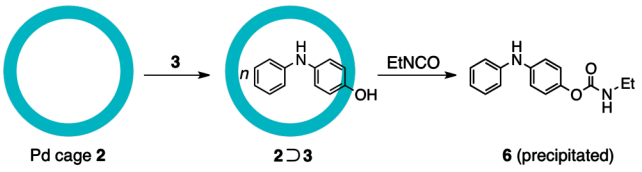


Figure 2. Plot showing the relationship between the NMR yield of each component **3**−**6** and the time of exposure of inclusion complex **1**⊃**3** to vaporous EtNCO.

Scheme 2. Chemoselective Acylation of 3 with Pd_6L_4 Cage 2 in Solution



4, in situ-formed **6** was not converted into **7**. These results led us to conclude that there are two competing reaction pathways in the network crystals **1**: (1) N-acylation of **3** followed by O-acylation (**3** → **5** → **7**) and (2) O-acylation of **3** without further reaction (**3** → **6**). On the basis of the crystal structure of **1**⊃**3**, we reasoned that path (1) occurs in the large interstitial pores, where the substrates are mobile, and path (2) takes place in the cavity of the M_6L_4 cage, where N-acylation is completely suppressed by the protection effect of the cage.

To confirm the inhibition of N-acylation by the cage, a control experiment with discrete Pd_6L_4 cage **2** was examined in solution. When powdered **3** was suspended in an aqueous solution of host **2**, the solution color turned dark-red, and the encapsulation of **3** was clearly indicated by the upfield shift of the guest signals in the ^{1}H NMR spectrum (Scheme 2; also see the SI). The protons of the unsubstituted phenyl ring of **3** were shifted more than those of the 4-hydroxyphenyl group (see the SI), consistent with the inclusion geometry of **3** in the **1**⊃**3** complex, where the N site is shielded but the O site is exposed. When the solution of **2**⊃**3** was treated with 5 equiv of **4**, O-acylated product **6** was selectively formed. The product was no longer a suitable guest for the cage and precipitated as a colorless solid. This result strongly supports the conclusion that N-site protection and O-selective acylation occur within the networked M_6L_4 cages of **1**.

In conclusion, the unique structural feature of networked M_6L_4 cages **1** has facilitated the design of a bimolecular reaction via the successive introduction of two substrates into the cavities of a crystalline coordination network. Highly efficient host−guest interactions in the cages control the substrate geometry in the crystal, resulting in high reaction selectivities (here, chemoselectivity in the acylation of an aminophenol). We note that the events observed in the M_6L_4 cage units are exactly the

same as those in discrete Pd_6L_4 cage **2**. Hence, the rich host–guest chemistry of **2** in solution[10] can in principle be translated into solid-state chemistry, offering various potential applications of coordination network materials.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was supported by KAKENHI, Japan Society for the Promotion of Science.

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(8) X-ray data for **1**⊃**3** have been deposited with the Cambridge Crystallographic Data Centre as entry CCDC-846614.

(9) The higher yield of **7** than **6** is attributable to the larger amount of guest **3** in the interstitial pores than in the cages. It is also possible for encapsulated guest **3** to slop out of the cage into the interstitial pores during the reaction.

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