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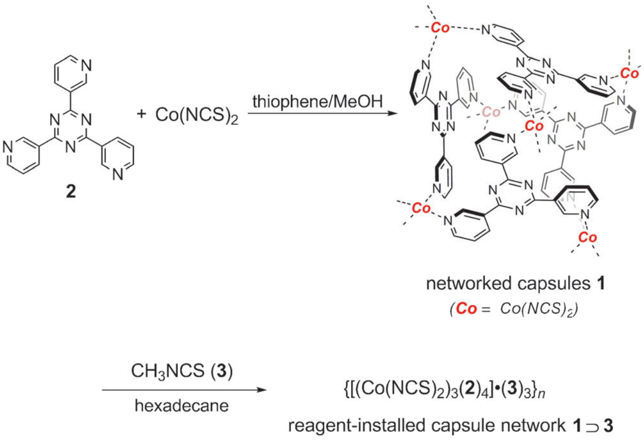
Molecular Capsules

Reagent-Installed Capsule Network: Selective Thiocarbamoylation of Aromatic Amines in Crystals with Preinstalled CH_3NCS**

*Yasuhide Inokuma, Guo-Hong Ning, and Makoto Fujita**

Porous coordination networks[1] have recently served as crystalline molecular flasks in which chemical reactions occur between incoming reagents and preinstalled substrates within the pores. Since the substrates are in most cases covalently or noncovalently fixed on the network framework,[2,3] the products cannot be isolated unless the complex is demolished. With a view to practical applications in organic synthesis, we had the idea of "reagent-installed porous networks" in which common organic substrates are converted to desired products by simply passing them through the pores. Such reagent-installed networks are particularly useful if troublesome reagents (e.g., highly volatile, unstable, toxic, or explosive ones) are stably preinstalled.

We recently synthesized porous coordination network **1** composed of two compartments: infinitely arrayed M_6L_4 capsules and the remaining interstitial voids (Scheme 1).[4] Within the capsule units, even reactive molecules are stably stored. In contrast, incoming substrates in the interstitial voids are fluid, and their reactivity is enhanced. Given these properties of **1**, we envisioned stable storage of reagents in the capsule units and triggering their delivery by introduction of substrates into the voids. Furthermore, the reagent installed in the complex may show unusual reactivity and selectivity in crystalline-state reactions. We have now synthesized network complex **1** encapsulating highly volatile CH_3NCS (**3**) by single crystal-to-single crystal (SCSC) reagent loading into as-synthesized **1**. Reagent **3** is strongly trapped in the capsule units and does not leach out of the capsule even if the network crystals are exposed to a solution of the substrate. We show that networked capsules $\mathbf{1}\supset\mathbf{3}$ can act as a crystalline reagent for thiocarbamoylation of aromatic amines with enhanced substrate selectivity and that, after the reaction, network **1** can be reused by reloading the reagent.



Scheme 1. Preparation of reagent-installed capsule network $\mathbf{1}\supset\mathbf{3}$.

Capsule network **1** was prepared from tris(3-pyridyl)triazine (**2**) and $Co(NCS)_2$ in thiophene/MeOH.[4] CH_3NCS (**3**) was easily introduced into the capsules by soaking the as-synthesized crystals of **1** in a solution of **3** in hexadecane at room temperature for 3 d, during which the supernatant was replaced three times with fresh guest solution. Treating the crystals with fresh hexadecane for 4.5 h washed out the surplus of **3** remaining in the interstitial pores to give reagent-installed capsule network $\mathbf{1}\supset\mathbf{3}$.

Reagent installation proceeded in an SCSC fashion, and the structure of $\mathbf{1}\supset\mathbf{3}$ was clearly analyzed by X-ray crystallography (Figure 1). Each capsule is occupied by four molecules of **3**, which are tightly packed through CH–π and π–π interactions with ligand **2**.[5] Importantly, no electron density assignable to **3** is found in the interstitial pores. These

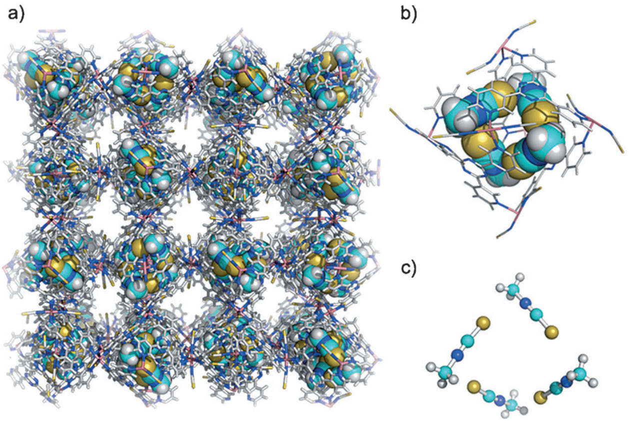


Figure 1. X-ray crystal structure of $\mathbf{1}\supset\mathbf{3}$: a) Network structure. b) One capsule subunit with guests shown as CPK models. c) Ball-and-stick representation of the four packed guest molecules **3**. (C light blue, S yellow, N blue, and H white).

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[*] Dr. Y. Inokuma, G.-H. Ning, Prof. Dr. M. Fujita
Department of Applied Chemistry, School of Engineering
The University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp

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observations are in good accordance with inductively coupled plasma (ICP) analysis, which determined a Co/S atomic ratio of 1/3. Elemental analysis agreed with the formula $\{[(\mathrm{Co(NCS)_2})_3(\mathbf{2})_4]\cdot(\mathbf{3})_3\cdot(\mathrm{C_{16}H_{34}})_x\}_n$ ($x \approx 5$), which indicates the presence of four molecules of **3** per capsule (i.e., 7 wt% inclusion; see Supporting Information).[6]

Leaching tests on **1⊃3** confirmed how strongly the guest reagents are held within the networked capsules. 1) Guest **3** did not leach out into the supernatant after washing crystals of **1⊃3** with hexadecane (Figure S1 in the Supporting Information). 2) Exposure of crystals of **1⊃3** (ca. 150 mg, containing ca. 10 mg of **3**) to air at room temperature for 3 d caused only a very small change (<1%) in Co/S ratio. The suppressed volatility of encapsulated **3** is in striking contrast to the highly volatile nature of neat **3**: 10 mg of solid **3** sublimed within 30 min under the same conditions. 3) Thermogravimetric/differential scanning calorimetry/mass spectrometry (TG-DSC-MS) analysis indicated that guest **3** remained encapsulated up to 200°C; after a gentle loss of 32 wt% due to evaporation of the hexadecane solvent in the pore, a steep weight loss with a sharp endothermic peak was recorded at 205°C, where encapsulated guest **3** (ca. 7 wt%) was released from network **1** (Figure S2 in the Supporting Information).

Introduction of aromatic amines into the interstitial pores triggered delivery of encapsulated reagent **3**, and thus network complex **1⊃3** was shown to be a useful reagent capsule that is switched on by substrate uptake. From incoming amine guests, thioureas were synthesized in situ. When crystals of **1⊃3** were soaked in a hexadecane solution of aniline (**4a**) (0.24 M, 0.75 equiv relative to $\mathrm{CH_3NCS}$), **4a** was quickly enclathrated into the pores of **1**, concomitant with crystal color change from pale red to deep orange. After 72 h, the resultant crystals were collected by filtration, digested with HCl(aq.), and extracted with $\mathrm{CH_2Cl_2}$ to give 1-methyl-3-phenylthiourea (**5a**) in 91% yield. In the supernatant, neither reagent **3** nor product **5a** was detected by ^{1}H NMR spectroscopy. Thus the reaction took place only in the network crystals.

Encapsulated **3** is a much milder reagent than neat **3**, and we observed enhanced substrate selectivity. A remarkable decrease in reaction rate was observed with a bulky aniline derivative. The bulky amine 2,6-dimethylaniline (**4b**) was enclathrated into network **1⊃3** as quickly as **4a**. However, thiourea **5b** was formed only in 11% yield after 72 h. The plot of reaction time versus conversion allowed us to estimate the k_{4a}/k_{4b} ratio to be 10.9 (Figure 2b). This value is considerably larger than that in a standard solution reaction ($k_{4a}/k_{4b} = 4.3$; Figure 2c),[7] that is, networked capsules **1⊃3** notably discriminate the difference in steric bulk around the amino groups of the substrates. Clearer results were obtained by a competition experiment: when a 1:1 mixture of **4a** and **4b** was treated with crystals **1⊃3**, thioureas **5a** and **5b** were initially formed in 91:9 ratio, in contrast to a control experiment in solution, which resulted in a 73:27 mixture (Figure S5 in the Supporting Information). Since inclusion of amines into the interstitial pores of **1** is nonselective,[8] the observed substrate selectivity is attributable to steric protection of **3** by the capsules.

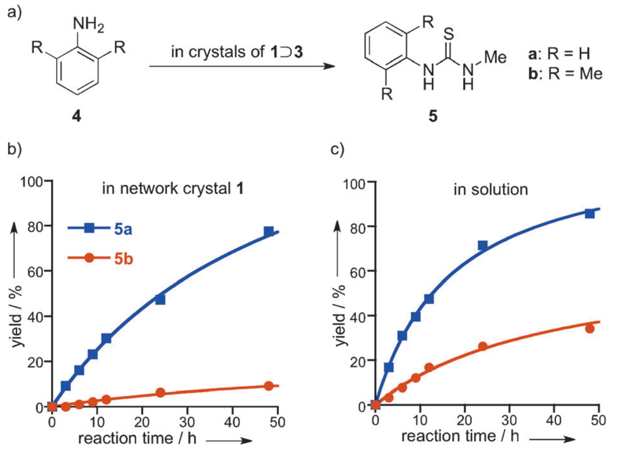
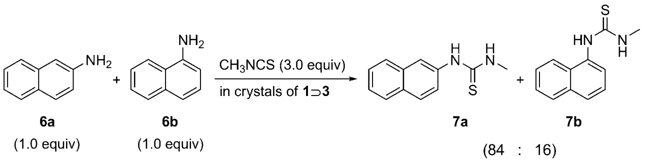


Figure 2. a) Synthesis of thiourea in network crystals of **1⊃3**. Product yield versus reaction time profiles b) in network crystals **1⊃3** and c) in solution. Initial conditions: $[\mathbf{4}]_0 = 0.24$ M and $[\mathbf{3}]_0 = 0.36$ M (for solution reactions). For crystalline-state reactions, 1.5 equiv of $\mathrm{CH_3NCS}$ was added as its inclusion complex **1⊃3**. The yield was determined by ^{1}H NMR spectroscopy.

Networked reagent capsules **1⊃3** were also able to discriminate 2- and 1-naphthylamine (**6a** and **6b**) in thiocarbamoylation (Scheme 2). When crystals of **1⊃3** were immersed in an equimolar solution of **6a** and **6b**, corresponding thioureas **7a** and **7b** were formed in 84:16 ratio over the initial 10 h. In contrast, the selectivity of the thiocarbamoylation in solution was very poor (**7a**:**7b** = 58:42).



Scheme 2. Selective formation of thiourea **7a** in network **1**.

Finally, we emphasize that capsule network **1** is reusable. After extraction of the products with thiophene/MeOH, reagent **3** could be reloaded into the capsule by the same procedure, and almost the same product selectivity was obtained with the recycled reagent capsules.

In summary, we have achieved SCSC installation of reagent **3** into networked molecular capsules **1** by simply soaking crystals in a reagent solution. While the reagent molecules were firmly encapsulated by capsule units, introduction of amines into the interstitial pores triggered reagent delivery. Moreover, we demonstrated substrate-selective thiocarbamoylation of amines in crystals **1⊃3**. Given strong guest binding and stabilization effects, networked capsules **1** would provide significant benefits when the reagents are tedious to handle (e.g., toxic or explosive), because these guests can be safely encapsulated into the network with ease. We believe that **1** can accommodate a variety of reagents and thus expand the scope of crystalline-state reactions.

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[5] Crystallographic data for $\mathbf{1}\supset\mathbf{3}$: $C_{26}H_{16}CoN_{10}S_2\cdot 0.36\,C_2H_3NS$, $M_r = 617.86$, cubic $Fd\bar{3}c$, $a=b=c=64.058(3)$ Å, $V=262\,853(21)$ Å^3, $T=90(2)$ K, $Z=192$, $\rho_{calcd}=0.749\ g\,cm^{-3}$, 8153 unique reflections out of 11 287 with $I>2\sigma(I)$, 390 parameters, final $R_1=0.1424$ [$I>2\sigma(I)$]. CCDC 846321 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.. Note that the refined occupancy of guest **3** is lower than that expected from ICP and elemental analyses, since it is disordered within the capsule, and was not fully resolved because of the high symmetry of the lattice.

[6] The unit lattice of **1** contains 64 M_6L_4 subunits, sixteen of which are open-mouthed M_6L_4 cages in which the guest molecules were not restrained.

[7] The reactions in solution followed second-order kinetics [first-order in CH_3NCS (**3**) and in aniline (**4**)], and thus the kinetic rate constants were calculated according to the reported procedure: a) *Chemical Kinetics*, 3rd ed. (Ed.: K. J. Laidler), Harper and Row, New York, **1987**; b) E. Dyer, J. F. Glenn, *J. Am. Chem. Soc.* **1957**, *79*, 366–369.

[8] Nonselective inclusion of **4a** and **4b** into network **1** was confirmed with crystals of $\mathbf{1}\supset\mathbf{3}$: when coordination network $\mathbf{1}\supset\mathbf{3}$ was soaked in a 1:1 solution of **4a** and **4b**, the system reached equilibrium within 1 h, and more than 80 % of the substrates was enclathrated in almost 1:1 ratio.