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Diels–Alder via Molecular Recognition in a Crystalline Molecular Flask

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S *Supporting Information*

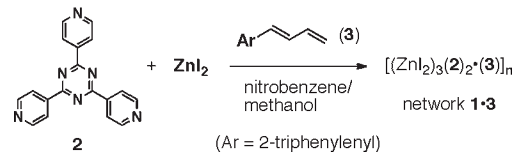
ABSTRACT: In the pore of a porous coordination network, Diels–Alder reactants, a diene and a dienophile, are recognized by donor–acceptor and multiple H-bond interactions, respectively, and fixed at ideal positions for the reaction. Heating the crystals promoted the Diels–Alder reactions with enhanced reactivity and controlled regioselectivity as clearly monitored by in situ X-ray crystallography.

The presence of large cavities in some coordination neworks[1] allows the design of chemical reactions to be carried out in the pores. These networks can be termed "crystalline molecular flasks,"[2] in which organic substrates can be efficiently trapped and allowed to undergo chemical transformations.[3] In virtue of their crystalline nature, fixing the substrates at predetermined positions enables the reactions in the pores to be topochemically controlled. However, unlike in solution chemistry, where host–guest interactions are generally ingeniously designed,[4] substrates in porous coordination networks often only fill the spaces in the structure, rather than interacting with specific sites in the pores. We have previously reported that coordination networks consisting of ZnI_2 and 1,3,5-tris(4-pyridyl)triazine ligand (**2**) show high molecular recognition ability in the pores.[5] Here, we show that network **1**, which is formulated as $[(ZnI_2)_3(\mathbf{2})_2]$, recognizes Diels–Alder[6,7] substrates (dienes and dienophiles) in the crystal, enhances their reactivity, and controls the reaction selectivity. The orientation of the substrates prior to the reaction has been analyzed by crystallography, enabling us to predict the enhanced reactivity and controlled selectivity.

Guest-embedded network **1•3** was prepared in a similar manner to its analogs described in our previous reports:[8] layering a methanol solution of ZnI_2 onto a nitrobenzene/methanol solution of **2** and diene **3** gave crystals of **1•3** in 84% yield (Scheme 1). Elemental analysis showed a compositional formula of $\{[(ZnI_2)_3(\mathbf{2})_2\bullet(\mathbf{3})]\bullet x(C_6H_5NO_2)\}_n$ (x = ca. 4) for as-synthesized network **1•3**.

Like the previously reported analogs,[3,8] network **1•3** exhibits a biporous framework (possessing pores A and B) and columnar π-stacks with alternating **2** and diene **3** (Figure 1a,b). The diene moiety of **3** is located at pore A with a planar conformation, and in pore B only nitrobenzene solvent molecules are found.

Scheme 1. Preparation of Guest-Embedded Network 1•3[a]



[a] Included solvent ($(C_6H_5NO_2)_{4.0}$) is omitted in the formula of **1•3**.

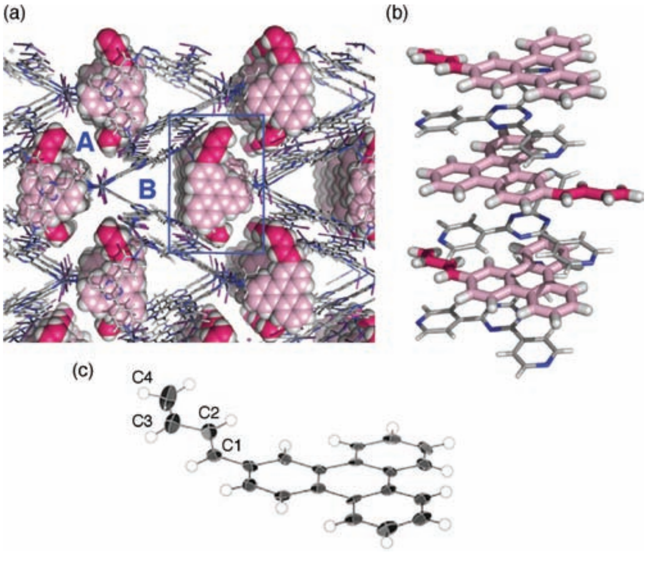


Figure 1. (a) Crystal structure of the as-synthesized network **1•3**. Triphenylene guest **3** is shown in CPK model. The diene moiety is represented in red color. The alternating columnar stack of **2** and **3** is located at the inserted square. (b) Side view of the columnar stack and (c) triphenylene **3** (ORTEP; 50% probability).

Because of efficient π–π interactions with ligand **2**, the Diels–Alder diene reactant **3** is geometrically well fixed and no disorder is observed even for the flexible diene moiety. The crystallographic analysis revealed that double bond C1=C2 in **3** is deeply embedded within a columnar π-stack, while double bond C3=C4 bulges into pore A. Large thermal ellipsoids on C3 and C4 (Figure 1c) indicate the conformational flexibility of the terminal double bond C3=C4, which allows the facile *s-trans* to *s-cis* isomerization and effective orbital interactions with incoming dienophiles.

The Diels–Alder dienophiles **4** were introduced into the crystals of **1•3** by diffusion from solution (Scheme 2). Prior to the diffusion of **4**, nitrobenzene that filled the pores of as-synthesized **1•3** was replaced with a more fluid solvent[9] such as cyclohexane by immersing the as-synthesized crystals **1•3** in the solvent for 1 d. Subsequently the crystal was immersed in

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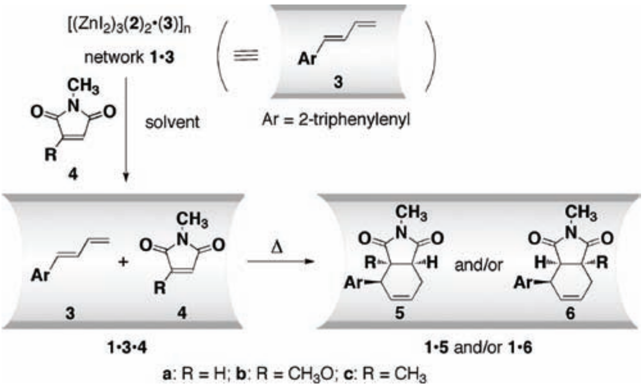
Scheme 2. Diels−Alder Reactions via Molecular Recognition within the Network 1



0.050 M cyclohexane solution of **4a** for 1 h at room temperature to give inclusion complex **1•3•4a**. In a similar way, inclusion complexes **1•3•4b** and **1•3•4c** were prepared. Enclathration of **4a**−**c** in the pores was confirmed by the microscopic FT-IR spectra of the crystals of the inclusion complexes **1•3•**(**4a**−**4c**), which exhibited a new band at 1709−1715 cm^{-1} attributable to the carbonyl stretching vibration of **4a**−**c** (Figure S1).

For inclusion complex **1•3•4b**, the inclusion geometry was directly analyzed by X-ray crystallography. The crystal structure of **1•3•4b** exhibits a well-aligned maleimide **4b** in pore A. The two carbonyl oxygens of **4b** are in close proximity with the edges of two triazine ligands **2**, which are located across **4b** and are almost cofacial with respect to **4b** (Figure 2a). The substrate **4b** is well-recognized by multiple C−H•••O hydrogen bonds[10] between the carbonyl oxygen of **4b** and Py-H_β proton of ligand **2** (Figure 2c). From the modeled H_β positions, the H•••O distances were estimated to be 2.59−2.88 Å. The diene moiety of **3** is located in parallel above and below the dienophile **4b** with an interfacial separation of <4.0 Å, ideal for the Diels−Alder reactions.

The computed electrostatic potential surfaces of Diels−Alder reactants **3**, **4b**, and triazine ligand **2** provide a qualitative understanding of the observed molecular recognition. One can expect an attractive interaction between the electron-rich π clouds of **3** and the electron-deficient triazine core of **2**. Additionally, Py-H_β protons of ligand **2** exhibit good hydrogen bond donor abilities and can interact with carbonyl groups of **4b** (Figure 3).

The suitable orientation of the substrates **3** and **4** in the pore allows us to predict their enhanced Diels−Alder reactivity. In fact, a facile Diels−Alder reaction in the pore was observed when the inclusion complexes **1•3•4** were heated. For **4a**, the inclusion complex **1•3•4a** was heated under reflux in cyclohexane. After 2 h, sampled crystals were digested with HCl, and after extraction, the quantitative formation of the Diels−Alder adduct **5a** with endo stereochemistry was confirmed by NMR spectroscopy. In a control experiment in a cyclohexane solution, the reaction conversion after 2 h was only 21%.

Since the reaction proceeded in a single-crystal-to-single-crystal fashion, the crystal structure after the reaction was directly analyzed by X-ray crystallography. As expected, the reaction occurred without large motion of the substrates **3** and **4a** and the endo stereochemistry of the adduct **5a** was unambiguously determined (Figure 2d).

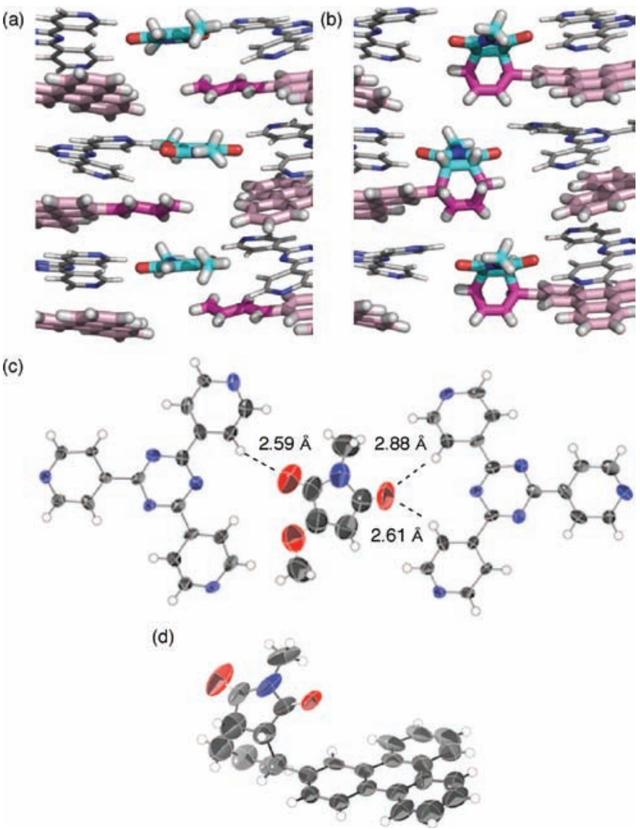


Figure 2. Crystallographic observation of the Diels−Alder reaction in the pore of complex **1**. Side views at pore A of (a) **1•3•4b** (before reaction) and (b) **1•5a** (after reaction). (c) Recognition of **4b** by the CH•••O hydrogen bonds in **1•3•4b** (d) Diels−Alder adduct **5a** formed in pore A (ORTEP; 50% probability level).

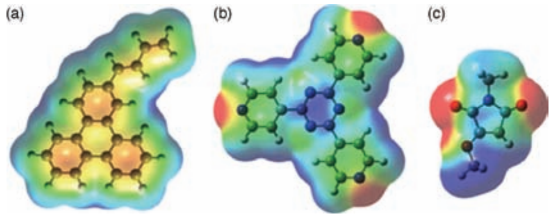


Figure 3. Electrostatic potential surfaces of (a) diene **3**, (b) triazine ligand **2**, and (c) maleimide **4b**. The structures are optimized at the B3LYP/6-31G* level. Red and blue represent negative and positive charge density, respectively. The plot scales have been set to the same color scale.

The enhanced Diels−Alder reactivity was more prominently observed with dienophile **4b**. The crystals of inclusion complex **1•3•4b** were heated under reflux in toluene for 7 d to give adduct **5b** in 80% yield after isolation from the crystals. The regioselective formation of so-called "*o*-isomer" **5b** is explained by orbital control. In stark contrast to the reaction within the pores, the Diels−Alder adduct was not formed in control experiments in solution or even under neat conditions because the energy level of the LUMO is increased by the methoxy substituent. Addition of ZnI$_2$ or triazine ligand **2** to the solution reaction did not result in the formation of **5b** (Figure S2). This enhanced reactivity in the network is ascribed to a reduction in the entropy cost by the preorganization of the substrates at suitable positions via molecular recognition.

Harnessing this preorganization, the regioselectivity was inverted within network **1**. For the 2-methyl derivative **4c**, a control experiment in refluxing CCl_4 solution resulted in the exclusive formation of the normal regioisomer **5c** (though conversion was only 7% even after 24 h). However, when the inclusion complex **1•3•4c** was heated under reflux for 24 h, the electronically unfavorable "*m*-isomer" **6c** was dominantly formed over the normal "*o*-isomer" **5c** (**5c**/**6c** = 40:60; 94% conversion).

This observed regioselectivity within network **1** can be also rationalized by the guest recognition process. Two diene partners **3** exist above and below the entrapped dienophile **4c**: one affords an orbitally favored adduct while another affords a sterically favored adduct (Figure S5). With methoxy substituted **4b**, only the orbitally favored pathway is selected because of the strong electronic effect of the substituent. Therefore, electronically favored **5b** was formed with high selectivity. In contrast, the electronic effect of the methyl group in **5c** is much weaker and thus a sterically favored pathway becomes competitive, bringing about a slight preference for **6c** over **5c**.

In summary, we have achieved crystalline state Diels−Alder reactions via precise molecular recognition within the porous coordination network. X-ray crystallographic analyses revealed that the orientation of the diene and dienophile were highly controlled prior to the reactions. Unlike diffusion-driven guest uptake by most common porous networks, our crystalline molecular flask can capture the guests through host−guest interactions (donor−acceptor stacking, H-bonding, etc.). These unique features of the crystalline flasks make possible (1) stoichiometric guest inclusion into crystals without guest disorder, (2) regio- and stereocontrolled transformations with high conversion, (3) X-ray observation of the reaction, and hence, (4) understanding the mechanistic insights of the reaction based on X-ray analysis. Further research into developing new regio- and stereocontrolled reactions in the pores, coupled with in situ crystallography, is now in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and physical properties of the compounds, including crystal structural data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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