

Remarkable Acceleration of Diels–Alder Reactions in a Self-Assembled Coordination Cage

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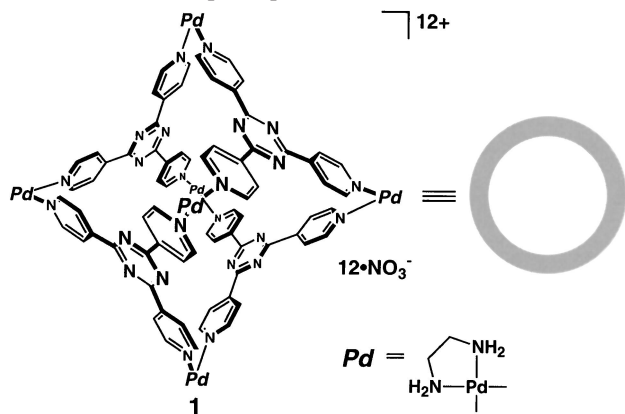
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(Received November 25, 2002; CL-021000)

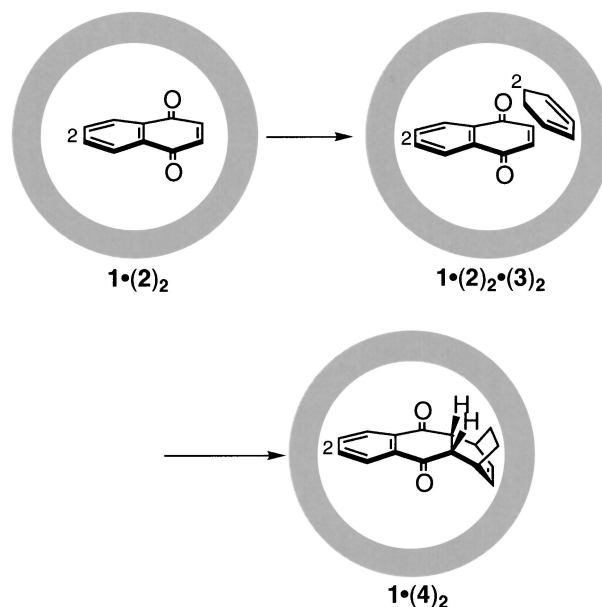
Self-assembled coordination cage **1** was found to accelerate Diels–Alder reactions in an aqueous media: e.g., 113-fold acceleration was observed in the reaction of isoprene with naphthoquinone.

Stabilization and activation of molecules enclathrated in cage compounds have recently attracted considerable attention in the Host–Guest chemistry.^{1,2} Acceleration of Diels–Alder reactions by artificial receptor molecules has been reported recently in hydrogen bond receptor systems³ and porphyrin receptor systems.⁴ However, in most cases the reaction was accelerated in organic solvents and the cavities are too small to bind large molecules.

Recently, coordination cage **1** that assembles from six metal ions and four ligands has been shown to strongly bind a variety of neutral guest molecules⁵ and promotes chemical transformations such as photodimerization,⁶ olefin oxidation,⁷ and silanol polycondensation.⁸ Here we report the remarkable ability of cage **1** for the acceleration of Diels–Alder reaction in an aqueous media. The cavity of cage **1** provides an isolated space which is large enough to promote the Diels–Alder reaction of medium to large molecules such as naphthoquinone (Scheme 1).



The acceleration effect was demonstrated by the room temperature Diels–Alder reaction of naphthoquinone (**2**) and 1,3-cyclohexadiene (**3**) in the presence of cage **1**: A suspension of naphthoquinone **2** (4.0×10^{-2} mmol) in hexane (0.5 mL) was stirred with a solution of **1** in D₂O (5.0 mM, 1.0 mL) at 25 °C for 0.5 h. The two phases were separated. Analysis of the aqueous phase by NMR spectroscopy showed the stoichiometric formation of **1**·(**2**)₂ complex (Figure 1a). The enclathration of **2** in the cage of **1** was supported by the significant upfield shifting of signals of **2** appearing around 6 ppm. The 1:2 stoichiometry was confirmed by the integration ratio of signals of **1** and **2** in the ¹H NMR spectrum. To this solution, 1,3-cyclohexadiene (**3**, 10 equiv. to **1**) was added (Figure 1b) and the mixture was stirred at



Scheme 1.

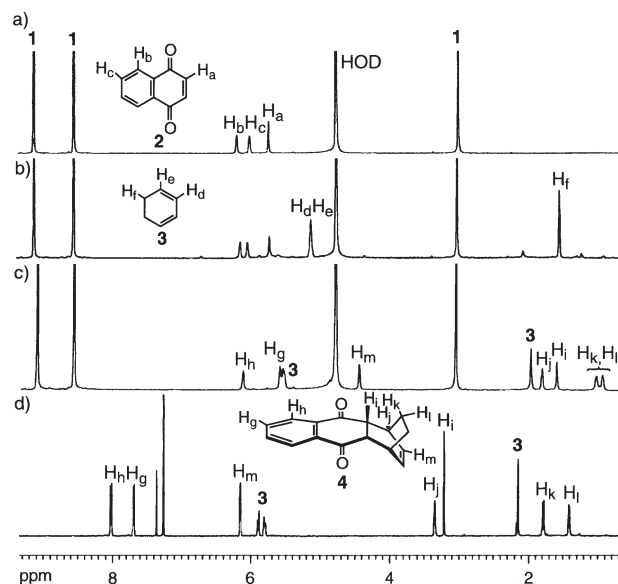


Figure 1. ¹H NMR monitoring of the D₂O phase in the Diels–Alder reaction of 1,4-naphthoquinone (**2**) and 1,3-cyclohexadiene (**3**). (a) Only 2 equiv. of naphthoquinone was enclathrated in the cavity of **1**. (b) 10 equiv. (vs **1**) of 1,3-cyclohexadiene was added to the solution. (c) After stirred at 25 °C for 24 h. (d) After being extracted with CDCl₃, was identified as Diels–Alder adduct **4**.

room temperature for 24 h. ^1H NMR showed the quantitative formation of a single product (Figure 1c), whose signals are also upfield shifted. After extraction with CDCl_3 , the product was isolated in a high yield as a sole product and was assigned as the Diels–Alder endo-adduct **4** by NMR (Figure 1d).⁹

Control experiments clearly showed that the reaction is remarkably accelerated by cage **1**. As shown in Figure 2a, the reactions in water suspension was much less efficient.^{10,11} Comparison of the reaction rates showed that the reaction was 21-fold accelerated by the addition of cage **1**. In CHCl_3 , the reaction was hardly promoted even at elevated temperature (80°C , 2–3 h). Even under neat conditions, the reaction was poorly promoted.¹²

The reaction was more dramatically accelerated when an acyclic diene, 2-methyl-1,3-butadiene (**5**) was employed: 113-fold acceleration was estimated for the reaction of **2** and **5** as shown in Figure 2b.¹³

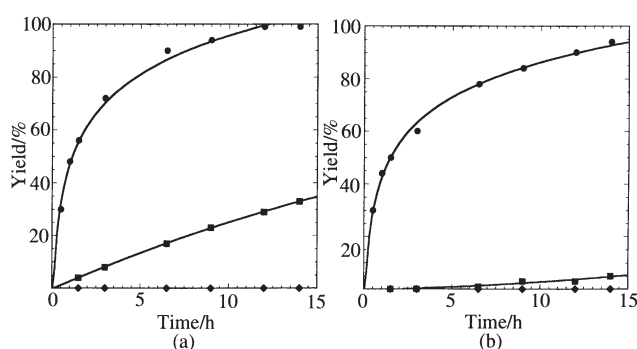


Figure 2. Time course of the Diels–Alder reactions of **2** with dienes **3** (a) and **5** (b) at 25°C . (●): in the presence of **1** in water, (■): in the absence of **1** in water, (◆): control experiment in CHCl_3 .

Interestingly, NMR study showed that the two substrates were enclathrated in a 2:2 stoichiometry in each cage regardless of the molar ratio of the substrates employed. Sharp guest signals (Figure 1b) also support the selective formation of $1\cdot(2)_2\cdot(3)_2$ complex. We suggest that the cavity binds more hydrophobic substrate **2** to give $1\cdot(2)_2$ complex but not $1\cdot(2)_3$ or $1\cdot(2)_4$ because of the steric demand of **2**. Subsequently, two molecules of smaller guest **3** will fill the remaining space to give rise to $1\cdot(2)_2\cdot(3)_2$ complex selectively. Such a pairwise selective enclathration of two different guests has been also discussed in hydrogen¹⁴ and coordination bond systems.¹⁵

The acceleration of the reaction in cage **1** is thus mostly interpreted by the pair-selective preorganization of the two substrates in the cage that reduces the entropy cost of the pericyclic reaction. Electronic interactions between the cationic cage and the substrates in the transition state may be also considered.

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- A suspension of naphthoquinone **2** (1.00×10^{-2} mmol) and 1,3-cyclohexadiene **3** (1.00×10^{-2} mmol) in H_2O (1 mL) was stirred at 25°C for 24 h. After extraction with CDCl_3 , the organic phase was monitored by ^1H NMR.
- A suspension of naphthoquinone **2** (0.19 mmol) in 1,3-cyclohexadiene **3** (5.25 mmol) was stirred at 25°C for 6 h. ^1H NMR showed the formation of **4** in 15% yield.
- Under similar condition as described for **3**, $1\cdot(2)_2\cdot(5)_2$ complex was also observed.
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