DOI: 10.1002/ejoc.201300652

Hexameric Capsule of a Resorcinarene Bearing Fluorous Feet as a Self-Assembled Nanoreactor: A Diels–Alder Reaction in a Fluorous Biphasic System

Shoichi Shimizu,*[a] Asuka Usui,[a] Masae Sugai,[a] Yuki Suematsu,[a] Seiji Shirakawa,[b] and Hayato Ichikawa[a]

Keywords: Calixarenes / Perfluorinated solvents / Solvent effects / Self-assembly / Supramolecular chemistry

A Diels–Alder reaction in a fluorous biphasic system was accelerated by a hexameric capsule of resorcinarene bearing fluorous feet. The reaction takes place predominantly within the capsule, which can be recovered as a fluorous solution and recycled after simple decantation.

Introduction

Artificial receptor molecules and self-assembled molecular structures have attracted considerable attention over the past two decades because of potential applications in many branches of supramolecular chemistry.[1] In particular, many research groups have intensively investigated the application of self-assembled nanocapsules based on non-covalent bonds such as hydrogen bonds and metal–ligand interactions as nanoreactors.[2] These nanocapsules bear an internal cavity, and their interior can provide new and specific chemical environments. Indeed, in most cases remarkable acceleration of the reactions and/or change in selectivity were observed as a result of the steric requirements of the host's cavity. Selectivity rarely approached the level observed in natural enzymes.[3] However, catalytic turnover was inhibited because of the binding of the products, with the exception of a limited number of self-assembled nanocapsules,[3b,4–9] particularly a few that involved carbon–carbon bond-forming reactions.[3b,4b,5a,5c,7,8]

The use of highly fluorinated and perfluorinated (fluorous) solvents and reagents has grown over the past decade. Most perfluoroaliphatic solvents are not miscible even with the most common organic solvents at room temperature. At elevated temperatures, however, a homogeneous system is formed, which separates again on cooling. Since Horváth and Rábai developed a fluorous biphasic system for the recycling of a fluorous catalyst through a liquid–liquid separation process,[9] the unique solubilizing properties have solved numerous problems in synthesis, catalysis, and molecular recognition/assembly.[10] Recently, we also demonstrated that a resorcinarene bearing fluorous feet (i.e., **1**) was soluble in wet fluorous solvents owing to the formation of hexameric capsules, $\mathbf{1}_6\cdot(H_2O)_8$,[11] and that in fluorous solvents these capsules exhibit more selective and/or enhanced properties as a result of fluorophobic effects through encapsulation (Figure 1).[12]

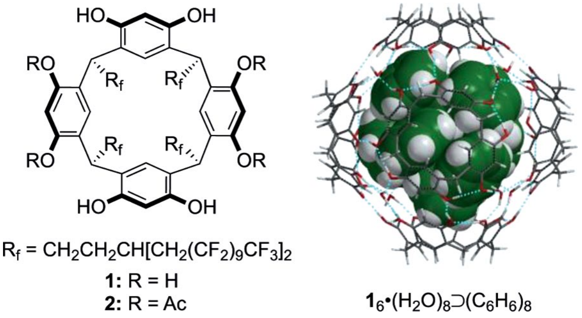


Figure 1. Structures of Teflon-footed resorcinarene **1** and tetraacetyl derivative **2** and model of hexameric assembly $\mathbf{1}_6\cdot(H_2O)_8$, encapsulating eight benzene molecules. Peripheral highly fluorinated alkyl groups (R_f) are removed for clarity.

In this context, it was hypothesized that supramolecular capsules may more effectively accelerate a reaction in fluorous solvents than in organic solvents. Furthermore, provided that an adequate release rate of the product from the capsule is realized at the reaction temperature without an extinguishing rate acceleration by the fluorophobic effect, a substantial catalytic turnover may be attained. Herein, we report the application of fluorous resorcinarene **1** to a Diels–Alder reaction in a fluorous biphasic system to realize an efficient catalytic reaction within a nanocapsule.

---

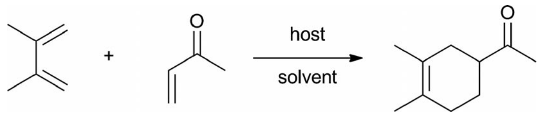
[a] Department of Applied Molecular Chemistry
College of Industrial Technology, Nihon University
Izumi-cho, Narashino, Chiba 278-8575, Japan
E-mail: shimizu.shouichi@nihon-u.ac.jp
Homepage: http://www.cit.nihon-u.ac.jp/
[b] Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502, Japan

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300652.

Results and Discussion

Initially, the activity of fluorous resorcinarene **1** was examined by conducting the model Diels–Alder reaction in perfluorohexane (FC-72), and the results are summarized in Table 1. Treatment of methyl vinyl ketone with 2,3-dimethyl-1,3-butadiene in FC-72 at 50 °C for 6 h afforded only a small amount of adduct (10%; Table 1, Entry 9), which is comparable to that afforded under neat reaction conditions (13%; Table 1, Entry 11). However, in the presence of fluorous resorcinarene **1**, the yield of the adduct increased to 74% (Table 1, Entry 5). Kumar and coworker[13] reported that Diels–Alder reactions of *N*-ethylmaleimide with 9-(hydroxymethyl)anthracene showed drastic rate accelerations in fluorous solvents with enhancements approaching those in water.[14] In the absence of **1**, no such fluorous acceleration was observed in this reaction, because the diene had no functional substituent to form a hydrogen bond with the dienophile in the transition state.[15] This acceleration has been attributed to catalysis by the cavity of $\mathbf{1}_6{\cdot}(H_2O)_8$ as a self-assembled nanoreactor and/or to acid catalysis by the hydroxy groups of **1**. No rate acceleration was observed when tetraacetylated resorcinarene **2** was added to the reaction mixture as a monomeric counterpart of **1**, as **2** could not form a hexameric capsule (Table 1, Entry 8). Consequently, it is clear that the cavity of hexameric capsule $\mathbf{1}_6{\cdot}(H_2O)_8$ provides an isolated space that promotes the Diels–Alder reaction and attains efficient catalytic turnover (38 times; Table 1, Entry 5); thus, the reaction takes place preferentially in the cavity of $\mathbf{1}_6{\cdot}(H_2O)_8$.[16] Incidentally, adequate yields were obtained at reaction tempera-

Table 1. Diels–Alder reaction.[a]



Entry	Host (mol-%)	Solvent	T [°C]	Time [h]	Yield [%][b]
1	**1** (10)[c]	FC-72	60	4	61
2	**1** (10)	FC-72	50	4	62
3	**1** (10)	FC-72	40	4	37
4	**1** (10)	FC-72	50	8	73
5	**1** (10)	FC-72	50	6	74
6	**1** (5)	FC-72	50	6	56
7	**1** (2.5)	FC-72	50	6	38
8	**2** (10)	FC-72	50	6	<18
9	none	FC-72	50	6	10
10	none	THF	50	6	<18
11	none	none	50	6	13

[a] Reaction conditions: 2,3-dimethyl-1,3-butadiene (4.9 mmol, 10 equiv.), 3-buten-2-one (0.49 mmol), host compound, H_2O (0.30 µL, 1.7×10^{-2} mmol), solvent (2.0 mL), 800 rpm. [b] Isolated yield. [c] $\mathbf{1}_6$ (1.67 mol-%).

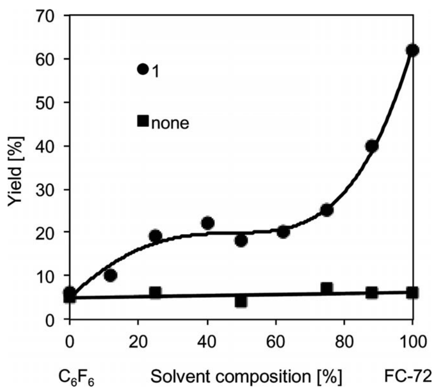
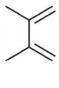
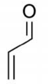
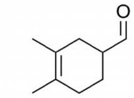
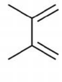
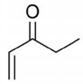
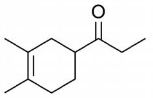
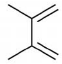
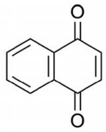
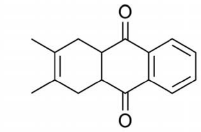
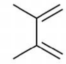
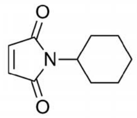
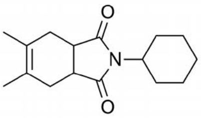
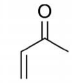
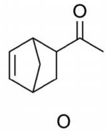
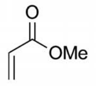
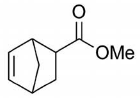
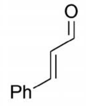
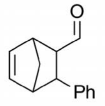
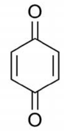
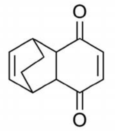
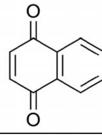
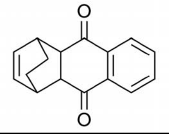


Figure 2. Effect of the solvent on the yield of Diels–Alder adduct for the reaction of methyl vinyl ketone with 2,3-dimethyl-1,3-butadiene.

Table 2. Diels–Alder reaction using various reagents.[a,b]

Entry	Diene	Deinophile	Product	Yield [%][c]	*endo*/*exo*[d]
1				63 (3)	– (–)
2				61 (<19)	– (–)
3				93 (6)	– (–)
4[e]				64 (5)	– (–)
5[e,f]				67 (29)	7.7:1 (5.6:1)
6[e]				55 (23)	5.5:1 (2.9:1)
7				28 (10)	1.2:1 (0.85:1)
8[e]				78 (15)	*endo* (*endo*)
9[e,g]				35 (7)	*endo* (*endo*)

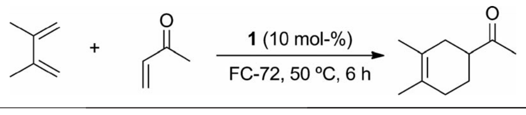
[a] Reaction conditions: diene (4.9 mmol, 10 equiv.), dienophile (0.49 mmol), $\mathbf{1}_6$ (1.67 mol-%), H_2O (0.30 µL, 1.7×10^{-2} mmol), FC-72 (2.0 mL), 50 °C, 6 h, 800 rpm. [b] Yield and *endo*/*exo* ratio in parentheses were obtained in a control reaction without **1**. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy (400 MHz). [e] Diene (1.0 equiv.). [f] Reaction time = 2 h. [g] Reaction time = 24 h.

tures higher than or equal to 50 °C, probably because FC-72 shows fair miscibility with the reactants at 50 °C (Table 1, Entries 1–3).

The effect of fluorous solvents on the reaction rate was examined for various C_6F_6/FC-72 solvent ratios (Figure 2).[17] It is interesting that in the absence of **1**, the yield was not affected by changes in the FC-72 content of the solvent. However, if the same reaction was carried out in the presence of hexameric capsule $\mathbf{1}_6\cdot(H_2O)_8$, the yield increased as the fluorous content was increased with a plateau region at approximately 50% FC-72 (C_6F_6/FC-72 = 1:1, v/v). The increase in yield was attributed to an increase in the association constant[12] of the capsule for the reactants because of fluorophobic effects. Those effects can be thought of as a reflection of the higher concentration of the reactants and a higher internal pressure inside the cavity of the capsule. Thus, the increase indicates that the reaction takes place predominantly within the cavity of the hexameric capsule. Furthermore, the nonlinear increase in the yield can be mainly correlated to preferential solvation of the interior and exterior of the hexameric capsule with C_6F_6 and FC-72. That is, it could be associated with preferential encapsulation of C_6F_6 molecules by the capsule and competition with the substrate molecules.

To probe the scope of the diene and dienophile components of the reaction in a fluorous biphasic system, nine other Diels–Alder reactions were conducted (Table 2). In all reactions, a rate acceleration (2.3- to 21-fold increase in yield) was observed in the presence of a hexameric capsule [1.67 mol-% as $\mathbf{1}_6\cdot(H_2O)_8$], and the corresponding adducts were obtained. Bulkier adducts were formed in low yields, which may be ascribed to steric factors (Table 2, Entries 7 and 9). Moreover, the presence of the hexameric capsule gave rise to higher *endo*/*exo* ratios than those obtained in the control reactions. For instance, in the reaction between methyl acrylate and cyclopentadiene, the *endo*/*exo* ratio increased from 2.9:1 to 5.5:1 (Table 2, Entry 7). The increase in the *endo* selectivity indicates that the reaction took place predominantly in the cavity of the hexameric capsule and that the internal pressure was rather high, because a high internal pressure in a water solution favors a more compact transition state, which results in the formation of the *endo* adduct.[18]

Table 3. Recovery and reuse of **1** in FC-72.[a]



Entry	Host **1**[b]	Yield [%][c]
1	1st use	50
2	2nd use	55
3	3rd use	61
4	4th use	58
5	5th use	60

[a] Reaction conditions: 2,3-dimethyl-1,3-butadiene (4.9 mmol, 10 equiv.), 3-buten-2-one (0.49 mmol), H_2O (0.30 µL, 1.7×10^{-2} mmol), FC-72 (2.0 mL), 50 °C, 6 h, 800 rpm. [b] $\mathbf{1}_6$ (1.67 mol-%). [c] Isolated yield.

The feasibility of the recovery and reuse of the fluorous resorcinarene in a fluorous solvent (FC-72) was evaluated. The results are summarized in Table 3. Although the yields of the adduct were rather low because of the lack of an extraction procedure, the activity of the hexameric capsule was retained after being consecutively recycled, even in the fifth run, and the yield was practically identical to that observed if a fresh hexameric capsule was used (Table 3, Entries 1–5).

Conclusions

We demonstrated herein that a hexameric capsule of resorcinarene bearing fluorous feet accelerates a Diels–Alder reaction much more effectively in a fluorous biphasic system than in an organic homogeneous system. The reaction takes place predominantly within the capsule, which can be recovered as a fluorous solution and recycled after simple decantation. Thus, as the concept of a fluorous biphasic system was effective in the Diels–Alder reaction with a supramolecular capsule, this tool provides the possibility of a new catalytic process through supramolecular catalysis.

Experimental Section

Typical Procedure for the Diels–Alder Reactions: Diene (4.9 mmol), dienophile (0.49 mmol), and H_2O (0.30 µL) were added to a solution of **1** (0.049 mmol in the case of 10 mol-%) in FC-72 (2 mL), and the mixture was stirred at 800 rpm at 50 °C for 4–8 h. The reaction mixture was diluted with FC-72 (5 mL), extracted with $CHCl_3$ (5 mL), and washed with FC-72 (5 mL). The combined extract was dried with anhydrous $MgSO_4$, and the solvents were evaporated. The product was purified by preparative GPC.

2: R_f = 0.16 [hexane/EtOAc/HFE-7100, 2:7:1 (v/v)], m.p. 56–57 °C. ^{1}H NMR [400 MHz, $(CD_3)_2CO/C_6F_6$, 3:1 (v/v)]: δ = 7.60 (br. s, 4 H), 7.34 (s, 2 H), 7.08 (br. s, 2 H), 6.68 (s, 2 H), 6.00 (br. s, 2 H), 4.62 [t, ^3J(H,H) = 7.6 Hz, 4 H], 2.68 (br. s, 4 H), 2.54–2.18 (m, 36 H), 1.76 (br. s, 8 H) ppm. Partial ^{13}C NMR [125 MHz, $(CD_3)_2CO/C_6F_6$, 3:1 (v/v)]: δ = 170.0, 154.7, 148.4, 135.3, 126.9, 126.7, 123.0, 118.3, 103.1, 36.0, 35.6 [t, ^2J(C,F) = 21.1 Hz], 34.4, 33.6, 27.2, 21.2 ppm. IR (KBr): $\tilde{\nu}$ = 3448, 2950, 2877, 1215, 1153, 652, 555 cm^{-1}. $C_{139}H_{64}F_{168}O_{12}$ (5081.69): calcd. C 32.14, H 1.27; found C 31.80, H 1.25.

Recycling Experiment: 2,3-Dimethyl-1,3-butadiene (4.9 mmol), 3-buten-2-one (0.49 mmol), and H_2O (0.30 µL) were added to a solution of **1** (0.049 mmol) in FC-72 (2 mL), and the mixture was stirred at 800 rpm at 50 °C for 6 h. The mixture was allowed to stand at 0 °C for 1 h, and then the fluorous phase (FC-72) containing $\mathbf{1}_6\cdot(H_2O)_8$ was transferred by syringe to a new flask for direct reuse in the next cycle. From the remaining organic phase, the product was isolated by preparative GPC.

Supporting Information (see footnote on the first page of this article): Synthetic route for **2**, characterization data and spectra of **2** and its synthetic intermediates, characterization data of the Diels–Alder adducts.

Acknowledgments

This work was supported by the Japan Society for the Promotion of Science (JSPS), through a Grant-in-Aid for Scientific Research (C) (no.22550125).

---

[1] a) P. W. N. M. van Leeuwen (Ed.), *Supramolecular Catalysis*, Wiley-VCH, Weinheim, **2008**; b) T. Schrader, A. D. Hamilton (Eds.), *Functional Synthetic Receptors*, Wiley-VCH, Weinheim, **2005**; c) J. W. Steed, J. L. Atwood in *Supramolecular Chemistry*, Wiley, Chichester, **2000**; d) J.-M. Lehn in *Supramolecular Chemistry*, VCH, Weinheim, **1995**; e) D. J. Cram, J. M. Cram in *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, **1994**.

[2] For reviews, see: a) M. J. Wiester, P. A. Ulmann, C. A. Mirkin, *Angew. Chem.* **2011**, *123*, 118–142; *Angew. Chem. Int. Ed.* **2011**, *50*, 114–137; b) M. Yoshizawa, J. K. Klosterman, M. Fujita, *Angew. Chem.* **2009**, *121*, 3470–3490; *Angew. Chem. Int. Ed.* **2009**, *48*, 3418–3438; c) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2009**, *42*, 1650–1659; d) T. S. Koblenz, J. Wassenaar, J. N. H. Reek, *Chem. Soc. Rev.* **2008**, *37*, 247–262; e) D. M. Vriezema, M. C. Aragonès, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, *Chem. Rev.* **2005**, *105*, 1445–1489; f) J. Rebek Jr., *Angew. Chem.* **2005**, *117*, 2104–2115; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068–2078; g) M. Yoshizawa, M. Fujita, *Pure Appl. Chem.* **2005**, *77*, 1107–1112; h) M. Hof, S. L. Craig, C. Nuckolls, J. Rebek Jr., *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508.

[3] a) M. Yoshizawa, M. Tamura, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 8160–8161; b) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251–254.

[4] a) M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85–88; b) D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2004**, *116*, 6916–6919; *Angew. Chem. Int. Ed.* **2004**, *43*, 6748–6751; c) C. J. Brown, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2009**, *131*, 17530–17531.

[5] a) T. Murase, Y. Nishijima, M. Fujita, *J. Am. Chem. Soc.* **2012**, *134*, 162–164; b) M. Yoshizawa, N. Sato, M. Fujita, *Chem. Lett.* **2005**, *34*, 1392–1393; c) T. Kusukawa, T. Nakai, T. Okano, M. Fujita, *Chem. Lett.* **2003**, *32*, 284–285; d) H. Ito, T. Kusukawa, M. Fujita, *Chem. Lett.* **2000**, *29*, 598–599.

[6] M. L. Merlau, M. P. Mejia, S. T. Nguyen, J. T. Hupp, *Angew. Chem.* **2001**, *113*, 4369–4372; *Angew. Chem. Int. Ed.* **2001**, *40*, 4239–4242.

[7] J. Kang, J. Santamaría, G. Hilmersson, J. Rebek Jr., *J. Am. Chem. Soc.* **1998**, *120*, 7389–7390.

[8] Recent literature has demonstrated that the encapsulated (N-heterocyclic carbene)–Au catalyst within a self-assembled, hydrogen-bonded hexameric capsule changes the selectivity of a reaction significantly by the second-sphere environment around the active site, as displayed by enzymes: A. Cavarzan, A. Scarso, P. Sgarbossa, G. Strukul, J. N. H. Reek, *J. Am. Chem. Soc.* **2011**, *133*, 2848–2851.

[9] I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72–75.

[10] For reviews, see: a) J.-M. Vincent, *J. Fluorine Chem.* **2008**, *129*, 903–909; b) J. A. Gladysz, D. P. Curran, I. T. Horváth in *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, **2004**; c) P. Kirsch in *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**, pp. 171–202.

[11] For a review on calixarene capsules, see: L. Avram, Y. Cohen, J. Rebek Jr., *Chem. Commun.* **2011**, *47*, 5368–5375.

[12] S. Shimizu, T. Kiuchi, N. Pan, *Angew. Chem.* **2007**, *119*, 6562–6565; *Angew. Chem. Int. Ed.* **2007**, *46*, 6442–6445.

[13] K. E. Mayers, K. Kumar, *J. Am. Chem. Soc.* **2000**, *122*, 12025–12026.

[14] a) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–164; b) D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

[15] J. I. García, J. A. Mayoral, L. Salvatella, *J. Org. Chem.* **2005**, *70*, 1456–1458.

[16] To obtain circumstantial evidence that the reaction takes place in the cavity of $\mathbf{1}_6\cdot(H_2O)_8$, we studied encapsulation of the substrates, methyl vinyl ketone and 2,3-dimethyl-1,3-butadiene, by the capsule in FC-72. If 2,3-dimethyl-1,3-butadiene was used as the sole guest at a molar ratio of 7.2:1 (diene/**1**), the methyl signal of the encapsulated diene appeared at $\delta = 0$ ppm with an upfield shift of about 1.4 ppm. Integration of the signal showed that an average of 4.6 diene molecules was detained in the capsule. To our surprise, in the case of methyl vinyl ketone at a molar ratio of 7.1:1 (dienophile/**1**), only a trace of the methyl signal of the encapsulated dienophile appeared at $\delta = 0.78$ ppm with an upfield shift of about 0.9 ppm. However, if both the diene and dienophile were used as double guests at a molar ratio of 100:1:1 (diene/dienophile/**1**), integration of the signals showed that 0.63 diene and 10.8 dienophile molecules were detained in the capsule at the same time. This result indicates that the presence of 2,3-dimethyl-1,3-butadiene promotes encapsulation of methyl vinyl ketone by the capsule in the fluorous FC-72 solvent. That is, a large excess amount of the diene may improve solubility of the dienophile in the fluorous solvent.

[17] In the solvent-effect experiments, before being submitted to the reaction conditions the reaction mixtures were homogeneous even at room temperature if the solvent contained less than 40% FC-72.

[18] a) R. Breslow, U. Maitra, *Tetrahedron Lett.* **1984**, *25*, 1239–1240; b) R. Breslow, U. Maitra, D. Rideout, *Tetrahedron Lett.* **1983**, *24*, 1901–1904.

Received: May 4, 2013