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Highly Efficient Cucurbit[8]uril-Templated Intramolecular Photocycloaddition of 2-Naphthalene-Labeled Poly(ethylene glycol) in Aqueous Solution

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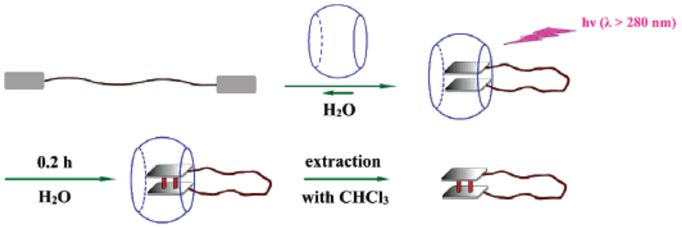

The photodimerization of water-insoluble 2-naphthalene-labeled poly(ethyl glycol) (**N-P$_n$-N**) in cucurbit[8]uril (CB[8]) aqueous solution was investigated. UV−vis, fluorescence, and ^{1}H NMR analysis reveal that CB[8] can encapsulate **N-P$_n$-N** to make a stable 1:1 inclusion complex **N-P$_n$-N@CB[8]** in aqueous solution. Irradiation of **N-P$_n$-N** in the CB[8] aqueous solution results in *intramolecular* photocycloaddition with remarkable selectivity and efficiency, whereas no photodimer could be detected in host-free solution.

Introduction

Enzymes may bind substrates through multiple interactions in elaborate pockets, thereby forcing the substrates into orientations that favor the specific reaction paths, representing the highest expression of chemical reaction.[1] The astonishing selectivity and efficiency that enzymes achieve at modest temperature have stimulated chemists to mimic enzyme-like reactions that proceed within restricted cavities.[2−6] Cucurbit[*n*]uril (CB[*n*]),[7] featuring a hydrophobic cavity and polar carbonyl groups surrounding the portals, has a remarkable

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(1) (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. (b) Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1378. (c) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997. (d) Svoboda, J.; König, B. *Chem. Rev.* **2006**, *106*, 5413. (e) Huang, C. H.; Bassani, D. M. *Eur. J. Org. Chem.* **2005**, 4041.

(2) (a) Ramamurthy, V., Ed.; *Photochemistry in Organized and Constrained Media*; VCH: New York, 1991. (b) Ramamurthy, V.; Schanze, K., Eds., *Molecular and Supramolecular Photochemistry*; Marcel Dekker: New York, 2001. (c) Inoue, Y.; Ramamurthy, V., Eds.; *Chiral Photochemistry*; Marcel Dekker: New York, 2004.

(3) (a) Weiss, R. G.; Ramamurthy, V.; Hammond, G. S. *Acc. Chem. Res.* **1993**, *26*, 530. (b) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (c) Turro, N. J. *Acc. Chem. Res.* **2000**, *33*, 637. (d) Scheffer, J. R. *Can. J. Chem.* **2001**, *79*, 349. (e) Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppili, S.; Joy, A.; Ramamurthy, V. *Acc. Chem. Res.* **2003**, *36*, 509. (f) Tung, C. H.; Wu, L.-Z.; Zhang, L. P.; Chen, B. *Acc. Chem. Res.* **2003**, *36*, 39.

(4) (a) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741. (b) Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013. (c) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743. (d) Bortolus, P.; Monti, S. In *Photochemistry in Cyclodextrin Cavities*: *Advances in Photochemistry*; Neckers, D. C., Volman, D. H., Bunau, G. V., Eds.; John Wiley: New York, 1996; pp 1−133.

(5) (a) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (b) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 966. (c) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5338.

(6) (a) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50. (b) Harada, A.; Li, J.; Kamachi, M. *Nature* **1994**, *370*, 126. (c) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748. (d) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251. (e) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 7000. (f) Yoshizawa, M.; Takeyama, Y.; Kusukawa, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1347. (g) Kaliappan, R.; Kaanumalle, L. S.; Natarajan, A.; Ramamurthy, V. *Photochem. Photobiol. Sci.* **2006**, *5*, 925.

(7) (a) Mock, W. L. *Top. Curr. Chem.* **1995**, *175*, 1. (b) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621. (c) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844.

(8) (a) Jeon, W. S.; Ziganshina, A. Y.; Lee, J. W.; Ko, Y. H.; Kang, J.-K.; Lee, C.; Kim, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4097. (b) Ko, Y. H.; Kim, K.; Kang, J. K.; Chun, H.; Lee, J. W.; Sakamoto, S.; Yamaguchi, K.; Fettinger, J. C.; Kim, K. *J. Am. Chem. Soc.* **2004**, *126*, 1932. (c) Sindelar, V.; Silvi, S.; Kaifer, A. E. *Chem. Commun.* **2006**, 2185. (d) Sobransingh, D.; Kaifer, A. E. *Org. Lett.* **2006**, *8*, 3247. (e) Feng, K.; Wu, L.-Z.; Zhang, L. P.; Tung, C. H. *Dalton Trans.* **2007**, 3991.

(9) (a) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938. (b) Lee, J. W.; Kim, K. P.; Choi, S. W.; Ko, Y. H.; Sakamoto, S.; Yamaguchi, K.; Kim, K. *Chem. Commun.* **2002**, 2692.

10.1021/jo701998e CCC: $40.75

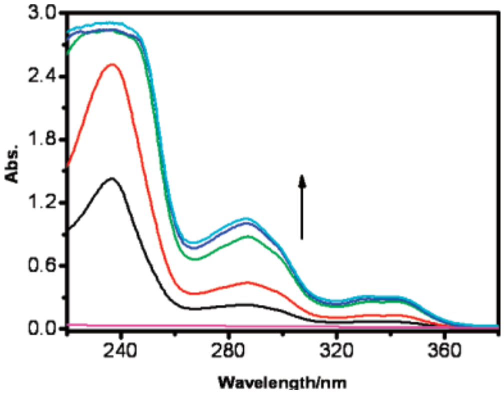
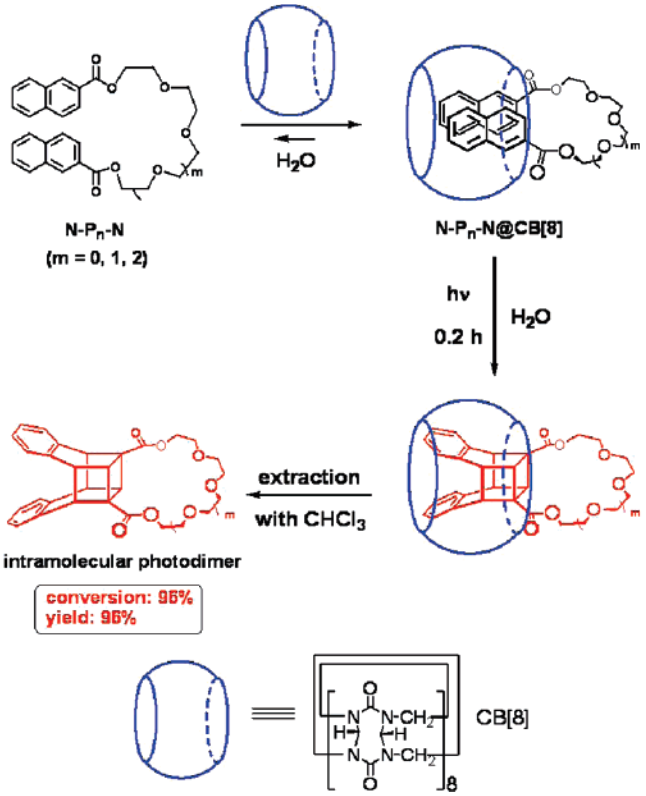


FIGURE 1. Absorption spectra of CB[8] (0.27 mM) with various concentration of **N-P$_4$-N** ([**N-P$_4$-N**]: 0, 0.17, 0.34, 0.68, 1.7, 2.0 equiv).

SCHEME 1. Cucurbit[8]uril-Templated Intramolecular Photocycloaddition of N-P$_n$-N in Aqueous Solution



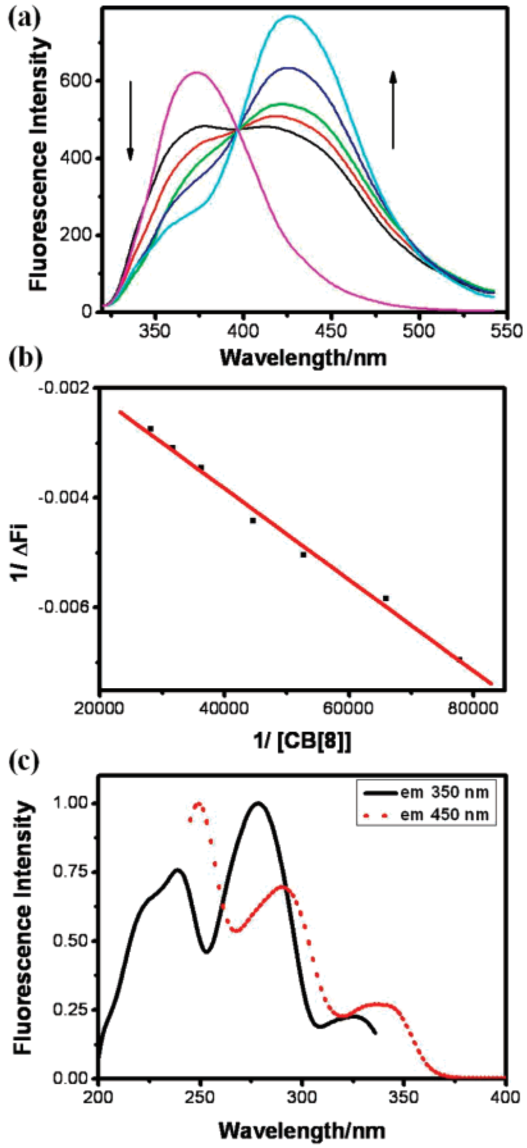


FIGURE 2. (a) Fluorescence spectra of **N-P$_4$-N** (19.8 μM) with various concentrations of CB[8] in aqueous solution (CB[8]: 0, 0.2, 0.4, 1.0, 2.0, 2.5 equiv). (b) Fluorescence spectral changes in intensity at 370 nm with the concentration of CB[8] excited at 286 nm. (c) Excitation spectra of **N-P$_4$-N@CB[8]** at λ_{em} = 350 (black) and 450 nm (red).

property of encapsulating hydrophobic or/and positively charged guest molecules in aqueous solution.[7−10] CB[8] is particularly attractive because it is able to accommodate two aromatic molecules within the cavity forming a 1:2 complex with desired orientations.[8−10] Kim[9] and Ramamurthy[10] recently found that CB[8] mediates intermolecular photodimerization of diaminostilbene, cinnamic acid, *trans*-1,2-bis(*n*-pyridyl)ethylenes, and stilbazoles either in the solid state or in aqueous solution. These studies prompted us to initiate a study on the photodimerization of a molecule with two reactive terminal aromatic groups separated by a long flexible chain. Can CB[8] be used as a template for exclusive *intramolecular* photodimerization of the included molecule?

With this in mind, we examined the interactions between CB[8] and water-insoluble neutral 2-naphthalene-labeled poly(ethylene glycol) (**N-P$_n$-N**, n = 3, 4, 5). The bifunctional **N-P$_n$-N** was selected as a typical reactant in this work because irradiation of alkyl 2-naphthoate gives a cubane-like photodimer in organic

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(10) (a) Pattabiraman, M.; Natarajan, A.; Kaanumalle, L. S.; Ramamurthy, V. *Org. Lett.* **2005**, *7*, 529. (b) Pattabiraman, M.; Natarajan, A.; Kaliappan, R.; Mague, J. T.; Ramamurthy, V. *Chem. Commun.* **2005**, 4542. (c) Pattabiraman, M.; Kaanumalle, L. S.; Natarajan, A.; Ramamurthy, V. *Langmuir* **2006**, *22*, 7605.

(11) (a) Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256. (b) Lei, L.; Wu, L.-Z.; Wu, X. L.; Liao, G. H.; Luo, L.; Zhang, L. P.; Tung, C. H.; Ding, K. L. *Tetrahedron Lett.* **2006**, *47*, 4725 and references cited therein. (c) Wu, X. L.; Lei, L.; Wu, L.-Z.; Liao, G. H.; Luo, L.; Shan, X. F.; Zhang, L. P.; Tung, C. H. *Tetrahedron* **2007**, *63*, 3133.

(12) (a) Tung, C. H.; Wu, L.-Z.; Yuan, Z. Y.; Su, N. *J. Am. Chem. Soc.* **1998**, *120*, 11594. (b) Tung, C. H.; Yuan, Z. Y.; Wu, L.-Z.; Weiss, R. G. *J. Org. Chem.* **1999**, *64*, 5156−5161. (c) Tung, C. H.; Wu, L. Z. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 1381. (d) Tung, C. H.; Li, Y.; Yang, Z. Q. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 947. (e) Xu, M.; Wu, L.-Z.; Zhang, L. P.; Tung, C. H. *Tetrahedron Lett.* **2001**, *42*, 9249−9252.

TABLE 1. The Binding Constant, Fluorescence Maximum, Conversion, and Quantum Yield for Photodimerization of N-P$_n$-N in Cyclohexane and CB[8] Aqueous Solution, Respectively

	N-P$_n$-N[a]				N-P$_n$-N@CB[8]				
n	λ_{em} [nm]	T_{irr}[b] [h]	conv [%]	Φ_{dim}[c] [%]	λ_{em} [nm]	K_a [M^{-1}]	T_{irr}[b] [h]	conv [%]	Φ_{dim}[c] [%]
3	371	2	8	2.2	430	4.0×10^3	0.25	94	30
4	373	2	10	2.5	433	6.0×10^3	0.25	96	37
5	370	2	11	2.6	431	1.6×10^4	0.25	96	40

[a] In cyclohexane. [b] Irradiation time. [c] The quantum yields for the product formation were determined by using the conversion for the photodimerization less than 15% at room temperature.

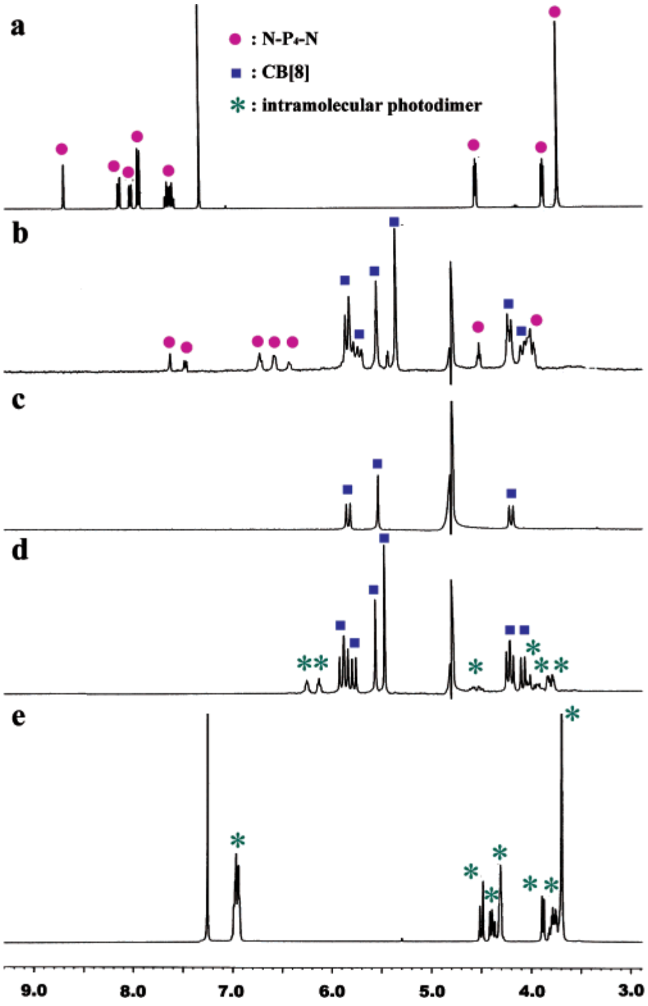

FIGURE 3. ^{1}H NMR spectroscopic analysis: (a) **N-P$_4$-N** in CDCl$_3$; (b) **N-P$_4$-N@CB[8]** in D$_2$O; (c) CB[8] in D$_2$O; (d) after irradiation of **N-P$_4$-N@CB[8]** for 30 min in D$_2$O; (e) after extraction with CDCl$_3$.

solvents.[11−12] More importantly, **N-P$_n$-N** may undergo either *intramolecular* or intermolecular reactions.[12] The former produces a macrocyclic ring-closure product, while the latter results in a dimer and oligomers. Generally, the *intramolecular* reaction can proceed in good chemical yields only at very low concentrations in solution since it suffers from the competition of polymerization. Owing to the hydrophilic character of poly(ethylene glycol) and the hydrophobic feature of naphthalene, we envision that CB[8] can capture the two terminal groups of **N-P$_n$-N** into its hydrophobic cavity to make a 1:1 inclusion complex like a molecular loop (Scheme 1). As a result, the intermolecular reaction of the bifunctional molecule might be prohibited, but the *intramolecular* photocycloaddition could proceed in high yield without competition.

In the present work, we report that CB[8] can interact with **N-P$_n$-N** forming highly stable 1:1 inclusion complexes of **N-P$_n$-N@CB[8]** in aqueous solution. Irradiation of **N-P$_n$-N** in CB[8] aqueous solution results in an exclusive *intramolecular* photocyclomer at room temperature (Scheme 1), while no intermolecular photodimers were detected by HPLC. Obviously, CB[8] is an effective reaction chamber to template the *intramolecular* photocycloaddition of **N-P$_n$-N** in aqueous solution. Such remarkable selectivity and rate acceleration are reminiscent of the behaviors of enzymes' pocket.

Results and Discussion

The interaction of CB[8] with **N-P$_n$-N** in aqueous solution was confirmed in terms of UV−vis, fluorescence, and ^{1}H NMR analysis. Compared with the host-free solution, the solubility and absorbance of **N-P$_4$-N** are remarkably enhanced (Figure 1), accompanied by a small red shift in the energy when it was added to a CB[8] aqueous solution. Strikingly, the fluorescent changes of **N-P$_4$-N** toward CB[8] are even more pronounced (Figure 2). In the absence of CB[8], **N-P$_4$-N** shows the monomer emission of 2-naphthoate. Progressive addition of CB[8] to **N-P$_4$-N** aqueous solution led to a growth with a maximum at ca. 430 nm (τ = 16.8 ns), typical excimer emission of naphthoate,[12] at the expense of the monomer emission at 370 nm (τ = 9.5 ns) (Figure 2a). The ratio of fluorescence intensities of excimer to monomer is independent of the concentration used (Figure S1, Supporting Information), suggesting that the excimer is *intramolecular*. The well-defined isoemissive point at 397 nm suggests that only **N-P$_4$-N** and **N-P$_4$-N@CB[8]** are present in the solution. Obviously, CB[8] encapsulates **N-P$_4$-N** to position the two end naphthalene groups in proximity. Figure 2b shows the plot of $1/\Delta F_i$ ($\Delta F_i = F_i - F_0$, where F_0 is the fluorescence intensity of **N-P$_4$-N** at 370 nm without CB[8] and F_i is the fluorescence intensity of **N-P$_4$-N** at 370 nm with various concentration of CB[8]). The linear plot (R = 0.9969) confirms the 1:1 interaction of host and guest and the binding constant was determined to be 6.0×10^3 M^{-1} according to eq 1. It is evident that the longer the poly(ether glycol) chain is, the higher the binding constant will be (Table 1). Such an enhancement may result from a combination of enhanced solubility and interaction of **N-P$_n$-N** and CB[8], respectively.

$$\frac{1}{\Delta F_i} = \frac{1}{K\alpha[\textbf{N-P}_4\textbf{-N}]}\frac{1}{[\mathrm{CB[8]}]} + \frac{1}{\alpha[\textbf{N-P}_4\textbf{-N}]} \qquad (1)$$

The excitation spectra for the monomer and excimer emissions, monitored at 350 and 450 nm, respectively, are generally similar. However, the spectrum for the latter is slightly but evidently red-shifted (Figure 2c). These observations further indicate that the excimer originates from the pairs of naphthalene groups that exist prior to the excitation. The other **N-P$_n$-N**

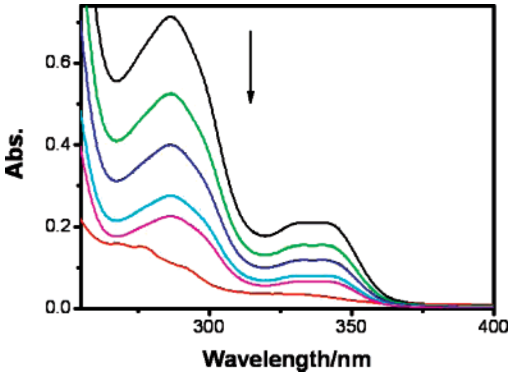

FIGURE 4. Absorption spectral changes of **N-P$_4$-N@CB[8]** with irradiation time (0 s, 25 s, 1 min, 3 min, 6 min, 12 min).

studied in this work show similar behavior (Figures S2−S9, Supporting Information).

The ^{1}H NMR spectrum of the 1:1 host/guest complex of **N-P$_n$-N** and CB[8] reveals encapsulation-induced upfield chemical shifts for the aromatic naphthoate resonances that are consistent with their inclusion in the shielding hydrophobic cavity.[8] The remainder of poly(ethylene glycol) resonances exhibit downfield shifts that result from the deshielding effect of the carbonyl groups of CB[8] on the portion of the guest that is located in the portal (Figure 3 and Supporting Information Figures S10−S12). Because no separate peaks for free and bound guests are observed, the rates for the encapsulating process are fast on the ^{1}H NMR spectroscopy time scale.

It is significant that irradiation of **N-P$_n$-N** in the presence of CB[8] is highly efficient and strictly selective. In general, the photochemical reaction was carried out in a Pyrex tube at room temperature. Irradiation of the 1:1 inclusion complexes of **N-P$_n$-N** and CB[8] quickly decreased the absorbance at the typical bands for **N-P$_n$-N@CB[8]** in aqueous solution. Figure 4 shows the typical spectral changes of **N-P$_4$-N@CB[8]** aqueous solution upon irradiation. The behavior of the other **N-P$_n$-N** is analogues to that of **N-P$_4$-N** (Figures S13 and S14, Supporting Information).

At the same time, one set of new signals emerged with the disappearance of the signal of **N-P$_n$-N@CB[8]** (Figure 3 and Supporting Information Figures S12−S14). The product analysis was performed by extraction with chloroform. As expected, the *intramolecular* photocyclomers were exclusively obtained throughout the irradiation periods (Figure 3). In spite of the conversion changing with irradiation time, no intermolecular products were detected by HPLC (Figures S18−S21, Supporting Information). Typically, after 25 s, 6 min, and 12 min of irradiation, the conversion of **N-P$_4$-N** approached 30%, 84%, and 96%, respectively, and the yield of *intramolecular* photocyclomer was up to 96% based on the consumption of the starting material. By contrast, irradiation of **N-P$_n$-N**-saturated aqueous solution results in no photodimer formation. These observations provide unambiguous evidence that CB[8] templates the *intramolecular* photocycloaddition of **N-P$_n$-N** with large rate accelerations in aqueous solution. The quantum yields (Table 1) for the product formation of **N-P$_n$-N** were determined to be ∼40%, which are the highest values obtained so far in the photodimerization of naphthoate derivatives either in organic solvents or in other supramolecular host systems.[11−12]

Conclusion

We have demonstrated that CB[8] can encapsulate the two naphthalene terminals of **N-P$_n$-N** into its hydrophobic cavity to form a highly stable 1:1 inclusion complex **N-P$_n$-N@CB[8]**, therefore leading to exclusive formation of *intramolecular* photocyclomer in aqueous solution upon irradiation with light with a wavelength longer than 280 nm. These results have stimulated us to further extend the scope of photochemical reactions within this fascinating supramolecular system that are being actively performed in our laboratory.

Experimental Section

Preparation of Inclusion Complexes. CB[8] was used as received. **N-P$_n$-N** and their *intramolecular* photodimers were prepared according to the literature method.[12] Typically, 100 mL of deionized water was added to the mixture of **N-P$_n$-N** (22.8 μmol) and CB[8] (22.9 μmol), and then the mixture was sonicated in an ultrasonic cleaner at 50 °C for 2 h. Filtration through 0.2 μm membrane afforded the desired inclusion complexes of **N-P$_n$-N@CB[8]**.

Photoirradiation of Inclusion Complexes of N-P$_n$-N@CB[8] in Aqueous Solution. The aqueous solution of **N-P$_n$-N** and CB[8] was sealed in a 14-mm inner diameter Pyrex tube under an argon atmosphere, then irradiated with a 500 W high-pressure mercury lamp. The Pyrex tube was used as a light filter to cut off light below 280 nm and guarantee irradiation with $\lambda > 280$ nm. A quartz jacket with water circulation was used to cool the lamp. The irradiation was followed by UV−vis absorption spectrum. Generally after ∼10 min of irradiation, the conversion was greater than 90%. The reaction mixture was extracted with chloroform for further analysis. All of the quantum yields for the product formation in the absence and presence of CB[8] were calculated with the conversion below 15%. Accordingly, the corresponding luminous flux taking part in the reaction can be determined. On the other hand, the total absorbed luminous flux can be measured by a photometer. The ratio of two luminous fluxes gave the correlated quantum yield. In our case, the quantum yield for the product formation of **N-P$_n$-N** ($n = 3, 4, 5$) was determined to be 30%, 37%, and 40%, respectively, which is more than ∼15 times higher than that of **N-P$_n$-N** in cyclohexane solution.

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Supporting Information Available: Experimental procedures and details. This material is available free of charge via the Internet at http://pubs.acs.org.

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