Journal of Photochemistry and Photobiology A: Chemistry 359 (2018) 33–39

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Manipulating [2 + 2] photodimerization of 1,4-dihydropyridines within γ-cyclodextrin

Wuji Sun, Qiangwen Fan, Hong Yan*

College of Life Science and Bioengineering, Beijing University of Technology, Beijing, 100124, China

ARTICLE INFO

Article history:
Received 7 February 2018
Received in revised form 28 March 2018
Accepted 29 March 2018
Available online 30 March 2018

Keywords:
DHPs
γCD
[2 + 2] Photodimerization
Spectral characteristics
DFT

ABSTRACT

Irradiation of 1,4-dihydropyridines (DHPs) in the presence of γ-cyclodextrin (γ-CD) performs an efficient formation of the cage-dimer under a medium-pressure mercury lamp. The cage-dimer yields for DHPs complexed within γ-CD may achieve approximately 80%, far higher than those in the non-complexed state. It is postulated that the available cavity volume in γ-CD is responsible for the observed selectivity. The formation of 1:2 host-guest inclusion complex plays an important role in this reaction, and manipulates DHPs to perform [2 + 2] photodimerization as expected. In order to investigate the inclusion process, the spectral characteristics were investigated and the theoretical study was performed using density functional theory (DFT).

1. Introduction

Photochemical reactions have attracted considerable interest of chemists because they often lead to rigid and highly symmetric products that are virtually inaccessible by thermal reactions, such as cubane [1–3] and pagodane [4]. In particular, our group has extensively studied the [2 + 2] photodimerization of 1,4-dihydropyridines (DHPs) and reported the head-tail cage dimers [5–7], 3,9-diazatetraasteranes, which hold promise as novel HIV protease inhibitors for their C_2 symmetry [8]. However, it is usually difficult to predict and control the outcome of photochemical reactions and various mixtures of photoproducts are obtained.

Previous studies done by our group have shown an understanding of photochemical reactivity of DHPs [6]. As shown in Scheme 1, irradiation of DHPs **1** with a 250 W medium-pressure mercury lamp leads to three different adducts, viz., *anti*-dimer **2**, *syn*-dimer **3** and cage-dimer **4**. The initially formed *syn*-dimer **3** is submitted to formation of cage-dimer **4** resulted from a [2 + 2] cycloaddition reaction of the intramolecular double bonds. We have used diethyl 1,4-dihydropyridine-3,5-dicarboxylate **1a** whose photochemical reaction has been investigated in solution as model compound. Photodimerization of a THF solution of **1a** resulted in *anti*-dimer **2a** (37%) and cage-dimer **4a** (41%). Due to the competing reaction, the yield of cage-dimer **4a** is comparatively poor in most cases requiring long irradiation times.

To achieve the goal of controlling photoproducts distribution, manipulation of the reactants by various templates has been the best solution to this problem. Previously micelles [9,10] and inorganic hosts [11] have been used to template [2 + 2] and [4 + 4] photodimerizations successfully. Recently, calixarenes [12], cucurbiturils [13,14] and cyclodextrins (CDs)15–17 have already been employed in template controlled photochemical reactions. Among these templates, γ-CD, macrocycles composed of 8 glucose units linked by 1,4 glycosidic bond, offers the advantages of structural flexibility and available free space [15] (Fig. 1). Herein, we present the experimental results of manipulating [2 + 2] photodimerization of DHPs within γ-CD. DFT method was performed to investigate the inclusion complex of γ-CD with DHPs.

2. Results and discussion

2.1. Chemistry

A series of DHPs was prepared by a cyclocondensation reaction of ethyl propiolate, aldehydes and amines in acetic acid [7,18]. The inclusion complex of γ-CD with DHPs was carried out under ultrasound irradiation, and the photodimerization of the complex was conducted by irradiation of medium-pressure mercury lamp (Scheme 2). In a typical experiment, **1a** (1 equivalents) was dissolved in THF. To this solution was added the aqueous solution

* Corresponding author.
E-mail address: hongyan@bjut.edu.cn (H. Yan).

https://doi.org/10.1016/j.jphotochem.2018.03.046
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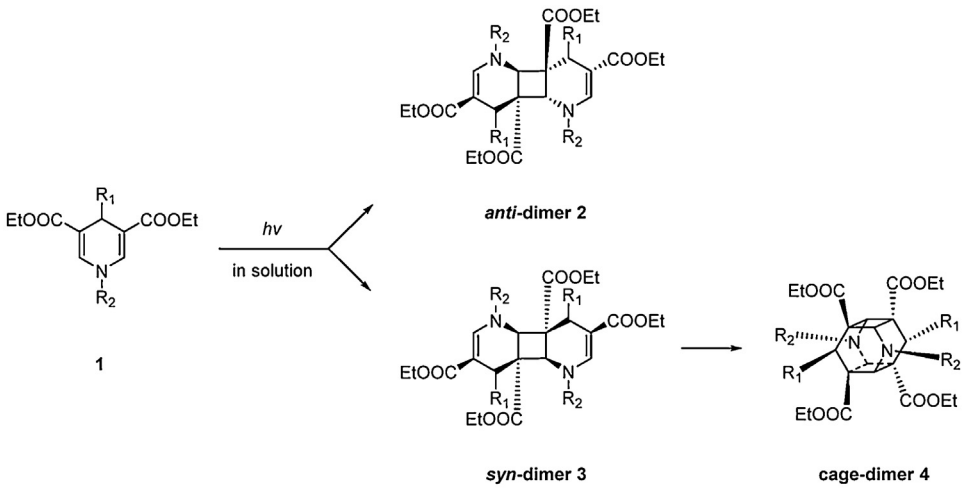


Scheme 1. [2 + 2] Photodimerization of DHPs in solution.

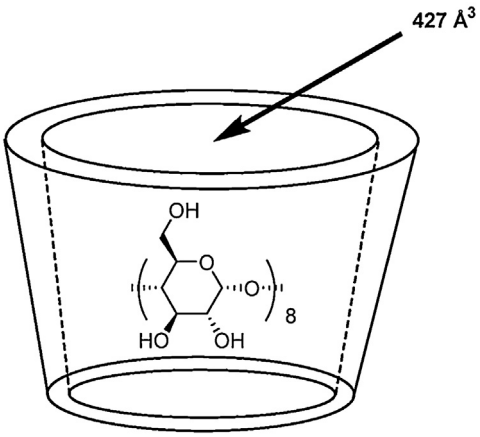
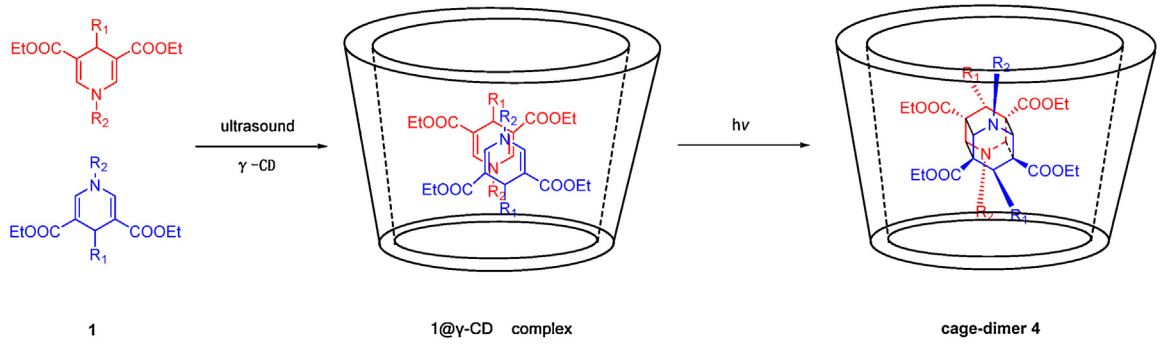


Fig. 1. Structure of γ-CD.

of γ-CD (0.5 equivalents) and the mixture was sonicated to obtain a clear homogeneous solution. Irradiation of a solution of the **1a**@γ-CD host-guest complex with a 250 W medium-pressure mercury lamp produced cage-dimer **4a** as major product (77%), and the *anti*-dimer **2a** was formed as minor product in a detectable amount compared to the yields of cage-dimer **4a** (41%) and *anti*-dimer **2a** (37%) in the non-complexed state. The results indicated that it was well established that γ-CD formed a 1:2 host-guest complex with **1a**. This is based on the reasoning that γ-CD with a large cavity volume 427 Å^3 will most likely form a 1:2 host-guest complex with DHPs [19]. γ-CD as the template not only improves the yields of photodimerizations but also gives rise to high stereoselectivities.

To examine the general applicability of γ-CD as a template, [2 + 2] photodimerizations of DHPs were attempted under the above conditions. Meanwhile the influence of γ-CD in the [2 + 2] photodimerization was also investigated, and the results were summarized in Table 1. Irradiation of a solution of **1a-1j** for 8 h generated cage-dimer **4a-4j** in 35%–63% total yields. By comparison, irradiation of **1a-1j** within γ-CD led to a significant rise in cage-dimer yields, and the yields varied predictably with the identity of the substituents. When R_1 is H, the cage-dimer yields for **1a-1d** complexed within γ-CD are increased by 35%–47% higher than in solution. This trait is especially obvious in other compounds. When R_2 is H, the cage-dimer yields for **1e-1g** are increased by 34%-46% higher than in the non-complexed state. Futhermore, when both R_1 and R_2 are aryl, the **1h-1j** complexed within γ-CD undergo a [2 + 2] photodimerization to the cage-dimer **4h-4j** with yields of approximately 80%. These results indicated that γ-CD had an important influence on the improvement of the photodimerization, and could manipulate [2 + 2] photodimerization of DHPs to generate the corresponding cage-dimer. The structures of cage-dimer **4a-4j** were characterized by



Scheme 2. [2 + 2] Photodimerization of DHPs within γ-CD.

Table 1
Yields of cage-dimer **4** upon irradiation of DHPs in solution and within γ-CD.

Entry	Reactant	R_1	R_2	Yields of cage-dimer **4** (%)	
				in solution[a]	within γ-CD[b]
1	**1a**	H	H	41[c]	77
2	**1b**	H	Ph	38	85
3	**1c**	H	4-MePh	48	83
4	**1d**	H	4-CF_3Ph	50	89
5	**1e**	Ph	H	40[c]	80
6	**1f**	3,4-diClPh	H	39	73
7	**1g**	3,4,5-triOMePh	H	35[c]	81
8	**1h**	Ph	Ph	62[c]	82
9	**1i**	4-OMePh	Ph	63[c]	88
10	**1j**	4-FPh	Ph	62[c]	78

[a] Each THF solution of **1a-1j** was irradiated with a 250 W medium-pressure mercury lamp for 8 h.
[b] Photochemical reactions of **1a-1j** within γ-CD were carried out under conditions similar to those of **1a-1j** in solution.
[c] The yields were reported in reference [6,7].

^{1}H NMR, ^{13}C NMR and HRMS. The single crystal X-ray diffraction of **4d** (CCDC number 1537604) was carried out which further proved that the photoproduct was the head-tail cage dimer (Fig. 2).

2.2. Spectral characteristics

The absorbance spectra of **1d** in THF/H_2O and in the presence of γ-CD are presented in Fig. 3. The absorption maximum of **1d** locate in the range of 340–430 nm shifted from 381 nm to 370 nm in the presence of γ-CD (0.5 equivalents), which is probably due to the ground state interactions between the manipulated two molecules of DHPs within γ-CD. The emission spectra of **1d** in THF/H_2O and in the presence of γ-CD are presented in Fig. 4. Fluorescence studies using **1d** indicated that there was a significant red shifting of the spectrum with the increase in intensity in the presence of 0.5 equivalents of γ-CD. In this case, emission due to **1d** (444–456 nm) was replaced by an intense emission around 449–471 nm. The fluorescence excitation spectrum recorded by monitoring emission at 461 nm was similar to that of the absorption spectrum

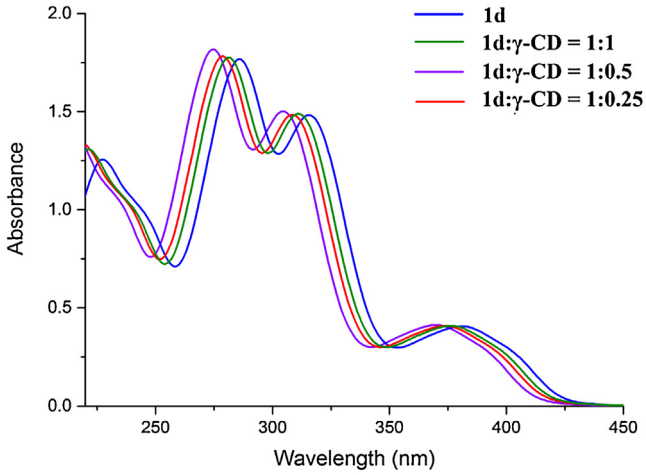


Fig. 3. The absorption spectra of **1d** (1×10^{-5} M) in the presence of γ-CD.

suggesting that the new intense red shifted emission is due to the formation of 1:2 host-guest complex. Furthermore, the rate constant (k_0) and lifetime (τ_0) of the excited state were estimated according to the Strickler-Berg equation [20].

$$k_0 = 1/\tau_0 = 2.880 \times 10^{-9}\, n^2\, \nu_f^2 \int \varepsilon d\ln\nu \quad (1)$$

In the Eq. (1), n was the refractive index of the solvent. ν_f was the emission frequency in wavenumbers, and approximated by the maximum emission wavelength in wavenumbers ($\boldsymbol{\lambda}_{ems}$, cm^{-1}). The integral $\int \varepsilon d\ln\nu$ represented the area of the absorption band from a plot of molar extinction coefficient (ε) against wavenumbers (ν, cm^{-1}). As shown in Table 2 and Fig. 3, the absorption maxima located in the range of 340–430 nm with the rate constant for about 10^8 s^{-1} and the molar extinction coefficient for about 10^4 M^{-1} cm^{-1}, indicating the lowest excitation states of **1d** are dominated by π-π* transition [21]. The lifetimes of π–π* states were affected much by the complexation of γ-CD, and the lifetimes increased from 1.41 ns to 6.21 ns in the presence of γ-CD

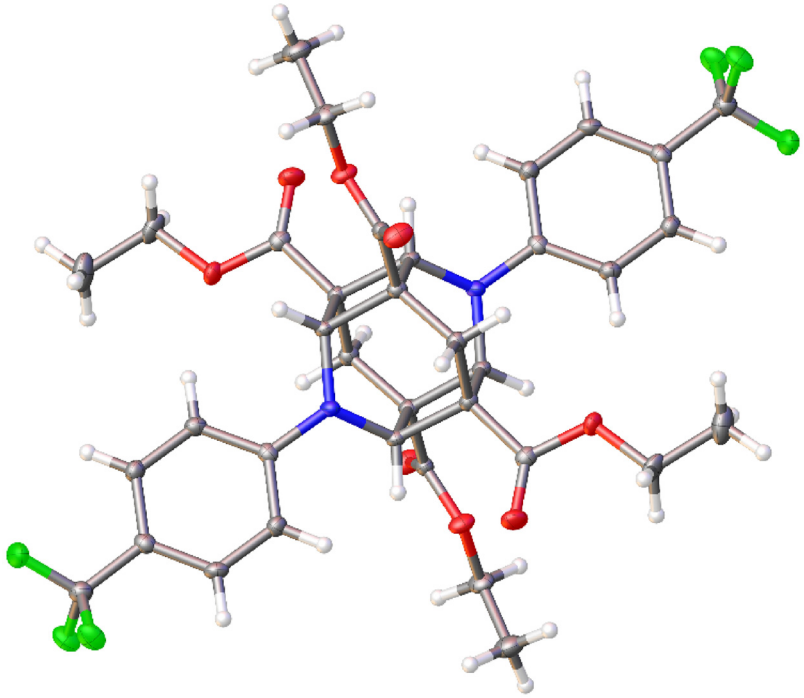


Fig. 2. X-ray crystal structure of cage-dimer **4d**.

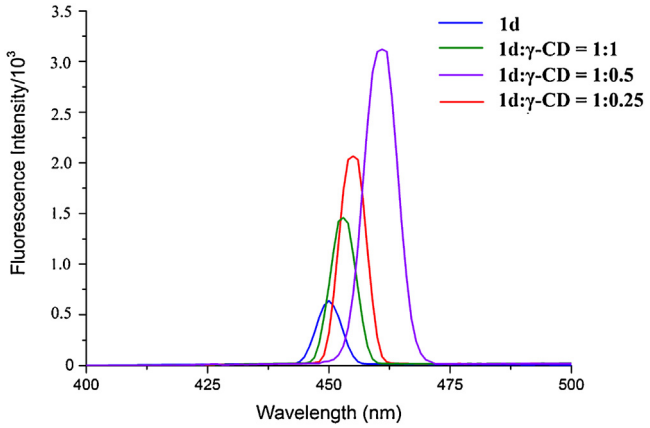


Fig. 4. The emission spectra of **1d** (1×10^{-5} M) in the presence of γ-CD.

Table 2
Strickler-Berg estimates of the rate constant k_0 and lifetime τ_0 of the excited state.

species	λ_{abs} (nm)	λ_{ems} (nm)	k_0 (10^8 s^{-1})	τ_0 (ns)
1d	370	450	7.08	1.41
1d:γ-CD = 1:1	374	453	4.88	2.05
1d:γ-CD = 1:0.5	381	461	1.61	6.21
1d:γ-CD = 1:0.25	376	455	5.95	1.68

Table 3
Energies of **1d** calculated at the B3LYP-D3/6-31G (d, p) theoretical level.

Energies (kJ mol^{-1})	host:guest = 1:1	host:guest = 1:2
E_{guest}	−3478561.7467	−3478561.7467
E_{host}	−12572033.1286	/
E_{com1}	−16050627.8791	−16050627.8791
E_{com2}	/	−19529235.4544
ΔE_{b1}	−33.0038	/
ΔE_{b2}	/	−45.8286

(0.5 equivalents). It was clear that the formation of 1:2 host-guest complex led to longer lifetimes of the excited state.

2.3. Theoretical study

In order to gain a better understanding of the cage-dimer formation, the theoretical study of **1d**@γ-CD host-guest complex as a model was investigated by means of DFT method [22]. The inclusion complex obtained by exploring the conformational space, was exposed to a full geometry optimization using the B3LYP-D3 function associated with the 6–31G (d, p) basis set [23]. To quantify the interaction between γ-CD and **1d** in the optimized geometries, the binding energy (ΔE_{b1} and ΔE_{b2}) were calculated at the same theoretical level according to the following relation (1) and (2):

$$\Delta E_{b1} = E_{com1} - (E_{host} + E_{guest}) \quad (1)$$

$$\Delta E_{b2} = E_{com2} - (E_{com1} + E_{guest}) \quad (2)$$

where E_{com1}, E_{com2}, E_{host} and E_{guest} were the Hartree-Fock (HF) energies of 1:1 host-guest complex, 1:2 host-guest complex, γ-CD and **1d** from optimization, respectively. The formation of 1:2 host-guest complex can be explained by a stepwise mechanism, involving the initial formation of 1:1 host-guest complex as represented by relation (1), followed by complexation of a second guest to give 1:2 host-guest complex described in relation (2). According to the relation (1) and (2), the binding energy ΔE_{b1} and ΔE_{b2} was calculated. The binding energy was usually an important parameter of the driving force towards inclusion, and the more negative value meant more favorable inclusion. It could be seen from Table 3 that the binding energy ΔE_{b2} was much larger than the binding energy ΔE_{b1}, which indicated that the formation of 1:2 host-guest complex was energetically favored. As displayed in Fig. 5, the optimal conformation showed two molecules of **1d** were accommodated within the cavity of γ-CD in a parallel and head-tail arrangement and the carbon atoms of C=C bond were held within reactive distance, which favored [2 + 2] photodimerization and the

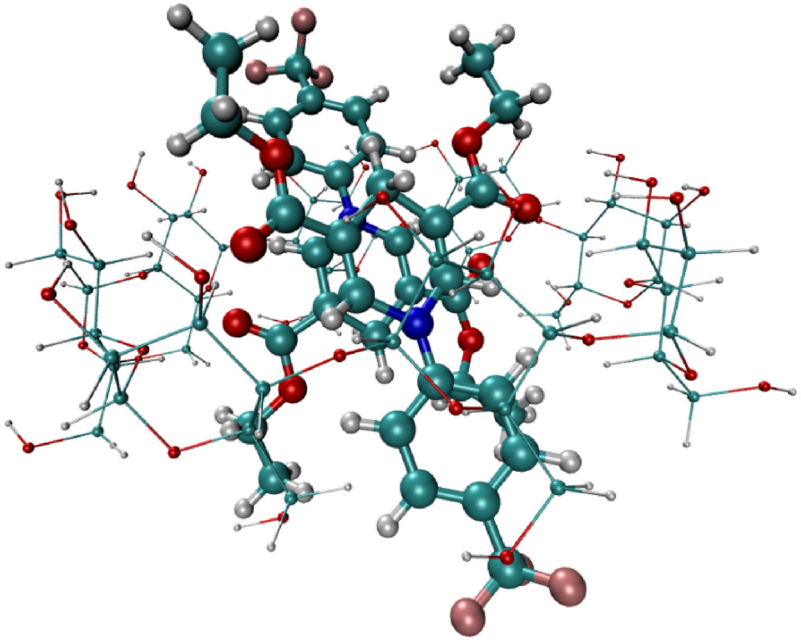


Fig. 5. The schematic drawing of **1d**@γ-CD complex.

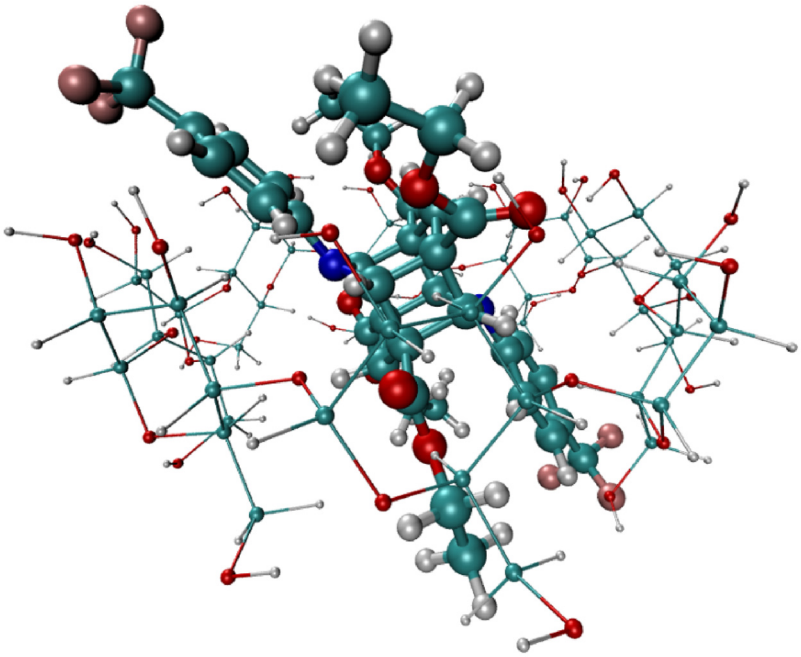


Fig. 6. The schematic drawing of cage-dimer **4d** within γ-CD.

formation of cage-dimer. However, *anti*-dimer and *syn*-dimer could barely be obtained in the complexed state. It was attributed that the cavity volume of γ-CD could not hold *anti*-dimer on the one hand, on the other hand, it drew two molecules of **1d** closer, thus forming cage-dimer directly from the cycloaddition reactions without formation of *syn*-dimer. Based on the optimal conformation and the cavity volume of γ-CD, it was clear that the cage-dimer appeared to better fit into the γ-CD cavity than other photoproducts, as depicted in Fig. 6.

3. Conclusions

In summary, a series of DHPs was prepared by a cyclo-condensation reaction of ethyl propiolate, aldehydes and amines in acetic acid, and irradiation of DHPs complexed within γ-CD was investigated under a mercury lamp. The results indicated that the [2 + 2] photodimerization of DHPs within γ-CD was manipulated as expected. The cage-dimer yields for DHPs complexed within γ-CD exhibited a significant improvement with the yields of about 80%, compared to that in the absence of γ-CD. The structures of cage-dimer **4a-4j** were determined by ^{1}H NMR, ^{13}C NMR, HRMS and single crystal X-ray diffraction analyses. The formation of 1:2 host-guest inclusion complex was supposed to play an important role in this reaction. The spectral characteristics of DHPs in the presence of γ-CD were investigated. The theoretical study of the inclusion complex was performed to investigate the inclusion process by DFT method. The γ-CD could manipulate two molecules of DHPs in a parallel and head-tail arrangement, and the optimal conformation promoted the formation of cage-dimer which not only improved the yields of photodimerizations but also gave rise to high stereoselectivities.

4. Experimental

4.1. General procedures

All of the chemicals were purchased from commercial sources and used without further purification. Ultrasound irradiation was performed in a GEX750-5C ultrasonic instrument. Irradiation for the photodimerization was conducted using an Osram HBO 250W medium-pressure mercury lamp. The melting points were determined on a XT-5A digital melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz respectively. HRMS were recorded using an Agilent G3250AA LC/MSD TOF mass spectrometer with an ESI source. The X-ray single-crystal diffraction was performed on CCD area detector. The UV–vis absorption spectra were measured on a SHIMADZU UV-2600 spectrophotometer in THF/H_2O solution. The fluorescence emission spectra were measured on a SHIMADZU RF-6000 spectrofluorometer in THF/H_2O solution.

4.2. General procedure for synthesis of DHPs (1a-1g)

A mixture of ethyl propiolate (0.10 mol), aldehydes (0.05 mol), amines (0.05 mol), and 5.0 mL of acetic acid was heated in a steam bath for 25 min. The product was crystallized from methanol/water (V:V = 4:1), then recrystallized from acetone/hexane (V:V = 1:1).

Diethyl 1,4-dihydropyridine-3,5-dicarboxylate (1a). Yield 66.4%, m.p. 108.2–109.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (t, 6H, CH_3), 3.24 (s, 2H, CH_2), 4.17 (q, 4H, *J* = 7.2 Hz, CH_2), 6.59 (brs, 1H, N*H*), 7.09 (d, 2H, *J* = 4.8 Hz, =C*H*).

Diethyl 1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1b). Yield 70.7%, m.p. 131.5–132.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.31 (t, 6H, CH_3), 3.35 (s, 2H, CH_2), 4.23 (q, 4H, *J* = 7.2 Hz, CH_2), 7.19–7.26 (m, 3H, Ar-*H*), 7.40 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.44 (s, 2H, =C*H*).

Diethyl 1-(4-methylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1c). Yield 75.1%, m.p. 129.1–130.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.29 (t, 6H, CH_3), 2.35 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 4.26 (q, 4H, *J* = 7.2 Hz, CH_2), 7.07 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.19 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.39 (s, 2H, =C*H*).

Diethyl 1-(4-trifluoromethylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1d). Yield 67.0%, m.p. 144.6–145.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 6H, CH_3), 3.35 (s, 2H, CH_2), 4.26 (q, 4H, *J* = 7.2 Hz, CH_2), 7.31 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.49 (s, 2H, =C*H*), 7.68 (d, 2H, *J* = 8.4 Hz, Ar-*H*).

Diethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1e). Yield 51.8%, m.p. 121.6–123.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (t, 6H, CH_3), 4.02–4.16 (m, 4H, CH_2), 4.91 (s, 1H, Ar-C*H*), 6.91 (brs, 1H, N*H*), 7.17–7.37 (m, 5H, Ar-*H*), 7.27 (d, 2H, *J* = 4.8 Hz, =C*H*).

Diethyl 4-(3,4-dichlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1f). Yield 47.0%, m.p. 168.1–169.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.22 (t, 6H, CH_3), 4.03–4.17 (m, 4H, CH_2), 4.88 (s, 1H, Ar-C*H*), 7.09 (brs, 1H, N*H*), 7.19–7.41 (m, 3H, Ar-C*H*), 7.33 (d, 2H, *J* = 5.2 Hz, =C*H*).

Diethyl 4-(3,4,5-trimethoxylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1g). Yield 60.5%, m.p. 181.7–182.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (t, 6H, CH_3), 3.78 (s, 3H, OCH_3), 3.81 (s, 6H, OCH_3), 4.05–4.15 (m, 4H, CH_2), 4.86 (s, 1H, Ar-C*H*), 6.58 (s, 2H, Ar-*H*), 7.27 (brs, 1H, N*H*), 7.36 (d, 2H, *J* = 5.2 Hz, =C*H*).

Diethyl 1,4-diphenyl-1,4-dihydropyridine-3,5-dicarboxylate (1h). Yield 42.5%, m.p. 134.6–136.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (t, 6H, CH_3), 4.04–4.18 (m, 4H, CH_2), 4.97 (s, 1H, Ar-C*H*), 7.15–7.48 (m, 10H, Ar-*H*), 7.67 (s, 2H, =C*H*).

Diethyl 4-(4-methoxylphenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1i). Yield 50.7%, m.p. 120.8–121.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.21 (t, 6H, CH_3), 3.77 (s, 3H, OCH_3), 4.06–4.16 (m, 4H, CH_2), 4.91 (s, 1H, Ar-C*H*), 6.79 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.29 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.26–7.48 (m, 5H, Ar-*H*), 7.65 (s, 2H, =C*H*).

Diethyl 4-(4-fluorophenyl)-1-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1j). Yield 60.4%, m.p. 136.0–136.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.20 (t, 6H, CH_3), 4.04–4.18 (m, 4H, CH_2), 4.95 (s, 1H, Ar-C*H*), 6.91 (t, *J* = 8.8 Hz, 2H, Ar-*H*), 7.44 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.29-7.48 (m, 5H, Ar-*H*), 7.65 (s, 2H, =C*H*).

4.3. General procedure for irradiation of DHPs in solution

DHPs (1 mmol) was dissolved in 200 mL of tetrahydrofuran, and the solution was poured into a photochemical reactor, which led to the N_2 protective gas. The reactor was irradiated with a 250 W medium-pressure mercury lamp as the light source for 8 h. Then the solvent was evaporated and the residue was purified by chromatography (ethyl acetate/petroleum ether = 1:5) on silica gel.

4.4. General procedure for irradiation of DHPs within γ-CD

In a typical experiment, DHPs (1 mmol) was dissolved in 100 mL of tetrahydrofuran. To this solution was added an aqueous solution of γ-CD (0.5 mmol, 100 mL), and the mixture was sonicated at 60 °C for 2 h to obtain a clear homogeneous solution. The mixture solution was irradiated with a 250 W medium-pressure mercury lamp under nitrogen for 8 h. The solution was concentrated under reduced pressure, and the precipitate was filtered off and recrystallized from dichloromethane/methanol (V:V = 4:1) to afford cage-dimer **4a-4j**.

Tetraethyl 3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4a). Yield 77.2%, m.p. 160.0–161.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.28 (t, 6H, CH_3), 2.36 (s, 2H, CH_2), 4.03 (s, 2H, C*H*), 4.16–4.22 (q, 4H, OCH_2); HRMS (ESI) *m*/*z* calcd 451.2075 for $C_{22}H_{31}N_2O_8$ $[M+H]^+$, found 451.2077.

Tetraethyl 3,9-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4b). Yield 84.9%, m.p. 234.6–235.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.33 (t, 6H, CH_3), 2.35 (s, 2H, CH_2), 4.26 (q, 4H, *J* = 7.2 Hz, CH_2), 4.85 (s, 2H, C*H*), 6.90 (t, 1H, Ar-*H*), 7.15–7.30 (m, 4H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 25.2, 47.0, 57.2, 61.4, 117.7, 120.5, 129.4, 150.1, 174.1; HRMS (ESI) *m*/*z* calcd 603.2701 for $C_{34}H_{39}N_2O_8$ $[M+H]^+$, found 603.2703.

Tetraethyl 3,9-bis(4-methylphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4c). Yield 82.9%, m.p. 228.9–230.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.32 (t, 6H, CH_3), 2.29 (s, 3H, CH_3), 2.34 (s, 2H, CH_2), 4.25 (q, 4H, *J* = 7.2 Hz, CH_2), 4.79 (s, 2H, C*H*), 7.03–7.09 (m, 4H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.2, 20.5, 25.1, 46.9, 57.3, 61.3, 117.7, 129.8, 129.9, 147.9, 174.2; HRMS (ESI) *m*/*z* calcd 631.3014 for $C_{36}H_{43}N_2O_8$ $[M+H]^+$, found 631.3019.

Tetraethyl 3,9-bis(4-trifluoromethylphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4d). Yield 89.2%, m.p. 255.0–256.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.34 (t, 6H, CH_3), 2.31 (s, 2H, CH_2), 4.28 (q, 4H, *J* = 7.2 Hz, CH_2), 4.92 (s, 2H, C*H*), 7.22 (d, 2H, *J* = 8.4 Hz, Ar-*H*), 7.53 (d, 2H, *J* = 8.4 Hz, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 25.2, 46.9, 56.8, 61.8, 116.8, 120.4, 121.8, 122.1, 122.4, 122.7, 123.1, 125.8, 126.7, 126.8, 128.5, 152.4, 173.5; HRMS (ESI), *m*/*z* calcd 739.2449 for $C_{36}H_{37}F_6N_2O_8$ $[M+H]^+$, found 739.2451.

Tetraethyl 6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4e). Yield 80.1%, m.p. 210.4–212.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.00 (t, 6H, CH_3), 3.02(br s, 1H, N*H*), 3.92-4.03 (m, 4H, CH_2), 3.93 (s, 1H, Ar-C*H*), 4.34 (s, 2H, C*H*), 7.14–7.23 (m, 3H, Ar-*H*), 7.54(d, 2H, Ar-*H*); HRMS (ESI) *m*/*z* calcd 603.2701 for $C_{34}H_{39}N_2O_8$ $[M+H]^+$, found 603.2704.

Tetraethyl 6,12-bis(3,4-dichlorophenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4f). Yield 72.9%, m.p. 213.5–214.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.07 (t, 6H, CH_3), 3.08 (br s, 1H, N*H*), 3.84 (s, 1H, Ar-C*H*), 3.96–4.05 (m, 4H, CH_2), 4.30 (s, 2H, C*H*), 7.29 (d, 1H, Ar-*H*),7.44 (d, 1H, Ar-*H*), 7.77 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.0, 43.3, 48.5, 54.6, 61.3, 129.7, 130.7, 131.1, 131.7, 133.2, 137.5, 172.5; HRMS (ESI) *m*/*z* calcd 739.1142 for $C_{34}H_{35}Cl_4N_2O_8$ $[M+H]^+$, found 739.1143.

Tetraethyl 6,12-bis(3,4,5-trimethoxylphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4 g). Yield 81.4%, m.p. 213.5–214.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.03 (t, *J* = 7.2 Hz 6H, CH_3), 3.04 (br s, 1H, N*H*), 3.80 (s, 9H, OCH_3), 3.82 (s, 1H, Ar-C*H*), 4.00 (q, *J* = 7.2 Hz, 4H, CH_2), 4.31 (s, 2H, C*H*), 6.85 (s, 2H, Ar-*H*); HRMS (ESI) *m*/*z* calcd 783.3335 for $C_{40}H_{51}N_2O_{14}$ $[M+H]^+$, found 783.3338.

Tetraethyl 3,6,9,12-tetraphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4h). Yield 82.3%, m.p. 255.9–256.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.97 (t, 6H, CH_3), 3.92–4.05 (m, 4H, CH_2), 3.96 (s, 1H, Ar-C*H*), 5.23 (s, 2H, C*H*), 6.94–7.37 (m, 10H, Ar-*H*); HRMS (ESI) *m*/*z* calcd 755.3327 for $C_{46}H_{47}N_2O_8$ $[M+H]^+$, found 755.3332.

Tetraethyl 6,12-bis(4-methoxylphenyl)-3,9-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4i). Yield 87.7%, m.p. 288.0–289.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.01 (t, 6H, CH_3), 3.67 (s, 3H, OCH_3), 3.92 (s, 1H, Ar-C*H*), 3.94–4.05 (m, 4H, CH_2), 5.21 (s, 2H, C*H*), 6.58 (t, *J* = 8.8 Hz, 2H, Ar-*H*), 6.95–7.37 (m, 5H, Ar-*H*), 7.01 (d, *J* = 8.8 Hz, 2H, Ar-*H*); HRMS (ESI) *m*/*z* calcd 815.3538 for $C_{48}H_{51}N_2O_{10}$ $[M+H]^+$, found 815.3544.

Tetraethyl 6,12-bis(4-fluorophenyl)-3,9-diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (4j). Yield 78.3%, m.p. 264.0–265.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.99 (t, 6H, CH_3), 3.94–4.07 (m, 4H, CH_2), 3.98 (s, 1H, Ar-C*H*), 5.21 (s, 2H, C*H*), 6.75 (t, *J* = 8.8 Hz, 2H, Ar-*H*), 6.97–7.40 (m, 5H, Ar-*H*), 7.09 (d, *J* = 8.8 Hz, 2H, Ar-*H*); HRMS (ESI) *m*/*z* calcd 791.3138 for $C_{46}H_{45}F_2N_2O_8$ $[M+H]^+$, found 791.3144.

4.5. Single crystal X-ray diffraction for 4d

Crystals of **4d** suitable for X-ray diffraction analysis were obtained by the slow evaporation of a methanol/dichloromethane solution of **4d** at room temperature. The single crystal X-ray diffraction measurements were conducted on a Rigaku Saturn CCD area-detector diffractometer using graphite monochromated MoKα radiation in the ω and φ scanning mode. An empirical absorption correction was applied using the ABSCOR program. All structures were solved by direct methods using the SHELXS

Table 4
Crystallographic data for **4d**.

Entry	**4d**
Empirical formula	$C_{36}H_{36}F_6N_2O_8$
Formula weight	738.67
Temperature	108 K
Wavelength	0.71070
Crystal system	Triclinic
Unit cell dimensions	a = 8.2463 (11) b = 9.4172 (11) c = 11.6964 (12) α= 77.849 (9) β= 71.326 (11) γ= 83.325 (10)
Volume	840.04 (17)
Z	1
Calculated density	1.460 Mg m^{-3}
Absorption coefficient	0.124 mm^{-1}
F(000)	384.0
Crystal size	0.30 × 0.25 × 0.24 mm^{-3}
Data/restraints/parameters	3311/0/237
Goodness-of-fit on F2	1.056
R indices (all data)	R_1 = 0.0395, wR_2 = 0.0941

program and refined by full matrix least-squares on F^2 using the SHELXL program. All of the hydrogen atoms were geometrically fixed using the riding model. The crystallographic data of **4d** were given in Table 4.

4.6. Theoretical study

The isolated γ-CD, DHPs, 1:1 host-guest complex and 1:2 host-guest complex were optimized at the B3LYP-D3/6-31G (d, p) theoretical level [23]. The polarized continuum model (PCM) was used in Consistent Reaction Field (SCRF) with THF/H_2O as solvent. All of the quantum chemical calculations were performed using the Gaussian 09 program package [24].

Acknowledgment

This work was financially supported by the Key Projects in the Beijing Municipal Natural Science Foundation (No. KZ201510005007).

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