Efficient photosensitized splitting of the thymine dimer/oxetane unit on its modifying β-cyclodextrin by a binding electron donor†

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Received 28th March 2006, Accepted 15th May 2006
First published as an Advance Article on the web 26th May 2006
DOI: 10.1039/b604529d

Two modified β-cyclodextrins (β-CDs) with a thymine dimer and a thymine oxetane adduct respectively, TD-CD and Ox-CD, have been prepared, and utilized to bind an electron-rich chromophore, indole or *N*,*N*-dimethylaniline (DMA), to form a supramolecular complex. We have examined the photosensitized splitting of the dimer/oxetane unit in TD-CD/Ox-CD by indole or DMA *via* an electron-transfer pathway, and observed high splitting efficiencies of the dimer/oxetane unit. On the basis of measurements of fluorescence spectra and splitting quantum yields, it is suggested that the splitting reaction occurs in a supramolecular complex by an inclusion interaction between the modified β-CDs and DMA or indole. The back electron transfer, which leads low splitting efficiencies for the covalently-linked chromophore–dimer/oxetane compounds, is suppressed in the non-covalently-bound complex, and the mechanism has been discussed.

Introduction

DNA repair has received increased attention in recent years as ozone depletion threatens to significantly increase DNA damage by UV radiation. The two major lesions formed in DNA by this radiation are the cyclobutane pyrimidine dimers (CPDs) and pyrimidine–pyrimidone (6–4) photoproduct, which constitute 70–80% and 20–30% of total photoproducts, respectively,[1] using thymine base as an example shown in Fig. 1. The two photolesions can be repaired through DNA photoreactivation catalyzed by CPD photolyase and (6–4) photolyase, respectively.

CPD photolyase is the monomeric protein that contains two non-covalently-bound chromophore/cofactors. One chromophore is a fully reduced flavin adenine dinucletide ($FADH^-$), the catalytic cofactor that carries out the repair function upon excitation by either direct photon absorption or resonance energy transfer from another chromophore, which is the antenna cofactor (methenyltetrahydrofolate or deazaflavin) that harvests sunlight. The model for the catalytic reaction is that the enzyme binds CPD in a light-independent reaction, the excited $FADH^-$ transfers an electron to CPD to generate a charge-shifted radical pair ($FADH^{\bullet}$–$CPD^{\bullet -}$), the dimer radical anion ($CPD^{\bullet -}$) undergoes spontaneous splitting and back electron transfer restores the dipyrimidine and the functional form of flavin ready for a new catalytic cycle.[2] As (6–4) photolyases have similar structures and the same chromophores, the same basic reaction mechanism has been proposed.[2c] Despite these similarities, however, certain important differences exist between the two classes of enzymes: such as the repair efficiency, CPD photolyases with a uniformly high quantum yield ($\Phi = 0.7$–0.9); and a low efficiency (0.05–0.1) for (6–4) photolyases.[2c] The mechanism for the difference remains unknown.

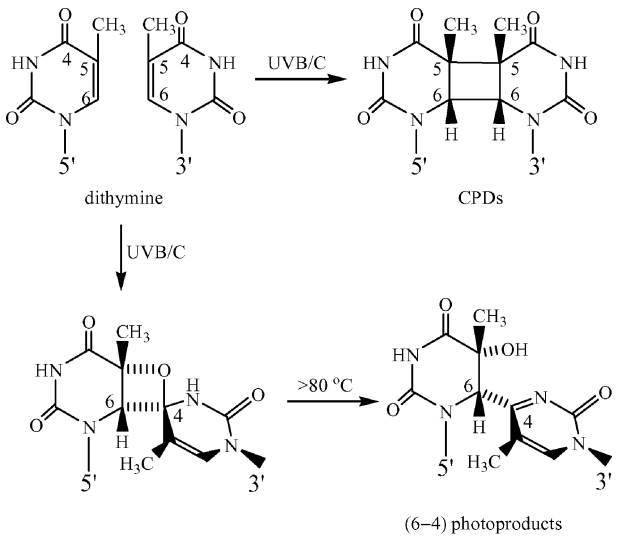

Fig. 1 Formation of the two major photoproducts between adjacent thymines in DNA under UV light, CPDs and (6–4) photoproducts.

The photosensitized repair of photoproducts by a covalently attached chromophore appears inefficient, such as $\Phi < 0.1$ for the indole–dimer system,[3] and *ca.* 0.2 for the tryptophan–oxetane system,[4] in aqueous solutions, and lower values of Φ for the corresponding flavin model system.[5] The factor limiting repair efficiency in covalent systems was thought to be back electron transfer within the charge-separated species formed upon forward electron transfer from an excited electron donor to the substrate. Furthermore, it has been discussed that the reasons leading to low repair efficiencies are back electron transfer for indole/tryptophan model systems, and an additional factor, non-radiative processes that include internal conversion and intersystem crossing of excited flavin, for flavin model systems. [4]

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† Electronic supplementary information (ESI) available: copies for ^1H and ^{13}C NMR spectra of compounds TD-CD and Ox-CD. See DOI: 10.1039/b604529d

Comparing the covalently-linked chromophore–substrate models with the enzyme–substrate complex, a significant difference is in their modes linking cofactor/chromophore and substrate, that is, one is the covalent, the nother is the non-covalent. Two research groups have presented small-molecule recognition units that can bind a uracil dimer, and the uracil dimer is split through photosensitization by chromophores attaching on the recognition unit.[6,7] Using indole-containing marocycles as recognition units, Rose and Goodman achieved the repair of a uracil dimer by photoinduced electron transfer from indole within a hydrogen-bonding complex with $\Phi > 0.1$ in both protic and aprotic solvents.[6] Another group utilized a zinc-cyclen moiety covalently linked to a reduced flavin derivative as an artificial photolyase model, by which the uracil dimer was recognized through a combination of charge and hydrogen-bonding interactions. The efficiency of the dimer splitting in the complex is four times as high as the bimolecular background reaction.[7] The distances between the chromophore and the dimer in two cases are longer than the covalently-linked models mentioned above.

In CPD photolyase, the back electron transfer can be efficiently suppressed, for CPDs are repaired with a quantum yield close to unity. Thus, the back electron transfer could also be suppressed in the simple complexes formed from a small-molecule recognition unit with the substrate because of higher splitting efficiencies of dimers in the complex models over the corresponding covalently-linked models.

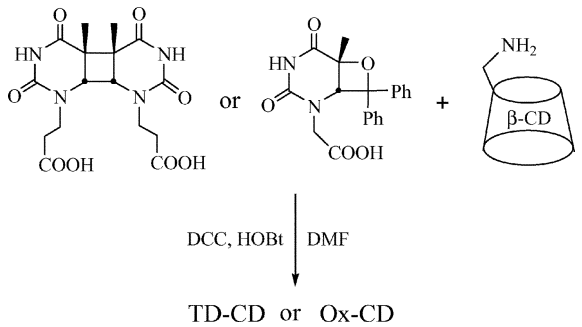
To estimate the efficiency in a supramolecular complex, we have prepared two modified β-cyclodextrins (β-CDs) with a *cis-syn* thymine dimer and a thymine oxetane adduct respectively, TD-CD and Ox-CD, which were intended to include an electron-rich chromophore such as indole and *N*,*N*-dimethylaniline (DMA), shown in Chart 1. We have observed efficient photosensitized splitting of the dimer/oxetane unit by the chromophore within a possible complex. This implies that the back electron-transfer process is suppressed in a supramolecular complex formed from the modified β-CD and the chromophore.

Results and discussion

Synthesis of the modified β-CDs, TD-CD and Ox-CD

The synthesis of ethyl *cis-syn* thymine cyclobutane dimer-yl-*N*,*N*′-dipropionate (TD, shown in Chart 1) was carried out according to the literature method.[3c] The thymine oxetane-1-acetate was prepared from the Paternò–Büchi reaction of the thymine and benzophenone.[4] Mono-6-deoxy-6-amino-β-cyclodextrin was prepared from β-cyclodextrin according to reported methods.[8]

The compound TD-CD was prepared through the condensation of the thymine dimer dicarboxylic acid and mono-6-deoxy-6-amino-β-cyclodextrin using dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) as coupling reagent in DMF (Scheme 1). Under the same conditions, the compound Ox-CD was gained using oxetane carboxylic acid instead of the dimer dicarboxylic acid. The reaction residues were isolated by column of macroporous resin, giving two compounds with yields of 19 and 16%, respectively.



Scheme 1 Synthesis of the model compounds. *Reagents and conditions*: DCC, HOBt, DMF, rt, 48 h.

Absorption and fluorescence emission spectra

Fig. 2 shows UV absorption spectra of two modified β-CDs and two photosensitizers, indole and DMA, and fluorescence emission spectra of the photosensitizers, in aqueous solutions. The spectra show that there is no overlap between the emission spectra of the indole and DMA and the absorption spectra of the TD-CD and Ox-CD, which have no significant absorption at above 290 nm.

Obvious changes of fluorescence emission of DMA were observed when the concentration of Ox-CD was increased gradually in aqueous solution of DMA (Fig. 3). As the concentration of Ox-CD increases, the fluorescence spectra show a decrease in intensity and a blue shift (the peak from 372 to 355 nm). In general, the fluorescence emission for DMA entering the hydrophobic cavity of β-CD becomes strong and shows a blue shift. A possible explanation for the blue shift and the decrease in intensity is the formation of a possible supramolecular complex by Ox-CD

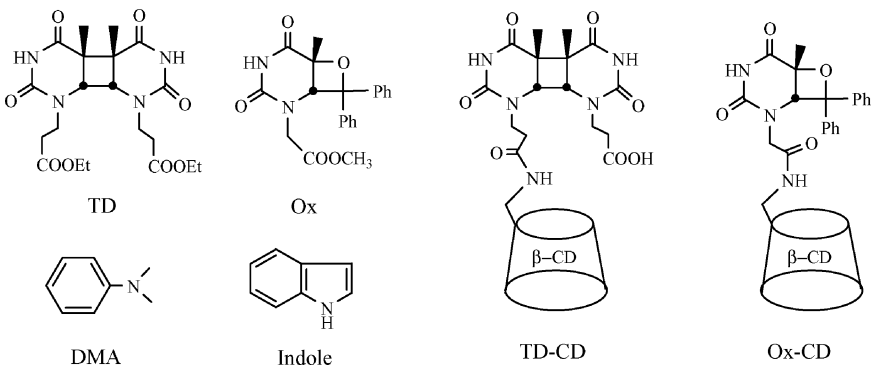


Chart 1

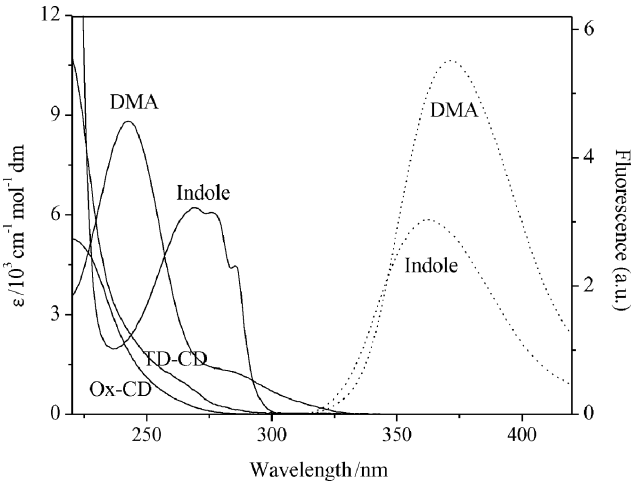


Fig. 2 UV absorption spectra of relative compounds (solid), and fluorescence emission spectra (dots) of indole and DMA upon excitation at 295 nm, in aqueous solutions.

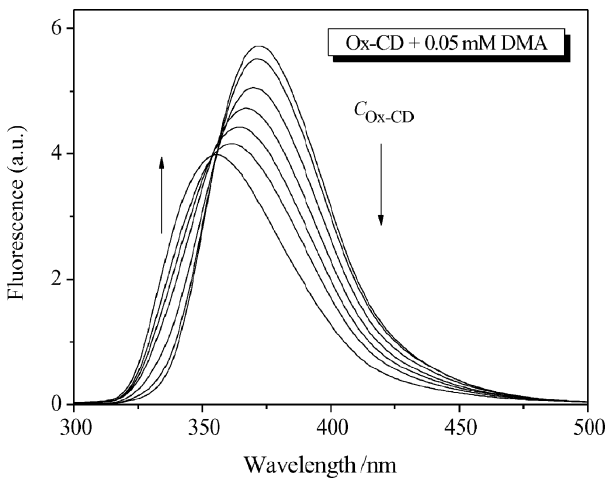


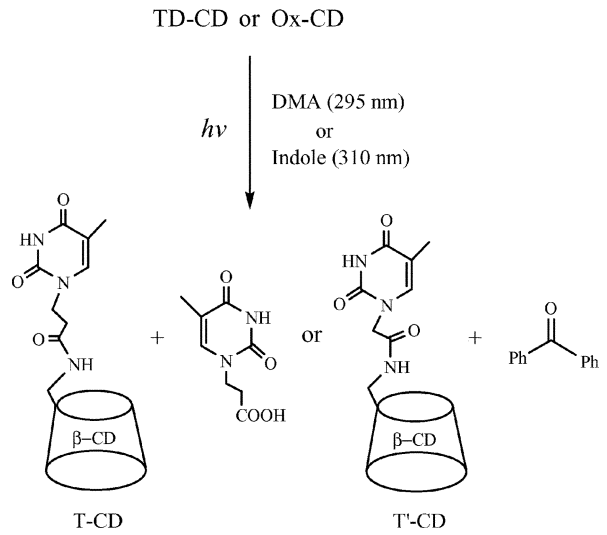
Fig. 3 Dependence of the fluorescence of 0.05 mM DMA on the concentration of Ox-CD (0–6.0 × 10^{-4} M, λ_{ex} = 295 nm).

including DMA, and in the complex, electron transfer from the excited DMA to the oxetane unit occurs to lead to fluorescence quenching instead of fluorescence enhancement.

Photosensitized splitting of the dimer/oxetane unit of TD-CD/Ox-CD by indole/DMA

To examine the photochemical behavior of the complex formed from Ox-CD and DMA, a photolysis experiment was performed. The cycloreversion of thymine oxetane to the thymine monomer and benzophenone was confirmed through measurement of the ^{1}H NMR spectra (Scheme 2). Likewise, photolysis of Ox-CD/TD-CD solutions containing indole led to the splitting of the oxetane/dimer, which was detected by ^{1}H NMR spectroscopy. The splitting reactions were clean conversions because no side products were detected.

The singlet–singlet energy transfer from the excited indole/DMA to the substrate TD/Ox unit should be ruled out, for there



Scheme 2

is no overlap between the emission spectra of the indole and DMA and the absorption spectra of TD-CD and Ox-CD. Since the TD-CD and Ox-CD have no significant absorption at above 290 nm, an internal filter effect is insignificant. A control experiment shows that no splitting of the oxetane unit for a 0.5 mM Ox-CD aqueous solution was detected upon irradiation with 310 nm light for 10 min in the absence of DMA. Hence, the splitting reaction may undergo an electron transfer from the excited indole/DMA to the oxetane/dimer. The driving force for the electron transfer can be estimated in terms of the Rehm–Weller equation,[9]

$$\Delta G\ (\mathrm{eV}) = [E_{ox} - E_{red} - e^2/\varepsilon R_{D^+A^-}] - \Delta E_{0,0}$$

where $\Delta E_{0,0}$ is the energy level of an excited photosensitizer, which is obtained from its fluorescence emission spectra, and E_{ox} and E_{red} are the oxidation potential of a donor and the reduction potential of an acceptor, respectively. The E_{red} of the dimer was reported to be between *ca.* −1.4 and −1.9 V,[10] and its average value, −1.7 V, was used in the calculation. Data in Table 1 showed that the electron-transfer reaction from the excited indole or DMA to the dimer would spontaneously occur. Although the value of E_{red} for the oxetane is unavailable, the excited oxidation potentials ($E_{ox}^* = E_{ox} - \Delta E_{0,0}$) for both indole and DMA are in the range, where the electron-transfer reaction has been confirmed, from −2.45 to −3.32 V.[13]

Two groups of control experiments revealed that the splitting reactions in the systems of Ox-CD/TD-CD and indole/DMA are not simple biomolecular reactions, for the splittings of the dimer/oxetane unit in the modefied β-CDs are more efficient than TD or Ox in the presence of indole or DMA (compare entries 1 and

Table 1 Excited oxidation potentials of photosensitizers and calculated ΔG values (eV) from the Rehm–Weller equation

	E_{ox}/V (SCE)	$\Delta E_{0,0}$	E_{ox}^*	ΔG
Indole	+0.96[a]	3.42	−2.46	−0.79
DMA	+0.53[a]	3.34	−2.81	−1.14

[a] From ref. 11, 12 respectively.

Table 2 Splitting quantum yields of the dimer/oxetane unit in various systems[a]

Entry	System	Φ
1	0.2 mM Ox-CD + 0.05 mM indole	0.13
2[b]	0.2 mM Ox-CD + 0.05 mM indole	0.01
3	0.5 mM Ox + 0.05 mM indole	<0.01
4	0.2 mM Ox-CD + 0.05 mM DMA	0.27
5[b]	0.2 mM Ox-CD + 0.05 mM DMA	0.01
6	0.2 mM TD-CD + 0.05 mM Indole	0.08
7[b]	0.2 mM TD-CD + 0.05 mM Indole	0.01
8	0.5 mM TD + 0.05 mM Indole	<0.01

[a] Irradiation with 295 nm light for the indole-containing systems and 310 nm light for the DMA-containing systems, 10 nm bandwidths. [b] 50% Methanol aqueous solution.

6 with 3 and 8, respectively, in Table 2). This shows that interactions exist between the modified β-CDs and indole or DMA. However, a very low efficiency for the TD-CD system was observed in the presence of DMA, similar to the TD system.

Splitting quantum yields of the dimer/oxetane unit

The splitting quantum yields of the dimer/oxetane unit in the systems of Ox-CD/TD-CD and DMA/indole were measured, and are listed in Table 2. Data in Table 2 result in three eductions, as follows: (1) a strong concentration dependence (Fig. 4); (2) more efficient splitting over the systems of free Ox/TD and indole/DMA; and (3) a solvent-dependent splitting efficiency (entries 1/2, 4/5 and 6/7), much more efficient in water over that in the binary solvent of water–methanol (v/v, 50 : 50) due to a higher binding constant for a CD complex in water. The results showed the formation of supramolecular complexes between Ox-CD/TD-CD and the chromophores, in which the photosensitized splittings of the dimer/oxetane unit occur. In addition, the splitting of Ox-CD by DMA is more efficient than the indole system. A larger driving force for electron transfer between Ox-CD and DMA over indole may be an important reason for it.

Furthermore, a titration experiment was carried out and is shown in Fig. 4. The splitting quantum efficiency did not reach a maximum, for it was limited by a low solubility of Ox-CD. According to the inclusion interaction in a ratio of 1 : 1, the double reciprocal plot of $1/\Phi$ *versus* $1/c_{\text{Ox-CD}}$ (Michaelis–Menten equation) gave the association constant K_s from the ratio of the intercept to the slope of the straight line fit: 780 M^{-1} for the Ox-CD–DMA system, and 730 M^{-1} the for Ox-CD–indole system.

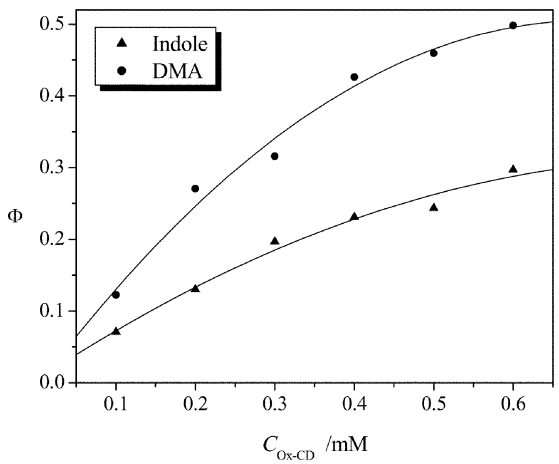


Fig. 4 Dependence of the quantum yield of splitting on concentration of Ox-CD aqueous solution containing 0.05 mM indole (λ_{ir} = 295 nm) or DMA (λ_{ir} = 310 nm).

It is evident that the quantum efficiencies in the complexes must be much higher than that in the covalently-linked models (Chart 2)[3c,4] composed of oxetane/dimer and a tryptophan residue, such as 0.093 for TD-Trp[3c] and 0.24 for Ox-Trp[4] in aqueous solutions. For example, the splitting quantum efficiencies are 0.16 for TD-CD/indole, and 0.24 for Ox-CD/indole in aqueous solution (at a ratio of 0.5 mM/0.05 mM), in which part indole molecules are included such as only 27% indole in the Ox-CD/indole complex in the solution. This implies that the photosensitized splitting reaction of the dimer/oxetane by an electron donor in a complex is highly efficient. Thus, back electron transfer of the radical ion pair upon electron transfer from an electron donor within a complex would be suppressed.

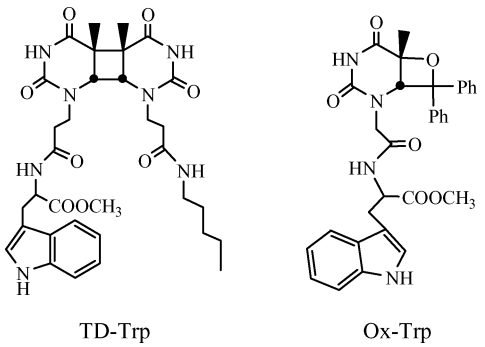


Chart 2

A recent ultrafast spectroscopic study[14] showed the charge shift with an quantum efficiency of 0.87, consistent with the repair quantum yield of 0.89, implying that the efficiency of the ring cleavage is nearly 100%. The active-site solvation was thought to be critical to strategically slowing down the charge recombination by dynamically tuning the redox potentials of reaction species and stabilizing the charge-shift radical intermediates, leaving enough time to cleave the cyclobutane ring to reach a maxium-repair quantum yield.

There may be a similar effect with the active-site solvation in the complex of Ox-CD/TD-CD and indole/DMA. After the forward electron transfer from the excited donor to the dimer/oxetane, the solvation of formed radical ions – a TD-/Ox- unit radical anion and a sensitizer radical cation – would occur, and more solvent molecules move to the interspace of the radical ion pair. This may change the redox potentials of the species, enlarge the distance of the two charge centers and stabilize the charge-separated radical pair. These would lead to a decrease in the driving force of back electron transfer, *i.e.* the charge recombination would be suppressed. However, the effects in a zwiterionic intermediate may not be well achieved for a covalently-linked model, at least the through-bond distance between a TD-/Ox- unit radical anion and a chromophore radical cation is constant, and the through-bond back electron transfer is the special mechanism for the

covalently-linked models. Therefore, it is further demonstrated that CPD photolyase binding the substrate and the active-site solvation in photoreactivation are important reasons why CPD photolyases can repair the substrates with high quantum efficiencies.

Despite the forward electron transfer (charge separation) in the tryptophan-containing model systems with similar quantum efficiencies (*ca.* 0.8)[3c,4] to CPD photolyase,[2c] the splitting quantum yields of the dimer or the oxetane are very low, *ca.* 0.1 for dimer–tryptophan models[3c] and *ca.* 0.3 for oxetane–tryptophan models[4] due to unproductive back electron transfer (charge recombination). In the case of flavin-containing systems, the deactivation of the excited flavin by non-radiative processes, which compete with forward electron transfer, is another important reason causing low splitting quantum yields.[4] Therefore, inefficient suppression of non-radiative processes and/or charge recombination may be responsible for the low repair efficiency of (6–4) photolyase. The mechanistic detail warrants co-crystal structures of photolyase–DNA complexes and ultrafast spectroscopic studies on (6–4) photolyase.

Experimental

General

β-Cyclodextrin was recrystallized three times and dried *in vacuo* at 100 °C for 12 h before use. Indole was purified by recrystallization from EtOH–water (1 : 10) before use. *N*,*N*-Dimethylaniline (DMA) was purified by distillation *in vacuo*. Deionized water was used throughout the experiments. The samples are fully aqueous solutions unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometer. The chemical shifts were referenced to acetone (δ 2.05, 29.8) in [D$_6$]acetone and DMSO (δ 2.50, 39.5) in [D$_6$]DMSO for ^{1}H and ^{13}C NMR, respectively. Mass spectra were measured on a Bruker BIFLEX™ III mass spectrometer. Elemental analysis was performed at the Analytic Center of University of Science and Technology of China. FTIR spectra were recorded on a BRUKER VECTOR22 infrared spectrometer. UV-Vis spectra were measured on a Shimadzu UV-2401PC spectrometer. Fluorescence emission spectra were measured on a Shimadzu RF-5301PC fluorescence spectrometer.

Measurement of quantum yield of splitting

The photosensitized splitting of the dimer/oxetane unit of TD-CD/Ox-CD by DMA or indole was first performed through determining the ^{1}H NMR spectra of solutions irradiated with a 300 W high pressure Hg lamp (λ > 290 nm) for 20 min. The solutions were prepared through dissolving TD-CD/Ox-CD and DMA/indole in D$_2$O in a Pyrex NMR tube, irradiating under ultrasonic waves for 15 min, then allowing to stand overnight.

The sample solutions (3 mL) of indole and DMA added to TD-CD or Ox-CD aqueous solutions were placed in quartz cuvettes (10 × 10 mm) with a Teflon stopper, and after standing for several hours at room temperature after ultrasonification for 15 min were then irradiated with 295 nm (for indole) or 310 nm (for DMA) light from a Shimadzu RF-5301PC spectrofluorophotomer. After certain time intervals, the absorbance of the irradiated solutions was recorded by a Shimadzu UV-2401PC spectrometer. The rates of the dimer/oxetane unit split were measured by the monitoring the increase in absorbance at 270 nm due to the regeneration of the 5,6-double bond of the thymines and benzophenone. The intensity of the light beam (I_0 einsteins/min) was measured by ferrioxalate actinometry.[13] Thus, the rate of photons absorbed was obtained from the absorbance (A) at 295 or 310 nm in terms of Beer's law, $I_a = I_0(1 - 10^{-A})$. The observed quantum yields of dimer/oxetane splitting of TD-CD/Ox-CD were calculated according to Φ = (rate of dimer/oxetane split)/(rate of photon absorbed). In order to avoid competition of absorbing between the model compound and the photosplitting products, the splitting reaction was controlled within 10% yield in the measurements.

Mono-6-deoxy-6-amino-β-cyclodextrin. ^{1}H NMR (300 MHz, D$_2$O, [D$_6$]acetone): δ = 3.46–3.69 (m, 14H), 3.87–4.02 (m, 28H), 5.09 (d, 7H). ^{13}C NMR (75 MHz, D$_2$O, [D$_6$]acetone): δ = 61.47, 73.05, 73.33, 74.52, 82.42, 82.59, 84.34, 103.08, 103.28.

6-Deoxy-6-*cis-syn* thymine dimer-β-cyclodextrin (TD-CD). A dimethylformide (DMF, 20 mL) solution of the *cis-syn* thymine dimer diacid (220 mg, 0.55 mmol) and 6-amino-β-cyclodextrin (0.57 g, 0.5 mmol) was stirred at 0–5 °C for 30 min. Dicyclohexylcarbodiimide (DCC) (160 mg, 0.75 mmol) and hydroxybenzotriazole (HOBt) (110 mg, 0.75 mmol) were added to the above mixture, and the solution was stirred at 0–5 °C for 2 h and then at room temperature for 2 d. After the insoluble material was removed by filtration, the filtrate was poured into acetone (200 mL) to precipitate the product. After being washed with acetone twice, the crude product was absorbed on a column of macroporous resin and eluted with an aqueous solution of ethanol (0 to 20%, v/v). The eluted solution was concentrated to obtain the desired product as a white powder (140 mg, 19%). Mp > 250 °C; ν_{max}(KBr)/cm^{-1} = 3419 s, 1702 s, 1646 s, 1155 m, 1081 m, 1034 s; ^{1}H NMR (300 MHz, D$_2$O, [D$_6$]acetone): δ = 1.30 (s, 6 H, CH$_3$), 2.47 (m, 4H, CH$_2$), 3.02 (m, 2H, CH$_2$), 3.11–3.79 (m, majority, proton of CD unit + CH$_2$), 4.02 (s, 2 H, CH), 4.90 (broad s, 7 H, H-1); ^{13}C NMR (75 MHz, D$_2$O, [D$_6$]acetone): δ = 17.05 (2C, CH$_3$), 33.00, 39.58, 39.73, 42.96, 47.34 (C), 47.42 (C), 59.20 (CH), 59.31 (CH), 59.64, 59.87, 69.68, 71.36, 71.48, 71.61, 72.32, 72.63, 80.46, 80.67, 82.39, 82.76, 101.41, 152.35, 152.39, 172.08, 172.73, 172.83; TOFMS (MALDI) calc. for [M + Na]$^+$ $C_{58}H_{89}N_5O_{41}$: 1535.3, found 1534.5.

6-Deoxy-6-oxetane-β-cyclodextrin (Ox-CD). Using the oxetane acid instead of the *cis-syn* thymine dimer diacid (183 mg, 0.5 mmol), the same procedure was performed, and the desired product Ox-CD was obtained as a white powder (115 mg, 16%). R_f = 0.18 (EtOAc–MeOH–AcOH 3 : 4 : 1); mp > 250 °C; ν_{max}(KBr)/cm^{-1} = 3424 s, 1705 s, 1155 m, 1081 m, 1032 s; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.58 (s, 3 H, CH$_3$), 3.22–3.76 (m, majority, proton of CD unit), 4.45 (m, 2 H), 4.84 (broad s, 7H, H-1), 5.73 (m, proton of CD unit), 7.27–7.44 (m, 10 H, Ar–H), 8.06 (s, 1 H, CONH), 10.39 (s, 1 H, NH); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.28 (CH$_3$), 47.68 (CH$_2$), 59.82, 59.93, 60.01, 65.11 (CN), 69.54, 72.08, 72.38, 72.99, 76.12 (*C*CH$_3$), 81.33, 81.54, 81.74, 83.37, 90.83 (O*C*C), 101.97, 102.07, 102.36, 124.89 (2C), 124.97, 125.51, 127.77, 128.25, 128.60 (2C), 139.61, 144.60, 151.26, 167.70, 169.86; Anal. calc. for $C_{62}H_{87}N_3O_{38}\cdot 6H_2O$ (1590.46): C, 46.82; H, 6.27; N, 2.64. Found: C, 47.07; H, 6.41;

N, 2.61%; TOFMS (MALDI) calc. for $[M + Na]^+$ $C_{62}H_{87}N_3O_{38}$: 1505.4, found 1504.6.

Acknowledgements

The authors are grateful for the financial support by the National Natural Science Foundation of China (Grant No. 30470444, 20332020).

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