First Asymmetric Photochemistry with Nucleosides and DNA: Enantiodifferentiating *Z–E* Photoisomerization of Cyclooctene

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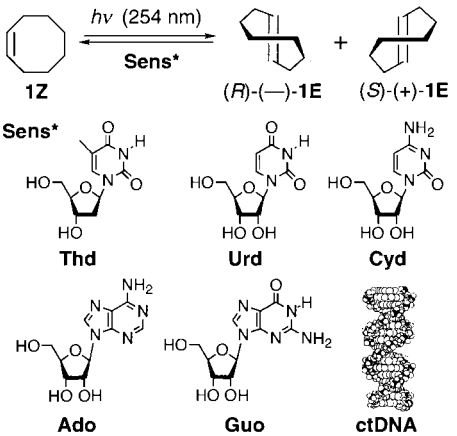
Thymidine and uridine, as well as calf thymus DNA (ctDNA), have been shown for the first time to function as chiral photosensitizers in aqueous solution, to effect the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene, giving the chiral (*E*)-isomer in enantiomeric excesses of up to 15%.

Enantiodifferentiating photosensitization is an attractive chirogen-effective method for transferring molecular chirality in the electronically excited state.[1,2] However, despite the considerable efforts devoted to asymmetric photosensitization, the enantiomeric excesses (ee's) obtained have not exceeded the original value (6.7%) reported by Hammond and Cole in 1965.[3] Recently, we have demonstrated that moderate to good ee's of up to 73% are attained in the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) to the chiral (*E*)-isomer (**1E**) when sensitized by chiral (poly)alkyl benzene(poly)carboxylates.[4] Mechanistic studies have revealed that the chiral recognition occurs within the intervening singlet exciplex, formed upon quenching of the excited sensitizer by **1**, and that the product's ee is governed externally by entropy-related factors such as temperature, pressure, and solvent, whilst internally by the steric and electronic effects of both sensitizer and substrate.[4]

Only a limited number of approaches have hitherto been made to the asymmetric photosensitization in supramolecular systems.[2a,b,5] In a recent study, we have investigated such an approach with the enantiodifferentiating photoisomerization of **1Z** using β-cyclodextrin 6-*O*-benzoate as a chiral sensitizing host, obtaining moderate ee's of up to 13% in aqueous solution.[6]

In previous studies,[4] we have consistently employed arenecarboxylates as chiral sensitizers, in which the chirogenic center is separated by at least three C–C/C–O bonds from the aromatic chromophore. In this context, nucleosides appear to be more promising as chiral sensitizers, since the optically active furanose moiety is directly connected to the chromophoric nucleobase in a more defined orientation. Furthermore, this approach may open a channel to the supramolecular asymmetric photosensitization with DNA used as a chiral sensitizing host in aqueous solution.

Most of the investigations on the photochemistry of nucleic acids have been related to skin cancer research,[7] while the photoinduced electron transfer through double stranded DNA (dsDNA) has attracted widespread interest of non photo-, bio- and physicochemists in the last decade.[8] Although photosensitized reactions[9] and modifications[10] of DNA and RNA have also been extensively investigated, nucleosides and DNA have rarely been employed as photosensitizers, probably due to their photolabile nature.[8] Nevertheless, these biomolecules, possessing both chromophoric nucleobase and furanose units, should function as aqueous based chiral sensitizers, and more importantly the lipophilic helical grooves of dsDNA should provide the chiral environment for supramolecular asymmetric photosensitization.



Scheme 1. Photoisomerization of (*Z*)-cyclooctene sensitized by nucleosides and ctDNA

In this first attempt to use nucleosides and dsDNA as chiral sensitizers/hosts, we employed the enantiodifferentiating photoisomerization of **1Z** as a bench-mark test system for examining their ability to transfer supramolecular chirality through the excited state interactions, since common nucleosides absorb around 260 nm UV light ($\varepsilon \doteqdot 10^4$), emit weak fluorescence around 330 nm ($\phi = 10^{-3}$–10^{-4}), and possess singlet energies (E_S) around 410 kJ/mol,[11] which are comparable to those of benzenecarboxylates[4b] and therefore expected to function as chiral photosensitizers.

Aqueous solutions containing **1Z** (0.23 mmol/dm^3) and representative nucleosides (0.1 mmol/dm^3) were irradiated at 254 nm at 25 °C under an argon atmosphere to give the (*E*)-isomer (**1E**) as the sole product, as detected by GC in varying chemical and optical yields. UV spectral examinations of the photostability of nucleosides under the irradiation conditions employed revealed that thymidine (Thd), adenosine (Ado), and guanosine (Guo) are highly stable even upon irradiation of up to 1 h, retaining at least 95% of the original absorbance around 260 nm. In contrast, uridine (Urd) is much more unstable under the irradiation conditions, affording almost no absorption at 260 nm after 1 h irradiation, most probably as a result of the well-documented photohydration reaction,[12] although the rate of decrease in absorbance was reduced to some extent in the presence of substrate **1Z**. The *E*/*Z* ratio at the photostationary state ($(E/Z)_{pss}$) and ee of **1E** obtained upon photosensitization with nucleosides and DNA are listed in Table 1, along with the relevant values for sensitizations with (–)-menthyl and 1,2;5,6-di-*O*-isopropylidene-α-D-glucofranyl (DAG) benzoates.[4b,13]

The photosensitizations with Thd and Urd gave remarkably high $(E/Z)_{pss}$ of 0.66 and 0.33, respectively, which are much greater than the ratios (0.26–0.27) obtained with the conventional singlet sensitizers such as menthyl and DAG benzoates,[4b,13] indicating efficient singlet energy transfer from Thd and Urd to **1Z**. In sharp contrast, the photosensitizations with Ado and Guo

afforded very low $(E/Z)_{pss}$ ratios of ca. 0.005. This contrasting behavior cannot simply be attributed to the sensitizer E_S but rather to the structural and electronic differences between the pyrimidine and purine nucleobases. CtDNA[14] gave a slightly better $(E/Z)_{pss}$ of 0.014 at 25 °C. As all of the nucleobases are paired and stacked tightly in ctDNA, the usual sensitization mechanism through the exciplex formation[4] is unable to occur. In a separate experiment using circular dichroism (CD) spectroscopy under comparable conditions, the addition of **1Z** to an aqueous solution of ctDNA gave rise to slight but appreciable changes in the CD spectrum. Since the resulting spectrum still retains the original shape characteristics of B-form DNA, the small changes observed would originate from the weak interaction of **1Z** molecules with the ctDNA. It is known that small hydrophobic molecules are bound to minor grooves, rather than to major grooves or phosphate backbone. The excited state(s) involved in this photosensitization are at present not clear, but the singlet mechanism may be favored since the photosensitizations of **1Z** with Thd under both argon and under air gave comparable $(E/Z)_{pss}$ and ee values at 25 °C (Table 1).

The produced **1E** was isolated from the irradiated solution through the conventional silver nitrate extraction technique,[4b] and was subjected to chiral GC analysis to give the ee values shown in Table 1. Although the sensitizations with the purine nucleosides, Ado and Guo, resulted in the formation of the racemic product with very low $(E/Z)_{pss}$, the use of the pyrimidine nucleosides, Thd and Urd, as chiral sensitizers gave (*S*)-(+)-**1E** in 5.2 and 3.1% ee, respectively. These ee's are not particularly high, but are appreciable improvements when compared to the previous values (0–2.7% ee) obtained in the photosensitization with a variety of chiral alkyl benzoates after a decade-long effort.[4] Probably the shorter tether connecting the chromophoric and chirogenic moieties, and the reduced conformational freedom of the pyrimidine nucleosides compared to those of the chiral benzoates, are jointly responsible for the enhanced ee's.

Interestingly, the photosensitization with ctDNA gave antipodal (*R*)-(–)-**1E** in increased ee's of 9.2% at 25 °C and 15.2% at 5 °C, but racemic **1E** at an elevated temperature (75 °C). Since the nucleosides used as chiral sensitizers consistently afford (*S*)-(+)-**1E**, an identical molecular sensitization mechanism with the component nucleoside units cannot rationalize the formation of antipodal product upon sensitization with ctDNA. The small CD spectral changes upon addition of **1Z** to the ctDNA solution, the rapidly decreasing ee's observed by increasing the temperature (in spite of the thermal stability of double strand ctDNA even at 90 °C), and the formation of the antipodal product strongly suggest that the formation of a supramolecular complex between **1Z** and ctDNA in the ground state, and the subsequent photoisomerization to chiral **1E**, are the essential factors for achieving highly enantiodifferentiating photosensitization. To confirm this, we performed the photosensitization with ctDNA in 50% aqueous methanol solution. In this solvent, hydrophobic **1Z** is highly soluble and therefore no supramolecular interactions between ctDNA and **1Z** are expected to occur, yet ctDNA maintains its original B-form. As shown in Table 1, the ee obtained in aqueous methanol solution greatly decreased to 0.9%, clearly indicating the crucial role of the supramolecular interaction with ctDNA in this enantiodifferentiating photosensitization.

In this study, we have demonstrated for the first time that common nucleosides and ctDNA function as chiral photosensitizers for the enantiodifferentiating isomerization of cyclooctene. However, this newly developed function of nucleosides and nucleotides should not be solely restricted to this particular system, but could readily be expanded to a wide variety of molecular and supramolecular asymmetric photochemistry. Further studies are currently underway to clarify the **1Z** nucleoside/nucleotide binding modes and photosensitization mechanisms presented here.

Table 1. Enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) sensitized by aromatic esters, nucleosides, and calf thymus DNA[a]

Sensitizer	*Es*[b]	Solvent	Temp/°C	$(E/Z)_{pss}$[c]	ee/%[d]
(–)-Menthyl Benzoate[e]	428.0	pentane	25	0.26	-2.7
DAG Benzoate[f]	428.0	pentane	25	0.27	-0.6
Thd[g]	406.7	H_2O	25	0.66	+5.2
Thd[g]	406.7	H_2O[h]	25	0.59	+4.6
Urd[g]	419.7	H_2O	25	0.33	+3.1
Ado[g]	420.9	H_2O	25	0.005	i
Guo[g]	403.8	H_2O	25	0.006	i
ctDNA[g]	j	H_2O	75	0.005	i
ctDNA[g]	j	H_2O	25	0.014	-9.2
ctDNA[g]	j	H_2O	5	0.008	-15.2
ctDNA[k]	j	MeOH-H_2O (1:1)	25	0.014	-0.9

[a] Irradiations performed at 254 nm for 30 min under argon atmosphere, unless stated otherwise. [b] Singlet energy of sensitizer in kJ/mol (references 4b and 11). [c] Photostationary state *E/Z* ratio obtained upon prolonged irradiation. [d] Enantiomeric excess of isolated **1E**, determined by chiral GC (Supelco β-Dex 225 column); error in %ee < ±0.5; the positive and negative ee values refer to the predominant formation of (*S*)-(+)- and (*R*)-(–)-**1E**, respectively. [e] [Sens] = 5 mmol/dm^3, [**1Z**] = 0.2 M (reference 4a). [f] [Sens] = 1 mmol/dm^3, [**1Z**] = 5 mmol/dm^3; DAG = 1,2;5,6-di-*O*-isopropylidene-α-D-glucofranyl (reference 13). [g] [Nucleoside] or [nucleotide in ctDNA] = 0.1 mM, [**1Z**] = 0.23 mmol/dm^3. [h] Irradiated under air. [i] Less than 0.5%. [j] Not determined. [k] [nucleotide in ctDNA] = 0.32 mmol/dm^3, [**1Z**] = 4.3 mmol/dm^3.

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