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Control of Conformer Population and Product Selectivity and Stereoselectivity in Competitive Photocyclization/Rearrangement of Chiral Donor–Acceptor Dyad

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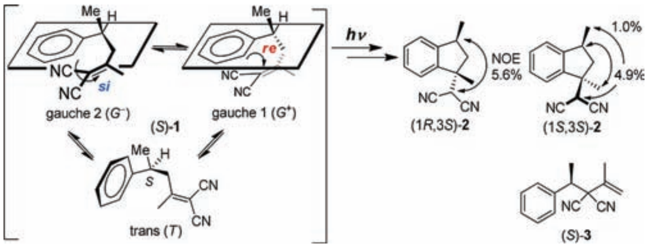
S *Supporting Information*

ABSTRACT: The conformer population and the relative excitation efficiency of each conformer, assessed by theoretical and experimental examinations, enabled us to precisely control the chemo- and diastereoselectivities of the competitive photocyclization/rearrangement reaction of a chiral donor–acceptor (D/A) dyad by irradiation wavelength, solvent polarity, and reaction temperature. Manipulating the ground- and excited-state conformer equilibria is essential for critically controlling the intramolecular D/A system, in sharp contrast to the rather divergent excited species involved in relevant intermolecular systems.

Precisely controlling stereochemistry is still a challenge in chiral photochemistry, despite the recent endeavors devoted to a variety of molecular, supramolecular, and biomolecular photochirogenic systems.[1] The encounter of chiral reactant or sensitizer with substrate and the subsequent chirality transfer should be accomplished within the lifetime of the excited species involved (~ns). Entropy-related environmental variants, such as temperature, solvent polarity, and pressure, are known to function as effective tools for manipulating the molecular geometry and recognition mode in the excited state and eventually the stereochemical outcomes in chiral photoreactions.[2] Another inherent advantage unique to photochemistry is the choice of excitation wavelength, allowing us to tune the stereochemical consequences beyond the fetters of ground-state thermodynamics. Indeed, selective excitation at the charge-transfer (CT) band affords regio- and diastereoselectivities that significantly differ from those obtained upon local-band excitation of the donor in the [2+2] photocycloaddition of stilbene with chiral fumarates and also in the Paternó–Büchi reaction of 1,1-diphenylethene with chiral *p*-cyanobenzoates.[3] The successful regio-/diastereocontrol by wavelength in these intermolecular donor–acceptor (D/A) systems prompted us to explore the general validity and elucidate the mechanistic details of wavelength-dependent photoreactions.

In this study, we prepared a chiral D/A dyad, (*S*)-1,1-dicyano-2-methyl-4-phenyl-1-pentene (**1**), as a tethered substrate for enhanced CT interactions and investigated the competitive photocyclization/rearrangement behavior (Scheme 1) under a variety of irradiation conditions. Photoirradiation of **1** afforded diastereomeric cyclization product **2** and rearrangement product **3**, as was the case with the related achiral analogues.[4,5] The diastereomers of **2** were separated by GC (see Figure S1 in the Supporting Information), and the stereochemistry was determined by differential NOE (Scheme 1 and Figures S9 and S10). The photorearrangement of **1** to **3** in cyclohexane is known to proceed with only ~85% stereoretention, presumably via the aromatic $\pi-\pi^*$ state.[6] The use of an intramolecular dyad facilitated the ground-state CT interactions, as evidenced by the CT band observed at longer wavelengths (Figure S2), and permits direct UV–vis and CD spectroscopic inspection of the ground-state complex. The cyclization occurs primarily from the energetically favored gauche conformers (G^+ and G^-) rather than trans conformer (T). The two gauche conformers are diastereomeric to each other, and the *re*- or *si*-face of the dicyanoethylene moiety faces, and is prone to react with, the phenyl ring (Scheme 1).

Scheme 1. Diastereodifferentiating Competitive Photocyclization/Rearrangement of 1 to 2 and 3 upon Direct and CT-Band Excitations[a]



[a]The stereochemistry of **2** was determined by differential NOE spectra. See the Supporting Information for details.

For a more rational and universal methodology for accurately controlling the chemo- and diastereoselectivities, we employed a combined experimental and theoretical approach to elucidate the conformer geometry, stability, population, and chiroptical properties relevant to this competitive chiral photocyclodimerization/rearrangement reaction. The calculations predict the relative extinction coefficient of each conformer at a given wavelength, enabling us to selectively excite the desired conformer and also to precisely control the product selectivities and diastereoselectivities in combination with the external variants, such as solvent and temperature. Indeed, the shift of equilibrium by varying solvent and temperature, monitored by CD spectroscopy, can nicely rationalize the photochemical

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behavior of **1**. In the intermolecular D/A systems reported previously, the differences in structure and/or solvation between the excited CT complex and the conventional exciplex are the source of the wavelength-dependent diastereoselectivity observed. In the intramolecular dyad system employed here, the number of possible conformations is greatly reduced to only a pro-*R*/*S* pair of *T*, G^+, and G^- conformers, the properties and population of which are critical functions of wavelength, solvent, and temperature to determine the product selectivities and diastereoselectivities through the conformational equilibria in the ground and excited states.

Photoirradiations of **1** were run at λ = 260−300 nm through band-pass filters (fwhm 10 nm) in acetonitrile at 25 °C to give **2** and **3** without any byproduct (Table S1). The **2**/**3** ratio gradually increased with increasing irradiation λ, while the diastereomeric excess (de) of **2** was practically constant at ~30% with 260−270 nm irradiations (local band excitation), but then leaped to 56−59% with 280−300 nm irradiations (CT band excitation). These results permitted us to choose 254 nm for direct excitation and 280 and 300 nm for CT excitation; note that the direct excitation is not completely direct, but the direct/CT excitation ratio is estimated as ~1.2 at 254 nm from the absorbance of the CT complex (deconvoluted ε_{CT}) relative to that of a 1:1 mixture of cumene and 1,1-dicyano-2-methyl-1-propene (estimated ε_{direct}), while the CT excitation was nearly selective btoh at 280 and 300 nm. Although **1** did not fluoresce in solution, the presence of oxygen did not affect the yield or product distribution (Table S2), suggesting that the contribution of triplet manifold and radical intermediate[7] is minor and the photoreaction proceeds mostly through the singlet manifold. The reaction was generally clean, and thus the product ratio was constant throughout the reaction (Table S3).

Table 1 summarizes the results of the photoreaction of (3*S*)-**1** under a variety of irradiation conditions (see also Table S4). While (1*R*,3*S*)-**2**, designated by positive de values in Table 1, was favored under most of the reaction conditions employed, (1*S*,3*S*)-**2** became predominant upon irradiation at 254 nm in acetonitrile. The sample concentration was kept low at 0.1 mM to expedite the direct comparison of the photobehavior with the spectral examinations. The **2**/**3** ratio became smaller in less polar solvents, indicating that the transition state or intermediate leading to cyclization is polar. In contrast, the rearrangement is sigmatropic in nature and hence less polarized.[4,6] In acetonitrile, the **2**/**3** ratio increased upon excitation at longer wavelengths and at lower temperatures (excepting the data obtained at −40 °C upon 280 nm irradiation). This can be explained by the equilibrium shift from extended trans to folded gauche with CT character in ground and/or excited states, facilitating cyclization to **2**. The de of **2** obtained in acetonitrile was also temperature-dependent, but the changing pattern was not very smooth. Upon CT excitation, (1*R*,3*S*)-**2** was consistently favored, and the de reached a maximum at 0 to −20 °C, while (1*S*,3*S*)-**2** was obtained as the major product only upon direct excitation in acetonitrile. This means that the excited CT complex formed upon excitation at 280 or 300 nm affords **2**, which is however epimeric to the one produced from the conventional exciplex generated upon direct excitation at 254 nm. The de's obtained upon CT excitation differed appreciably between 280 and 300 nm; the lower de's at 280 nm may arise from possible contamination by direct excitation. The de became much higher in CH_2Cl_2, but **2** was not detected in methylcyclohexane. The de of **2** was enhanced up to 90% in CH_2Cl_2 upon CT excitation at 300 nm.

Table 1. Temperature and Solvent Effects on the Product Ratio and Diastereoselectivity in Photocyclization/Rearrangement of 1 to 2 and 3 upon Direct (254 nm) and CT Excitations (280 and 300 nm)[a]

		excitation wavelength					
		254 nm		280 nm		300 nm	
solvent	temp/°C	**2**/**3**	% de[b]	**2**/**3**	% de[b]	**2**/**3**	% de[b]
MeCN	20	0.09	−24	0.33	+28	0.86	+57
	0	0.13	−17	0.44	+66	1.91	+63
	−20	0.27	−16	0.73	+52	2.26	+75
	−40	0.35	−14	0.53	+45	2.63	+51
CH_2Cl_2	20	0.01	+20	0.02	+82	0.61	+90
MCH[c]	20	<0.01	–	<0.01	–	<0.01	–

[a] [**1**] = 0.1 mM; irradiated under Ar at 254 nm for 1 h or at 280/300 nm for 2 h. [b] Diastereomeric excess of **2**; the + and − signs indicate favored formation of (1*R*,3*S*)- and (1*S*,3*S*)-**2**, respectively. [c] Methylcyclohexane.

Eyring analyses[8] of the de's obtained at various temperatures were performed by plotting the ln([(1*R*,3*S*)-**2**]/[(1*S*,3*S*)-**2**]) values against 1/*T* to give bent lines, irrespective of the irradiation λ (Table S5), clearly indicating switching of the diastereodifferentiation mechanism in the temperature range examined.[9] The stereochemistry of cyclization product **2** is a consequence of the ground- and excited-state equilibria as well as the relative rate of cyclization (*vide infra*). If the cyclization efficiencies are comparable for pro-*S*/*R*, the de of **2** directly reflects the conformer distribution in the ground state at lower temperatures, where the conformer equilibria become much slower (relative to the cyclization). Thus, at low temperatures, the Eyring plot gave a single straight line with the slope and intercept being obviously dependent on excitation λ (Tables 2 and S5), indicating the operation of a single, but distinct, diastereodifferentiation mechanism for direct (254 nm) and CT (280 nm) excitation. The activation parameters at 300 nm, gauged tentatively, gave trends similar to those at 280 nm. Contrasting trends between the direct and CT excitations are common to other D/A systems hitherto studied. The magnitudes of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ also depend on the mode of excitation; i.e., the parameters are significantly larger for the CT rather than direct excitation. This contrasting behavior upon direct versus CT excitation led us to the efficient wavelength control in chiral photoreaction.[3] The difference in activation parameter, however, becomes less significant at higher temperatures (Table S5), where the fast excited-state equilibrium cancels the effect of selective direct/CT excitation (*vide infra*).[10]

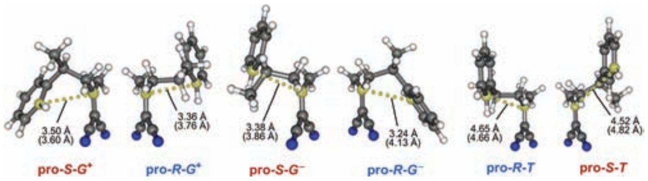
Table 2. Activation Parameters for the Preferential Formation of (1*R*,3*S*)-2 over (1*S*,3*S*)-2 upon Direct and CT Excitations of 1[a]

excitation mode	wavelength/nm	$\Delta\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
direct	254	+0.82	−5.9
CT	280	−8.1	+42
	300	−20[b]	+96[b]

[a] See the Supporting Information for the Eyring plots. [b] Tentative value derived from the de's obtained at two different temperatures.

For better understanding of the photochemical behavior, we applied the theoretical calculations to this intramolecular D/A system. The geometrical optimizations were performed at the SCS-MP2/TZVPP level, which has been shown to provide the most reliable energies and geometries, comparable to the CCSD(T) level, for medium-to-large molecules.[11] All possible conformations of **1** were initially considered, and 6 out of 54 conformers were found feasible; see the structures in Table 3 (see also SI for the details of geometry search). These are pro-*R*/*S* pairs of trans and two gauche conformations with respect to the central C3−C4 bond (Chart S1), and the trans pair cyclize to antipodal products. As can be seen from the Boltzmann distributions in Table 3, the pro-*R*- and pro-*S*-G^+ conformers are of primary importance in considering the product stereoselectivity. The preference for pro-*S*-G^+ in the ground state is further emphasized in acetonitrile compared to the gas phase, as supported by the relative energies and populations obtained by using a relatively simple PCM-type solvation model (COSMO).[12]

Table 3. Relative Energies ΔE and Conformer Populations (in Parentheses) in Gas Phase and in Acetonitrile Calculated by the SCS-MP2 Methods[a]



		ground state		
conformation		gas phase	acetonitrile	excited state
gauche-1	pro-*S*, −ac	≡ 0 (55.0)	≡ 0 (69.7)	1.5 (6.6)
(G^+)	pro-*R*, +sc	0.20 (39.0)	0.32 (22.0)	1.1 (11.7)
gauche-2	pro-*S*, −ac	2.1 (1.7)	2.4 (1.2)	1.8 (3.9)
(G^-)	pro-*R*, +ac	2.7 (0.5)	2.3 (1.4)	≡ 0 (77.0)
trans	pro-*S*, +ac	1.8 (2.7)	1.6 (4.5)	3.2 (0.4)
(*T*)	pro-*R*, −sc	2.3 (1.1)	2.4 (1.3)	3.2 (0.4)

[a] Relative SCS-MP2/TZVPP energies (in kcal mol^{-1}) and Boltzmann populations (%) at 25 °C in gas phase or in acetonitrile (COSMO, $\varepsilon = 36.64$). The excited-state energies and populations are based on the RI-CC2 excitation energies for the ground-state geometries. The numbers in the figure show the distance between the atoms to be bonded upon cyclization, while those in the parentheses are for the diastereomeric product (if formed).

The first excitation energies of the six conformers were calculated by the linear-response resolution-of-identity approximate coupled-cluster theory (RI-CC2).[13,14] Although the vibrational zero-point energies were not taken into account in our calculations, the conformer preference was switched to favor the G^- conformer, in particular pro-*R* rather than pro-*S*, in the excited state. Thus, the (1*S*)-product should be favored, unless the excited-state equilibrium is slower than the photocyclization. In this relation, it should be noted that our calculations predicted that the trans conformers are less populated both in the ground and excited states, despite the previous suggestion of the trans conformer as a precursor to the rearrangement product.[4] In any case, the ensemble[15] of pro-*R*/*S*-*T*, -G^+, and -G^- is indispensable for explaining the diastereodifferentiation mechanism.

CD spectra are sensitive to conformational changes in solution.[16] Hence, experimental and theoretical CD spectral studies provided further insights into the mechanism of the solvent, temperature, and wavelength dependences observed in the photoreaction of **1**. The CD spectra of **1** were recorded in a variety of solvents (Figure 1a) to exhibit a negative Cotton effect at ∼260 nm in acetonitrile, which was inverted in sign in less polar solvents to eventually afford the strongest positive Cotton effect in nonpolar methylcyclohexane. Such a dramatic solvent dependence can be readily rationalized if the pro-*S*-G^+ conformer is favored in acetonitrile, while the pro-*R*-G^+ gradually becomes dominant in less polar solvents, since the theoretical CD calculations predicted negative and positive Cotton effects at ∼250−270 nm for pro-*S*- and pro-*R*-G^+ conformers, respectively (Figure 1c). Experimentally, the negative Cotton effect at ∼260 nm in acetonitrile was further enhanced by lowering temperature (Figure 1b), indicating the existence of the equilibrium between the pro-*S* and the pro-*R* forms that gradually shifts to the pro-*S* side at lower temperatures.

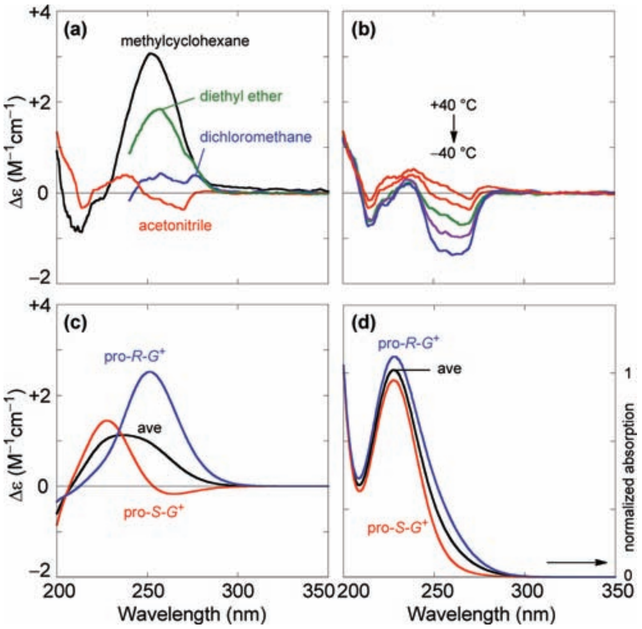
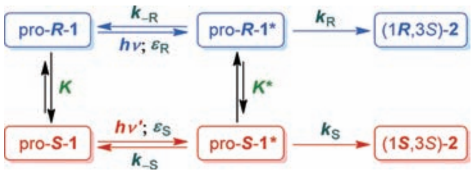


Figure 1. (a) Experimental CD spectra of (*S*)-**1** in methylcyclohexane, diethyl ether, dichloromethane, and acetonitrile (from top to bottom at 260 nm) at 20 °C. (b) Experimental CD spectra of (*S*)-**1** in acetonitrile at +40, +20, 0, −20, and −40 °C. (c) Theoretical CD calculated for pro-*R*- and pro-*S*-G^+ conformers of (*S*)-**1** and the average; all obtained by Boltzmann population-weighted averaging of the six conformers (shown in Table 3) at the RI-CC2/TZVPP level. The spectra were red-shifted by 0.4 eV and scaled by a factor of 10. (d) Theoretical UV spectra of **1**.

Scheme 2 illustrates the diastereodifferentiation mechanism and the species involved in the photocyclization of **1**. In the ground state, the pro-*R*/*S*-G^+ conformers are predominant (highlighted by boldface) and equilibrated with the other minor conformers (e.g., G^- and *T*). These conformations are represented by two ensembles, pro-*R*- and pro-*S*-**1**, and their equilibrium by one constant *K*. Upon irradiation, these conformers are vertically excited to the Franck−Condon states, which are subsequently subjected to the excited-state equilibrium with constant *K** (Table 3), favoring pro-*R* (highlighted in Scheme 2), as well as the competition with

Scheme 2. Factors Controlling the Diastereodifferentiating Photocyclization of 1[a]



[a] K and K* represent the apparent equilibrium constants between the pro-R/S conformer ensembles (each composed of T, G^+, and G^-) in the ground and excited states, respectively.

cyclization (k_R/k_S) and deactivation (k_{-R}/k_{-S}). Furthermore, the extinction coefficients of pro-R- and pro-S-**1** are not equal to each other ($\varepsilon_R \neq \varepsilon_S$) and vary with the excitation wavelength. Hence, the conformer population in the ground state is not directly reflected in the product distribution. Taking into account these factors and the mechanism proposed, we can rationalize the effects of solvent, temperature, and wavelength as follows: (1) The preference for the (1R)-product in dichloromethane, than in acetonitrile, is attributable mostly to the ground-state equilibrium shift to pro-R, as supported by the experimental and theoretical CD spectra. (2) Since the Eyring plots of the de values are bent, the diastereodifferentiation mechanism is likely to be switched in the temperature range examined, for which the decelerated ground-state equilibrium, relative to the excited-state equilibrium at lower temperatures, would be responsible. (3) Irradiation at longer wavelength leads to the selective excitation of pro-R, as supported by experiment and theory (Figure 1d).

We have shown that both the product selectivity and diastereoselectivity can be critically controlled by irradiation wavelength in this intramolecular D/A dyad system. The stereochemical outcomes of photocyclization are significantly affected also by solvent polarity and temperature, mostly due to the shift of the ground-state conformer equilibrium. The excited CT state generated upon excitation at the CT band behaves differently from the conventional exciplex formed upon local-band excitation. At higher temperatures, the excited-state conformer equilibrium competes with the deactivation (k_{-R} and k_{-S}) and cyclization (k_R and k_S) to achieve a population different from that in the ground state. Interestingly, the **2**/**3** ratios and de values obtained upon CT excitation at 280 and 300 nm differed significantly, as a result of the different spectral features of the G^+ and G^- conformers, enabling us to fine-tune the stereochemical outcomes. We may conclude that manipulating the excited-state ensemble is essential for critically controlling the stereochemical outcomes of photoreaction by temperature, solvent polarity, and most effectively by irradiation wavelength.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, details of theoretical calculation, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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