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Wavelength Control of Diastereodifferentiating Paternó−Büchi Reaction of Chiral Cyanobenzoates with Diphenylethene through Direct versus Charge-Transfer Excitation

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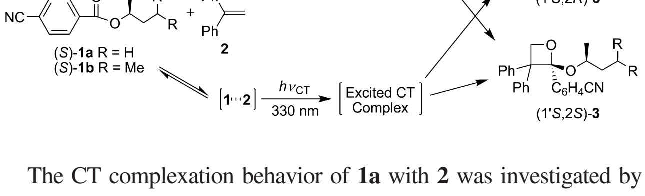
The Paternó−Büchi reaction provides us with a versatile route to a variety of chiral oxetanes, which are often found in biologically important molecules, including taxol, preussin, and oxetanocin, and are recognized as promising drug-discovery modules.[1] Thus, the manipulation of stereoselectivity[2] by the use of allylic strain[3] and hydrogen-bonding interactions[4] has been a target of intensive study. Most Paternó−Büchi reactions are known to proceed through triplet 1,4-biradical intermediates, which either revert to the starting materials or cyclize to the corresponding oxetanes after spin inversion.[5] The stereochemistry of the product is thus determined in the initial addition[6] and/or the second cyclization.[7] Because of this mechanistic complexity in oxetane formation, the Eyring-type treatment, in which the logarithm of stereoselectivity is plotted against reciprocal temperature, often gives a bent plot, indicating a switching of the mechanism in the temperature range employed.[8] More recently, the role of the singlet manifold in the Paternó−Büchi reaction has been revealed from the stereochemical viewpoint.[9]

In the present study, we report the wavelength-dependent diastereodifferentiating Paternó−Büchi reaction of chiral *p*-cyanobenzoates (**1a**, **1b**) with 1,1-diphenylethene (**2**). In our recent study of the [2 + 2] photocycloaddition of stilbene with chiral fumarates, we revealed that direct excitation of stilbene and selective excitation of the CT band afford the same cyclobutane but with totally different diastereoselectivities.[10] This result indicates that the excited CT complex differs in structure and reactivity from the conventional exciplex and that these excited-state complexes do not interconvert. The effect of excitation wavelength on the photophysical behavior of the CT complex has also been investigated spectroscopically.[11] These observations prompted us to further explore the general validity and feasibility of the wavelength-dependent photochemistry based on the CT excitation as a conventional yet powerful tool for critically manipulating the product's stereochemistry. Intriguingly, this photocycloaddition reaction exhibited the opposite temperature dependence upon CT versus direct excitation, reflecting the different degrees of freedom in the excited species involved (see below).

Scheme 1. Diastereodifferentiating Photocycloaddition of **1** to **2** upon Direct and CT-Band Excitation



The CT complexation behavior of **1a** with **2** was investigated by UV−vis spectroscopy and found to have a modest binding constant ($K = 0.04$ M^{-1}) in methylcyclohexane at 25 °C (see Figure S1 in the Supporting Information). Irradiation of a concentrated solution of **1a** (0.2 M) and **2** (1 M) at 254 nm led to the formation of a diastereomeric mixture of oxetanes **3a** in good combined yield (Scheme 1), in accordance with the previous reports for achiral analogues.[12] The yield and diastereomeric excess (de) of **3a** were not affected by the addition of oxygen (air), in accord with the singlet mechanism (Table S1). The de of **3a** remained constant at 65% upon excitation at 254 and 290 nm but gradually decreased to 43−46% when the wavelength was shifted to 310−320 nm, and eventually the epimeric product was obtained in 4% de upon excitation at 330 nm (Table S2).[13] These results clearly indicate that the excited CT complex formed upon excitation at longer wavelengths affords the same adduct **3a** but that this adduct is epimeric to the one produced from the conventional exciplex generated upon direct excitation at shorter wavelengths. We confirmed the absolute configuration of the products by X-ray crystallography; the minor isomer has the 1′*S*,2*R* configuration (Figure 1, left).

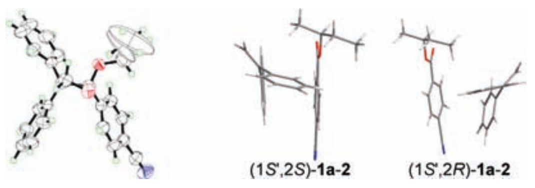


Figure 1. (left) ORTEP drawing of the minor isomer, (1′*S*,2*R*)-**3a**. (right) Structures of the diastereomeric CT complexes that are precursors to (1′*S*,2*S*)- and (1′*S*,2*R*)-**3a**, optimized at the DFT-D-B-LYP/TZVP level. The Tg$^+$ conformers in the chiral group are shown.

Mechanistic elucidations of Paternó−Büchi reactions often rely on temperature-dependence studies.[7,8] Interestingly, the de values of **3a** or **3b** obtained upon direct and CT excitation of a methylcyclohexane solution of **1a** or **1b** and **2** (Table 1) showed opposite temperature-dependence profiles. Thus, when the temperature was lowered from 25 to −50 °C, the de decreased from 77 to 34% for **3a** and from 74 to 66% for **3b** upon direct excitation. In sharp contrast, the same temperature change improved the de from 3 to 26% for **3a** and from 18 to 44% for **3b** upon CT excitation. This contrasting behavior unambiguously confirms that the conventional exciplex and the excited CT complex do not share a common structure but have distinctly different structures and reactivities that give cycloadduct **3** with significantly different diastereoselectivities and temperature dependencies.

From the Eyring analyses[14] of the de's using plots of ln{[(1′*S*,2*S*)-**3**]/[(1′*S*,2*R*)-**3**]} versus 1/*T* (Figure S2), we obtained the differential activation enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy ($\Delta\Delta S^{\ddagger}$) (Table 2). The Eyring plots gave nice straight lines that had different slopes and intercepts with opposite signs, indicating the operation of a single but distinct diastereodifferentiation mechanism for each substrate

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and excitation mode. As a consequence of the opposite temperature dependence of the de, oppositely signed $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values were obtained for the direct and CT excitations. It should be noted that the positive de, or the preferred formation of (1′*S*,2*S*)-**3**, is an incidental phenomenon only in the temperature range employed and that the epimeric product should be obtained at lower and higher temperatures upon direct and CT excitation, respectively.

Table 1. Temperature Effects on the Diastereoselective Paternó−Büchi Reaction of **1a** or **1b** with **2** upon Direct and CT Excitation[a]

	% de of **3a**		% de of **3b**	
temperature (°C)	direct	CT	direct	CT
50	77	3	74	18
25	64	4	71	22
0	63	3	−	−
−25	43	24	−	41
−50	34	26	68	44

[a] Using a methylcyclohexane solution of **1** (0.2 M) and **2** (1.0 M) irradiated at 290 nm for direct excitation (3 h for **3a** or 5 h for **3b**) and at 330 nm for CT-band excitation (10 h for **3a** or 13 h for **3b**).

Table 2. Activation Parameters for the Formation of Diastereomeric Oxetanes **3a** and **3b** in the Paternó−Büchi Reaction of **1a** or **1b** with **2** upon Direct and CT Excitation[a]

substrate	excitation mode	$\Delta\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})
1a	direct	+6.4	+39
	CT	−3.3	−10
1b	direct	+1.6	+21
	CT	−3.8	−9

[a] See Figure S2 in the Supporting Information for the Eyring plots.

The magnitudes of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ also depend on the mode of excitation, i.e., the activation parameters are significantly larger for direct excitation than for CT excitation, except for the $\Delta\Delta H^{\ddagger}$ for **1b**. In this Paternó−Büchi reaction occurring in the singlet manifold, the photocyclization likely proceeds through a concerted mechanism or a short-lived singlet 1,4-biradical, and hence, the diastereofacial-differentiating complexation of chiral cyanobenzoate **1** with alkene **2** plays a decisive role in determining the product's de (unless the efficiency of the subsequent cycloaddition considerably differs between the diastereomeric complexes). If this is the case, the activation parameters gained upon direct and CT excitation directly reflect the enthalpic and entropic contributions to the exciplex and CT complex formation, respectively. The first excited singlet state of cyanobenzoates is mostly $\pi-\pi^*$ in nature but borrows some intensity from the $n-\pi^*$ state, as indicated by the theoretical calculations (Figure S3). When such an excited state of cyanobenzoate interacts with an electron-rich alkene to form an exciplex, the interaction is expected to occur near the carbonyl group. The larger $\Delta\Delta S^{\ddagger}$ values for the direct excitation may be related to the relatively flexible structure of the exciplex thus formed. On the other hand, the CT complexation is achieved in general by maximizing the π overlap between the donor and acceptor to give a conformationally rigid structure,[15] which is also supported by the dispersion-corrected DFT calculations[16] (Figure 1, right). Because of the strong $\pi-\pi$ stacking, the excited CT complex is not be able to gain conformational freedom upon excitation, and the entropic difference between the members of the diastereomeric pair should be much smaller than that for the exciplex pair, in nice agreement with the experimental results (Table 2). The lower selectivities upon CT excitation may be attributed to the fact that the chiral auxiliary is located at a more distant position from the point of interaction (arene−arene) in the CT complex than in the exciplex, where the interaction occurs at the carbonyl (to give oxetane). The diastereoselectivities at low temperatures, where the enthalpy dominates the steric consequence of the peripheral modification (from **1a** to **1b**, Table 2), and the substantial solvent effect (Figure S4) jointly support this conclusion. The stereoselectivities in acetonitrile were low for both excitation modes, presumably because of dissociation of the radical ionic species, keeping distinctly different linear correlations.

In this study, we have demonstrated for the first time that the conventional exciplex and the excited CT complex are independent, noninterconvertible excited species that possess distinctly different structures and reactivities, occasionally leading to opposite stereochemistries. The magnitude of $\Delta\Delta S^{\ddagger}$ is appreciably larger for the direct excitation than for the CT excitation. This seems reasonable, as the exciplex is relatively flexible and susceptible to environmental variants such as temperature, while the CT complex is better stacked to each other in the ground state and seems to be less flexible in the excited state, giving the significantly smaller differential activation parameters.

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Supporting Information Available: Experimental procedures, theoretical calculations, spectroscopic data, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059. (b) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carrieira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736.

(2) (a) Griesbeck, A. G.; Fiege, M. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 2000; Vol. 6, p 33. (b) Fleming, S. A.; Bradford, C. L.; Gao, J. J. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1997; Vol. 1, p 187.

(3) (a) Bach, T.; Jödicke, K.; Kather, K.; Fröhlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 2437. (b) Bach, T.; Jödicke, K.; Kather, K.; Hecht, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2271.

(4) (a) Griesbeck, A. G.; Bondock, S. *J. Am. Chem. Soc.* **2001**, *123*, 6191. (b) Adam, W.; Peters, K.; Peters, E. M.; Stegmann, V. R. *J. Am. Chem. Soc.* **2000**, *122*, 2958. (c) Bach, T.; Bergmann, H.; Harms, K. *J. Am. Chem. Soc.* **1999**, *121*, 10650.

(5) (a) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 3819. (b) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1981**, *103*, 6255.

(6) Lhiaubet-Vallet, V.; Encinas, S.; Miranda, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 12774.

(7) Buschmann, H.; Scharf, H.-D.; Hoffmannn, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

(8) (a) Abe, M.; Kawakami, T.; Ohata, S.; Nozaki, K.; Nojima, M. *J. Am. Chem. Soc.* **2004**, *126*, 2838. (b) Adam, W.; Stegmann, V. R. *J. Am. Chem. Soc.* **2002**, *124*, 3600. (c) Adam, W.; Stegmann, V. R.; Weiknötz, S. *J. Am. Chem. Soc.* **2001**, *123*, 2452.

(9) (a) Griesbeck, A. G.; Fiege, M.; Bondock, S.; Gudipati, M. S. *Org. Lett.* **2000**, *2*, 3623. (b) Griesbeck, A. G.; Bondock, S.; Cygon, P. *J. Am. Chem. Soc.* **2003**, *125*, 9016.

(10) (a) Saito, H.; Mori, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1900. (b) Saito, H.; Mori, T.; Wada, T.; Inoue, Y. *Org. Lett.* **2006**, *8*, 1909.

(11) (a) Nicolet, O.; Banerji, N.; Pagès, S.; Vauthey, E. *J. Phys. Chem. A* **2005**, *109*, 8236. (b) Levy, D.; Arnold, B. R. *J. Phys. Chem. A* **2005**, *109*, 2113.

(12) Shigemitsu, Y.; Katsuhara, Y.; Odaira, Y. *Tetrahedron Lett.* **1971**, *12*, 2887.

(13) We chose 330 and 290 nm for CT and direct excitation, respectively. Although the irradiation at 290 nm may excite a hidden CT band, its effect seems to be small, as the de was distinctly different or even opposite in sign.

(14) Eyring, H. *J. Chem. Phys.* **1935**, *3*, 107.

(15) (a) Rosokha, S. V.; Kochi, J. K. *J. Org. Chem.* **2002**, *67*, 1727. Also see: (b) Kobayashi, T.; Yoshihara, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2603.

(16) Grimme, S.; Antony, J.; Schwabe, T.; Müuck-Lichtenfeld, C. *Org. Biomol. Chem.* **2007**, *5*, 741.

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