JOC Article

Origin of a Large Temperature Dependence of Regioselectivity Observed for [2 + 2] Photocycloaddition (Paternò-Büchi Reaction) of 1,3-Dimethylthymine with Benzophenone and Its Derivatives: Conformational Property of the Intermediary Triplet 1,4-Diradicals

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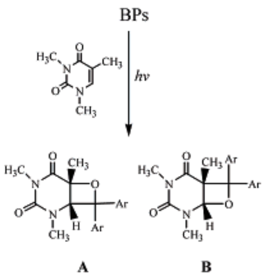

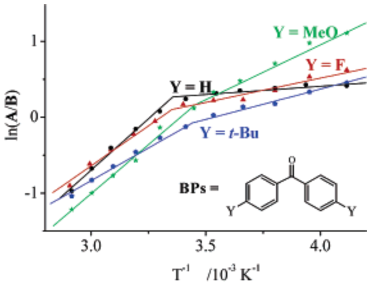

The [2 + 2] photochemical additions of 1,3-dimethylthymine (DMT) with benzophenone and its 4,4′-substituted derivatives (BPs), difluoro, di-*tert*-butyl, and dimethoxy benzophenones, have been investigated at a temperature range from −40 to 70 °C. The photochemical reactions, which are cycloaddition of the 5−6 double bond of DMT with the carbonyl group of BPs, the so-called the Paternò-Büchi (PB) reaction, reveal largely temperature-dependent regioselectivity. The chemical yields of one series of regioisomers, **2**, decrease with the increase of the reaction temperature, but those of another regioisomer series, **3**, increase, and thus the ratio of **2/3** is strongly dependent on the temperature (**2/3** = ca. 70:30 to 30:70). The temperature dependence of the regioselectivity yields two linear functions in the corresponding Eyring diagrams. The Eyring plot with changed slopes is clearly indicative of the change for the selectivity-determining step in the PB reaction, in which the triplet 1,4-diradicals play a crucial role. Computational studies reveal the conformational equilibrium structures of the triplet 1,4-diradicals, energy barriers between the conformers, and the conjectural equilibrium constants from relative potential energies of the stable conformers. A proposed mechanism can reasonably explain the temperature-dependent regioselectivity and chemical yields of two regioisomers varying with the reaction temperature.

Introduction

Since the original report of [2 + 2] photochemical addition to form an oxetane, the Paternò-Büchi (PB) reaction has been developed into a reliable method for the construction of substituted oxetanes,[1−4] taking advantage of the propensity of the oxetanes to undergo ring opening in different fashions depending on reaction conditions to furnish products with delicate structures. Recent research interest in this area concentrates on the different factors that influence the stereo- and regioselectivity; in particular, the influences of temperature have attracted much attention.[5,6] The temperature dependence of the stereoselectivity in the PB reaction has been well

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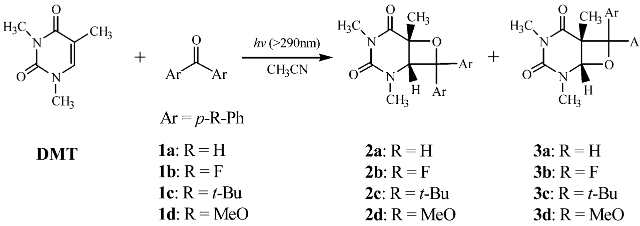
SCHEME 1



established,[7−10] and the results form the basis of the *isoinversion principle*.[11] In contrast, the temperature dependence of the regioselectivity has scarcely been reported.[5,6,11]

A [2 + 2] cycloaddition of the 5−6 double bond of the 5′ thymine with the C4 carbonyl (or amino) of the 3′ thymine (cyctosine) generates an oxetane (or azetidine) ring, which undergoes ring opening at temperatures above −80 °C by C4−O bond cleavage to give the observed (6−4) photoproduct, which is the second major lesion induced in DNA by UV radiation.[12] The (6−4) lesion can be exclusively repaired to the original bases by (6−4) photolyases. It is proposed that the initial binding of the (6−4) lesion induces a back rearrangement of the (6−4) photoproduct into the oxetane (or azetidine) intermediate, and the photochemical step involves cycloreversion of the intermediates via electron transfer from a full-reductive flavin.[13] To determine whether the cycloreversion reactions occur via the proposed electron-transfer mechanism, Falvey and co-workers prepared thymine oxetane adducts through photocycloaddition of carbonyl compounds (including benzophenone) with the 5−6 double bond of 1, 3-dimethylthymine (DMT).[14] Only one regioisomer, *head-to-head* oxetanes (including **2a**, see Scheme 1) were obtained for all carbonyl partners. In an early study, only a *head-to-head* oxetane was obtained from the photochemical reaction of benzophenone with thymine.[15] In a more recent report, to understand a cross-linked structure of oligomer duplexes that contain a benzophenone-substituted uridine, the photoreaction between benzophenone and DMT was further investigated as a model, and another regioisomer, *head-to-tail* oxetane **3a**, was isolated in a better yield (38%) than **2a** (27%).[16] We have further investigated the photochemical reaction at various temperatures and found that the regioselectivity of the reaction is strongly temperature-dependent.

Recently, with help of computational calculations, a conclusive mechanism for rationalizing the temperature-dependent regioselectivity in photochemical reactions of 2-methylfuran or 3-methyfuran with benzaldehyde or benzophenone has been reported.[6] The regioselectivity was the selection between two double bonds of a substituted furan. In contrast, the regioselectivity in the photochemical reaction of benzophenone with DMT is the O-attacked site selection on the single double bond of DMT.

In this paper, we reported a notable temperature effect on the regioselectivity in the PB reactions of 1,3-dimethylthymine (DMT) with benzophenone and its derivatives (BPs), 4,4′-substituted benzophenones, in a temperature range from −40 to 70 °C. In contrast to the S-shaped Eyring plots of the regioselectivities in the PB reaction of furan derivatives with benzophenone,[6] Eyring plots characterized by two lines with an inversion point were found in our system. The nonlinear Eyring plots clearly indicated the dominance change of regioselection steps in the PB reactions. On the basis of computational studies for the potential energies of intermediary triplet 1,4-diradicals, it has been demonstrated that the conformational property of the triplet 1,4-diradicals is responsible for the temperature-dependent regioselectivity.

Results and Discussion

The photochemical reactions of DMT with four BPs in acetonitrile solutions give two regioisomers, *head-to-head* oxetanes **2** and *head-to-tail* oxetanes **3** (Scheme 1). These [2 + 2] cycloaddition reactions are initiated by pure triplet excited states of benzophenones (^{3}BPs*) (vide infra). Attack of ^{3}BPs* on either C5 or C6 of DMT results in the formation of two 1,4-diradicals in triplet, which undergo an intersystem crossing (ISC) process to a singlet and further ring closure to form products **2** and **3**.

The cycloaddition reactions are clean photochemical reactions, and only two regioisomers, **2** and **3**, as well as a very small amount of side products such as cyclobutane dimers of DMT and a photolysis product of BPs formed at high temperature, were detected. Using ferrioxalate actinometry,[17] quantum yields (Φ) for the photochemical reactions of DMT with **1a**−**d** were measured through irradiating with 313 nm monochromatic light at 20 °C. The values of Φ are 0.08 for **1a**, 0.14 for **1b**, 0.11 for **1c** and 0.11 for **1d**. The efficiencies of these photochemical reactions are comparable.

The regioselectivity (the ratio of **2**/**3**) is independent of concentrations of the reactants, including different concentrations (1:2 to 250:500 mM/mM) of DMT and BPs at the same ratio of DMT/BPs (1:2) and different ratios (4:1 to 1:8) of DMT/BPs (data not shown). Since the best yield was obtained from the ratio of DMT/BPs = 1:2, the ratio of DMT/BPs was employed in all experiments except the above mention. The photochemical reactions (such as 10 mM DMT and 20 mM BPs) can be quenched by 10 mM *trans*-dicyanoethylene (a triplet quencher). These results rule out a reaction pathway initiated by the singlet excited states of BPs.

Control experiments showed that photoproducts **2** and **3** are thermostable in the temperature range under investigation. When samples irradiated at 0 °C were kept in a water bath at 70 °C for 1 h, no thermolysis of photoproducts was observed within an experimental error

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TABLE 1. Temperature Dependence of Regioselectivity for the [2 + 2] Photocycloaddition of DMT with Benzophenone (1a)[a]

temp (°C)	**2a** (mM)	**3a** (mM)	**2a/3a**	t^b (min)
−38	1.14	0.72	61:39	6
−30	1.12	0.74	60:40	8
−19	0.95	0.62	61:39	6
−11	1.14	0.75	60:40	8
1	1.05	0.74	59:41	8
9	1.04	0.76	58:42	8
21	0.92	0.87	56:44	8
30	0.81	0.75	52:48	8
40	0.66	0.77	46:54	8
51	0.60	0.90	40:60	8
60	0.43	0.83	34:66	8
70	0.25	0.66	27:73	8

[a] DMT:**1a** = 2 mM/4 mM, values determined by HPLC directly on the crude product mixture. [b] Irradiation time.

TABLE 2. Temperature Dependence of Regioselectivity for the [2 + 2] Photocycloaddition of DMT with 4,4′-Difluorobenzophenone (1b)[a]

temp (°C)	**2b** (mM)	**3b** (mM)	**2b/3b**	t^b (min)
−40	0.83	0.42	66:34	7
−30	0.41	0.22	65:35	7
−20	0.46	0.27	63:37	7
−10	0.37	0.26	59:41	7
0	0.34	0.27	56:44	7
10	0.35	0.28	56:44	7
21	0.90	0.76	54:46	10
32	0.75	0.79	49:51	10
41	0.65	0.81	45:55	10
51	0.58	0.89	39:61	10
61	0.46	0.85	35:65	10
71	0.37	0.91	29:71	10

[a,b] See Table 1.

TABLE 3. Temperature Dependence of Regioselectivity for the [2 + 2] Photocycloaddition of DMT with 4,4′-Di-*tert*-butylbenzophenone (1c)[a]

temp (°C)	**2c** (mM)	**3c** (mM)	**2c/3c**	t^b (min)
−40	0.35	0.19	65:35	5
−30	0.33	0.21	61:39	5
−20	0.53	0.38	58:42	5
−10	0.68	0.57	54:46	5
0	0.47	0.41	53:47	5
10	0.77	0.75	51:49	6
20	0.90	1.02	47:53	10
30	0.74	0.97	43:57	10
40	0.67	1.06	39:61	10
50	0.56	1.07	34:66	10
60	0.49	1.12	30:70	10
70	0.40	1.13	26:74	10

[a,b] See Table 1.

TABLE 4. Temperature Dependence of Regioselectivity for the [2 + 2] Photocycloaddition of DMT with 4,4′-Dimethoxybenzophenone (1d)[a]

temp (°C)	**2d** (mM)	**3d** (mM)	**2d/3d**	t^b (min)
−40	11.3	3.2	78:22	8
−30	9.7	3.2	75:25	8
−20	10.1	3.8	73:27	8
−10	6.2	3.1	67:33	8
1	8.1	5.0	62:38	8
10	5.4	3.9	58:42	8
17	3.3	2.9	53:47	8
30	3.9	4.4	47:53	8
40	1.8	3.2	36:64	8
50	1.7	3.6	32:68	8
60	1.1	3.0	27:73	8
70	1.0	3.4	23:77	8

[a] DMT:**1d** = 30 mM/60 mM, values determined by ^{1}H NMR (300 MHz) in acetonitrile-d_3 directly on the crude product mixture; sum of the aromatic signals of phenyl groups were taken as internal standard. [b] Irradiation time.

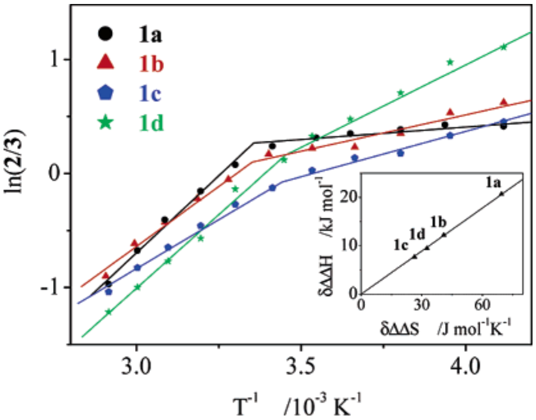

FIGURE 1. Eyring plots for the photoreaction of DMT with compounds **1**. Inset: $\Delta\Delta H^{\ddagger}/\Delta\Delta S^{\ddagger}$ diagram.

±5%. However, in the presence of a trace of acid, photoproducts **3** easily decompose to the starting meterials, DMT, and the corresponding BPs, and **2** are stable. This may be the reason the *head-to-tail* oxetane **3a** was not obtained in previous works.[14,15]

The regioselectivities of **2** versus **3** in the PB reactions of DMT with BPs were obtained in the temperature range −40 to 70 °C and are listed in Tables 1−4. The regioselectivities depend largely on the reaction temperature. The reactions for all four BPs with DMT reveal very similar temperature-dependent behaviors. The chemical yields of **2a**, **2b**, and **2d** diminish with the increase in the reaction temperature, whereas the yields of **3b** and **3c** increase markedly. The change of the yields of **3a** and **3d** are irregular, and the yield of **2c** increases in the low-temperature region (−40 to 30 °C) and decreases in the high-temperature region (30 to 70 °C). Thus, oxetanes **2** are major regioisomers at low temperature (**2/3** ≈ 70:30 at −40 °C), whereas they become minor products at high temperature (**2/3** ≈ 30:70 at +70 °C).

The regioselectivity data of Tables 1−4 have been plotted in Figure 1 against the inverse absolute temperature according to the Eyring formalism:[18]

$$\ln\left(\frac{k_2}{k_3}\right) = \ln\left(\frac{\mathbf{2}}{\mathbf{3}}\right) = -\frac{\Delta\Delta H^{\ddagger}}{RT} + \frac{\Delta\Delta S^{\ddagger}}{R} \qquad (1)$$

where k_2 and k_3 are rate constants of the overall formation of regioisomers **2** and **3**, respectively.

The Eyring plots obtained are nonlinear across the whole temperature range. The nonlinear Eyring plot is indicative of a change of the selectivity-determining step during the change in the reaction temperature.[11,19−21]

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TABLE 5. Inversion Temperature, T_{inv}, and Parameters of Activation, $\Delta\Delta H^{\ddagger}_1$, $\Delta\Delta S^{\ddagger}_1$ ($T > T_{inv}$) and $\Delta\Delta H^{\ddagger}_2$, $\Delta\Delta S^{\ddagger}_2$ ($T < T_{inv}$)

BPs	$\Delta\Delta H^{\ddagger}_1$, $\Delta\Delta H^{\ddagger}_2$ (kJ mol^{-1})	$\delta\Delta\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta\Delta S^{\ddagger}_1$, $\Delta\Delta S^{\ddagger}_2$ (J mol^{-1} K^{-1})	$\delta\Delta\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	T_{inv} (K)
1a	−22.5	20.7	−73.3	69.4	297.9
	−1.8		−3.9		
1b	−17.5	12.2	−57.8	40.8	298.3
	−5.3		−17.0		
1c	−14.3	7.7	−49.8	26.4	290.4
	−6.6		−23.4		
1d	−21.5	9.5	−72.7	32.5	289.6
	−12.0		−40.2		

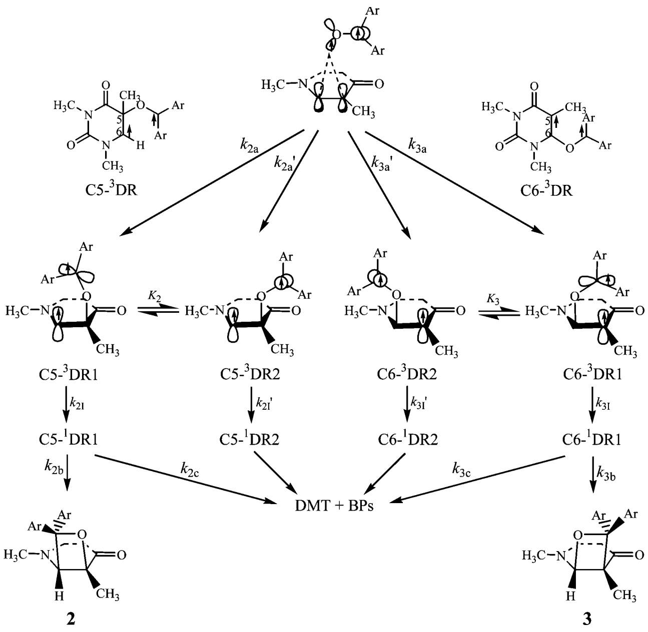
Furthermore, strict linearities (most of correlation coefficients $R > 0.99$) on both sides of the inversion points were found. The temperature at the point of inversion is called the inversion temperature, T_{inv}, of the system. The inversion temperature reveals two sets of parameters of activation ($\Delta\Delta H^{\ddagger}_1$ and $\Delta\Delta S^{\ddagger}_1$ ($T > T_{inv}$), $\Delta\Delta H^{\ddagger}_2$ and $\Delta\Delta S^{\ddagger}_2$ ($T < T_{inv}$)), which were obtained from the slope and intercept of the linear plot for each system. Table 5 presents the inversion temperature, T_{inv}, and values for the parameters of activation $\Delta\Delta H^{\ddagger}_{1,2}$ and $\Delta\Delta S^{\ddagger}_{1,2}$. These large parameters of activation are unprecedented, such as $\Delta\Delta H^{\ddagger}_1$ ranging from −14.3 to −22.5 kJ mol^{-1}, much higher than the published values of −4.2,[11] 4.3,[5] and −4.8 kJ mol^{-1}. [6] Therefore, the regioselectivity in the PB reaction is strongly temperature-dependent.

Moreover, an excellent linearity exists in the plot of $\delta\Delta\Delta H^{\ddagger}$ (= $\Delta\Delta H^{\ddagger}_2 - \Delta\Delta H^{\ddagger}_1$) against $\delta\Delta\Delta S^{\ddagger}$ (= $\Delta\Delta S^{\ddagger}_2 - \Delta\Delta S^{\ddagger}_1$) ($R > 0.999$) shown in the inset of Figure 1. The fit line passes through the origin of the coordinate. The linear correlation in the $\delta\Delta\Delta H^{\ddagger}/\delta\Delta\Delta S^{\ddagger}$ diagram was called the *principle of isoinversion*[7,11] The slop of the straight line is the isoinversion temperature, $T_i = 296$ K, which is a characteristic parameter of the dominance change of regioselection steps in the PB reactions.

The [2 + 2] photochemical reactions are the PB reactions initiated by pure triplet states of benzophenone derivatives (Scheme 2). After photochemical excitation of the ketones and subsequent dissipation processes, the two triplet 1,4-diradical intermediates C5-^{3}DR and C6-^{3}DR are formed in the different yields by selectively attacking C5 or C6 of DMT. The triplet diradical intermediates undergo ISC process to a singlet and may subsequently undergo two reaction pathways: cleavage to the reactants or ring closure to oxetanes. Since the lifetime of a singlet diradical is usually quite short, the conformations of triplet diradicals play an important role to determine the product selectivity.[22−25]

In the PB reaction, there are four factors that determine the regioselectivity:[6] (i) initial O-attacked site selection on the double bond by ^{3}BPs*, $k_{2a} + k_{2a'}$ versus $k_{3a} + k_{3a'}$; (ii) equilibrium constants, K_2 (= [C5-^{3}DR2]/[C5-^{3}DR1]) versus K_3 (= [C6-^{3}DR2]/[C6-^{3}DR1]), the factor operating only when the conformational change is faster than the ISC process; (iii) relative rate constants of the ISC processes in the triplet 1,4-diradicals, $k_{2I}/k_{2I'}$ versus $k_{3I}/k_{3I'}$; and (iv) relative rate constants of the bond-forming and bond-breaking step from the singlet 1,4-diradical C5-^{1}DR1 and C6-^{1}DR1, k_{2b}/k_{2c} versus k_{3b}/k_{3c}. According to the Curtin-Hammett principle,[26] the ratios of the productive conformers of singlet diradicals C5-^{1}-DR1 and C6-^{1}DR1 are determined not only by the populations of C5-^{3}DR1 and C6-^{3}DR1 but also by the relative rate constants of the ISC processes, $k_{2I}/k_{2I'}$ and $k_{3I}/k_{3I'}$.

SCHEME 2



In general, the rate constant of ISC process is insensitive to temperature, so the ratios of $k_{2I}/k_{2I'}$ and $k_{3I}/k_{3I'}$ would be independent of the reaction temperature. The populations of C5-^{3}DR1 and C6-^{3}DR1 are determined by the rate constants of the formations of triplet diradicals, $k_{2a}+ k_{2a'}$, $k_{3a}+ k_{3a'}$, and equilibrium constants K_2, K_3, respectively. When the conformational changes are faster than the ISC processes, the kinetic description of the regioselectivity (eq 4) can be evaluated from the steady-state assumption for the regiomeric 1,4-diradical intermediates, C5-^{3}DR and C6-^{3}DR, and application of relationships 2 and 3:

$$\mathbf{2} = k_{2b} \int [\text{C5-}^1\text{DR1}]\, dt \tag{2}$$

$$\mathbf{3} = k_{3b} \int [\text{C6-}^1\text{DR1}]\, dt \tag{3}$$

$$\mathbf{2/3} = \frac{(k_{2a} + k_{2a'})}{(k_{3a} + k_{3a'})} \times \frac{\dfrac{k_{2b}}{k_{2b} + k_{2c}}}{\dfrac{k_{3b}}{k_{3b} + k_{3c}}} \times \frac{\dfrac{k_{2I}}{k_{2I'}}\left(\dfrac{k_{3I}}{k_{3I'}} + K_3\right)}{\dfrac{k_{3I}}{k_{3I'}}\left(\dfrac{k_{2I}}{k_{2I'}} + K_2\right)} \tag{4}$$

If the difference of rate constants of ISC processes between the two conformers of triplet diradical is negligible ($k_{2I} \approx k_{2I'}$, $k_{3I} \approx k_{3I'}$), eq 4 can be simplified as eq 4a. That is, the regioselectivity (**2/3**) can be determined

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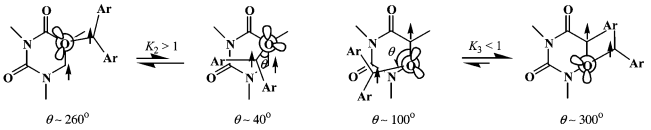
SCHEME 3. Conjectural Equilibrium Constants K_2 and K_3 from the Calculated Potential Energies of Conformers of Triplet 1,4-Diradicals C5-^{3}DR and C6-^{3}DR



C5-^{3}DR2 C5-^{3}DR1 C6-^{3}DR2 C6-^{3}DR1

by the difference of the rate constants between the formations of two diradicals ($k_{2a}+ k_{2a'}$, $k_{3a}+ k_{3a'}$), the equilibrium constants (K_2, K_3) and the relative rate constants of the bond-forming and bond-breaking step from the singlet 1,4-diradical (k_{2b}/k_{2c} and k_{3b}/k_{3c}).

$$\mathbf{2/3} = \frac{(k_{2a} + k_{2a'})}{(k_{3a} + k_{3a'})} \times \frac{\dfrac{k_{2b}}{k_{2b} + k_{2c}}}{\dfrac{k_{3b}}{k_{3b} + k_{3c}}} \times \frac{1 + K_3}{1 + K_2} \qquad (4a)$$

If $k_{2b}/k_{2c} = k_{3b}/k_{3c}$ and $(k_{2a}+k_{2a'})/(k_{3a}+k_{3a'}) = k_{2a}/k_{3a}$ then

$$\mathbf{2/3} = \frac{k_{2a}}{k_{3a}} \times \frac{1 + K_3}{1 + K_2} \qquad (5)$$

When the conformational changes are slower than the ISC processes at low temperature, the regioselectivity (**2**/**3**) can be simply determined by the rate constants of the formation for the productive conformers of two triplet diradicals C5-^{3}DR1 and C6-^{3}DR1:

$$\mathbf{2/3} = \frac{k_{2a}}{k_{3a}} \qquad (6)$$

Therefore, when the conformational interchange increases to reach and even exceed the ISC process with increase in the reaction temperature, the regioselectivity would reveal a nonlinear Eyring plot, which should be two linear functions with an inversion point.

To further estimate the temperature-dependent change of the mechanism, the potential energy surfaces (PES) around the dihedral angle θ (deg) of the triplet diradicals, C5-^{3}DR and C6-^{3}DR, were calculated at the UB3LYP/3-21G level of theory with Gaussian 03.[27] The PES analysis showed that, among the possible conformers of C5-^{3}DR and C6-^{3}DR, only four conformers, gauche-in conformers C5-^{3}DR1 (θ = ca. 40°) and C6-DR2 (θ = ca. 100°) and gauche-out conformers C5-^{3}DR2 (θ = ca. 260°) and C6-DR1 (θ = ca. 300°), were energy minimum structures (Scheme 3). The *trans* conformers (θ = 180°) were not stable structures. The gauche-in conformers C5-^{3}DR1 and the gauche-out conformers C6-^{3}DR1 are productive and would undergo ring closure to oxetanes, and the conformers C5-^{3}DR2 and C6-^{3}DR2 are unproductive and would cleave to go back to the starting materials, after the ISC proceeds to the singlet states. The PES for the four systems showed the energy barriers between the two stable conformers are 4−6 kcal mol^{-1}. Thus, the rate constants for the conformational transformation between the equilibrium structures can be estimated to be 10^8−10^6 s^{-1} at −40 °C, 10^9−10^7 s^{-1} at +23 °C, and 10^9−10^8 s^{-1} at +70 °C. Since the lifetimes of the triplet 1,1-diphenyl-2-oxabutane-1,4-diyl diradicals were reported to be similar (1.5[28,29] and 2.5−4.5 ns[6]), the rates of the ISC processes of the 1,4-diradicals, C5-^{3}DR and C6-^{3}DR, can be expected to be in the time scale, that is, $k_{\mathrm{ISC}} \approx 10^8$ s^{-1}. Hence, it is possible that the increase of the conformational interchange undergoes the process from slower to faster than the ISC process with increase in the reaction temperature.

TABLE 6. Potential Energy Difference (kcal mol^{-1}) between the Productive Conformer and Unproductive Conformer of Triplet 1,4-Diradicals

BPs	C5-^{3}DR	C6-^{3}DR
1a	+0.7	−1.4
1b	+1.0	−1.4
1c	+0.4	−1.4
1d	+0.4	−1.8

The potential energies of the two stable conformers were obtained by further optimizing the conformers at UB3LYP/3-21G level, and their relative potential energies are listed in Table 6. The potential energies of the productive conformers C5-^{3}DR1 are higher than the unproductive conformers C5-^{3}DR2. When the conformational interchange is faster than the ISC process, the population of C5-^{3}DR1 would be lower than that of C5-^{3}DR2, i.e., the equilibrium constant $K_2 > 1$. However, the potential energies of the productive conformers C6-DR1 are lower than those of the unproductive conformers, C6-DR2, and thus $K_3 < 1$. This implies that the population of C5-^{3}DR1 with a higher potential energy would decrease, and the population of C6-^{3}DR1 with a lower potential energy would increase, when the exchange of two conformers is faster than the ISC processes at high temperature. Hence, the chemical yield of oxetane **2** at high temperature is expected to be lower than that at low temperature, and the chemical yield of oxetane **3** is expected to be right contrary to that of **2**. The deduction is in agreement with the experimental results.

Both experimental and computational results support the temperature-dependent change of the mechanisms. Through theoretical calculations, Abe and co-workers obtained two straight lines with different slopes in the Eyring diagram for the regioselectivity of the reaction of furans with benzophenone.[6] This theoretical prediction is agreement with our experimental results (Figure 1) and observation of the regioselectivity in the PB reaction of an asymmetric olefine with phenylglyoxalate by Scharf et al.[11]

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In summary, we observed a largely temperature-dependent regioselectivity in the PB reaction of DMT with benzophenone and its three 4,4′-substituted derivatives. The photochemical reactions of all four benzophenone derivatives with DMT reveal similar regioselectivities and the yields of oxetanes **2** decrease and those of their regioisomers **3** increase with increasing reaction temperature. Thus the major photoproducts are **2** at low temperature and become **3** at high temperature. The Eyring plots of the regioselectivities exhibit strict linearities on both sides of inversion temperatures. The existence of inversion temperatures implies that each temperature region has its dominant selection step.

The relative rate constants between the ISC process and the conformational exchange of the intermediary 1,4-diradicals and the equilibrium constants between the productive conformer and unproductive conformer are responsible for the temperature-dependent regioselectivity. When the conformational transformation is faster than the ISC process at high temperature, the population of the productive conformers (C6-^{3}DR1) with low potential energies would increase and those of the productive conformers (C5-^{3}DR1) with higher potential energies would decrease. Thus, at high temperature, the chemical yields of oxetanes **3** are expected to be higher than those anticipated from only the initial O-attacked site selection (eq 6), and those of oxetanes **2** are contrary. The Eyring plots observed in the reactions are reasonably explained by the switching between two mechanisms (eq 5 and 6) in the temperature range (−40 to +70 °C). These findings on the reaction are helpful to understand the temperature-dependent regioselectivity in a PB reaction mediated by a pure triplet excited state of a carbonyl compound.

Experimental Section

General Methods. 1,3-Dimethylthymine (DMT), 4,4′-di-*tert*-butylbenzophenone (**1c**),[30] and 4,4′-dimethoxybenzophenone (**1d**)[31] were not commercially available and were prepared by literature methods. Other materials were obtained from commercial suppliers and were used without further purification. Solvents of technical quality were distilled before use.

Under a nitrogen atmosphere, an acetonitrile solution of DMT (100 mM) and benzophenone derivatives (200 mM) was placed in a Pyrex reactor (transmitted light >290 nm) and irradiated with a 300-W high-pressure Hg lamp for 5−10 h. The solvent in the reaction mixture was removed in vacuo. The residual material was subjected to flash chromatography with silica-H gel as absorbent. Two regioisomeric products **2** and **3** were obtained.

Photoproduct Assay The Paternò-Büchi reactions of DMT with BPs were performed in acetonitrile or acetonitrile-d_3. The solution of reactants was placed in a Pyrex NMR tube (transmitted light > 290 nm), bubbled with high purity N_2 for 15 min, and then irradiated with a 125-W high-pressure Hg lamp at various temperatures. The ratio of the reactants (DMT/BPs = 1:2) was selected in all measurements. Photoproducts **2** and **3** have no significant absorption for light above 290 nm. Hence, a secondary photolysis of the oxetane products (**2** or **3**) should not occur without a prolonged irradiation. Control experiments showed that the regioselectivity of the two isomers had no change at the yield range from 20% to 90%, within an experimental error ±5%. Compositions in the photoreaction mixture were quantified by HPLC with a C-8 reverse-phase column. A flow rate of 1 mL/min and column temperature of 30 °C were employed in all HPLC analyses, using standard solutions containing neat DMT, BPs (**1a**, **1b**, and **1c**), and two corresponding products (**2a**, **2b**, **2c** and **3a**, **3b**, **3c**) as references. Under the same reaction conditions, the products in the reaction of DMT with **1d** in acetonitrile-d_3 were assessed by ^{1}H NMR spectroscopy (300 MHz) directly on the crude product mixture, using the sum of the aromatic signals of phenyl groups as internal standard.

Quantum Yield Measurements To measure the quantum yield of the PB reaction of compounds **1a**−**d** with DMT, a 0.5-mL sample (acetonitrile-d_3 solution, BPs/DMT = 60:30 mM) was placed in a NMR tube, bubbled with high purity N_2 for 15 min, and then irradiated with a 313 nm monochromator light beam from a low-pressure Hg lamp with a monochromator. The number of photoproduct molecules was evaluated through measurement of ^{1}H NMR. The number of absorbed light quantum per minute was determined by ferrioxalate actinometry.[17] Both values were used to calculate the yield (= number of photoproduct molecules/number of absorbed photons), with the error within ±10%.

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Supporting Information Available: Analytical and spectral characterization data; copies of the ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra for compounds **2a**−**d** and **3a**−**d**; typical charts of HPLC and NMR for photoproduct analysis; and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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