

Short communication

Notable solvent effects on the regioselectivity in the Paternò–Büchi reaction of 1,3-dimethylthymine with 4-methoxybenzophenone

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Abstract

Notable solvent effects on the regioselectivity and the photochemical efficiency were observed in the Paternò–Büchi (PB) reaction of 1,3-dimethylthymine (DMT) with 4-methoxybenzophenone (MBP). As a comparison, photochemical reactions of 4,4'-difluorobenzophenone (DFBP) and benzophenone (BP) with DMT were performed under the same condition. With increasing the proportion of water in the solution, besides the PB reaction, an electron-transfer reaction was observed in the DFBP–DMT system. The PB reaction of BP–DMT system revealed similar effects on the regioselectivity and the efficiency with that of MBP–DMT system, but the latter is more remarkable. The notable solvent effects may be responsible for a strongly solvent-dependent properties of the excited triplet MBP.

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1. Introduction

The regioselectivity and stereoselectivity in the Paternò–Büchi (PB) reaction, which is a photochemical [2 + 2] cycloaddition of a carbonyl compound with an alkene, have attracted considerable attention [1–4]. From the mechanistic points of view, recent researches focus on factors that influence the regioselectivity and the stereoselectivity [4–9]. For most cases, the predominant isomer formed can be correctly predicted from consideration of the more stable diradical (in triplet) intermediate formed by addition of the carbonyl oxygen to the carbon–carbon double bond. This is one of reasons why studies on the regioselectivity are relatively scarce comparing to the stereoselectivity. However, the regioselectivity is not always simply predicted from the stability of the intermediate diradicals. When two regioisomeric diradicals possess similar stability, other factors must play important roles in determining the regioselectivity. For example, in the PB systems with regioisomeric diradicals of similar stability, notable substituent and temperature effects on the regioselectivity have been observed in the photochemical reactions of substituted furans [6,7],

1,3-dimethylthymine (DMT) [9–11] and 1,3-dimethyluracil (DMU) [10,11] with aromatic carbonyl compounds.

Using benzene and acetonitrile/methanol as solvents, solvent effects on the regio- and diastereoselectivity in PB reactions were discussed, focusing on whether a photoinduced electron transfer occurred [5,12,13] or a hydrogen-bonding exciplex formed [14].

The nature and energy level of the lowest triplet state (T_1) for 4-methoxybenzophenone (MBP) are strongly solvent-dependent, n, π^* character, 288 kJ mol⁻¹ in organic solvent and π, π^* , 275 kJ mol⁻¹ in water [15]. Hence, the photochemical reaction of MBP with DMT in acetonitrile–water binary solvents would allow to investigate the effect of the nature and energy level of the lowest triplet state on the PB reaction. In this paper, we reported a notable solvent effect on the regioselectivity of PB reaction of 1,3-dimethylthymine and 4-methoxybenzophenone through measuring product ratio crude product mixture of reaction in acetonitrile–water binary solvents.

2. Materials and methods

2.1. Materials

1,3-Dimethylthymine (DMT) was prepared from thymine. Acetonitrile-*d*₃ and water-*d*₂ was purchased from Beijing

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Chongxi High-Tech Incubator Co., Ltd. and benzene- d_6 from Aldrich Chemical Co., Inc. Other materials were obtained from commercial suppliers and used as received without further purification. ^1H and ^{13}C NMR spectra were measured with a Bruker AV 300 spectrometer operating at 300 MHz and 75 MHz, respectively. Mass spectra were obtained with a Micromass GCF TOF mass spectrometer.

2.2. Characterization for photoproducts of PB reaction of DMT and MBP

2.2.1. (*exo*- and *endo*-) (Z)-2,4,6-Trimethyl-8-phenyl-8-*p*-methoxyphenyl-7-oxa-2,4-diazabicyclo[4.2.0]octane-3,5-dione (**1**)

^1H NMR (300 MHz, acetone- d_6 , TMS): δ = (1.66, 1.69) (s, 3H, CH_3), (2.76, 2.85) (s, 3H, NCH_3), (3.08, 3.09) (s, 3H, NCH_3), (3.76, 3.80) (s, 3H, OCH_3), (4.87, 4.91) (s, 1H, CH), 6.87–7.45 (m, 9H, $\text{H}_{\text{benzene}}$). ^{13}C NMR (75 MHz, acetone- d_6): δ = (170.5, 170.3) (NCOC), 160.1, 152.2 (2C), 146.0, 140.9, 137.6, 132.5, 129.2, 128.8, 128.4 (2C), 128.0, 127.7, 126.7, 126.1, 114.5, 114.2, 92.1, 92.0, 77.3 (2C), 66.5, 66.4, (55.6, 55.5) (OCH_3), (35.7, 35.6) (NCH_3), (27.5, 27.4) (NCH_3), (24.1, 24.0) (CH_3). ν_{max} (KBr)/ cm^{-1} = 1714s, 1674s, 748m. TOFMS (EI) calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$ (M) $^+$: 366.1580, found: 366.1585.

2.2.2. (*exo*- and *endo*-) (Z)-2,4,6-Trimethyl-7-phenyl-7-*p*-methoxyphenyl-8-oxa-2,4-diazabicyclo[4.2.0]octane-3,5-dione (**2**)

^1H NMR (300 MHz, acetone- d_6 , TMS): δ = (1.42, 1.43) (s, 3H, CH_3), (2.65, 2.72) (s, 3H, NCH_3), (3.10, 3.11) (s, 3H, NCH_3), (3.71, 3.77) (s, 3H, OCH_3), (5.39, 5.41) (s, 1H, CH), 6.81–7.51 (m, 9H, $\text{H}_{\text{benzene}}$). ^{13}C NMR (75 MHz, acetone- d_6): δ = 170.1 (NCOC), (159.9, 159.7), 152.5, 144.0, 143.0, 135.5, 134.5, 131.8, 130.2, 128.9, 128.4, 128.0 (2C), (127.6, 127.3), 126.1, 125.8, 125.0, 114.4, 113.9, 90.4 (2C), (88.7, 88.6), (55.5, 55.4), (53.6, 53.3) (OCH_3), 32.9 (NCH_3), 27.7 (NCH_3), (20.2, 19.9) (CH_3). TOFMS (EI) calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4$ (M) $^+$: 366.1580, found: 366.1587.

2.3. Photoproduct assay

The solution of reactants was placed in a Pyrex NMR tube (>290 nm), bubbled with high purity N_2 for 10 min, and irradiated with 125 or 300 W high-pressure Hg lamp. The yields of photoproducts were assessed by ^1H NMR spectroscopy (300 MHz) directly on the crude product mixture, using the sum of the aromatic signals as internal standard. The ratios of two regioisomeric oxetanes were obtained from their peak area of

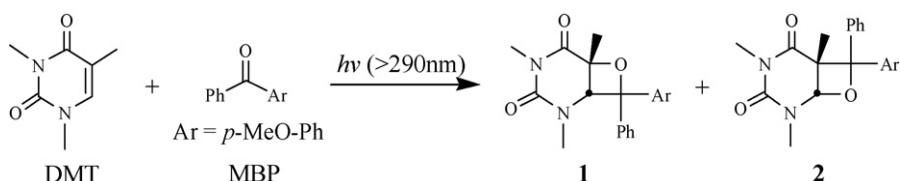
H-1 on the ^1H NMR spectra, and the experimental was error within $\pm 5\%$.

3. Results and discussion

The photochemical reaction of DMT with MBP gives two regioisomers, A-type oxetane (**1**) and B-type oxetane (**2**) as shown in Scheme 1. The PB reaction is initiated by pure triplet MBP undergoing two diradical intermediates, which possess similar stability to give two regioisomeric oxetanes like other benzophenone derivatives (BPs) [9,10]. Both **1** and **2** have two possible diastereomers, *endo*-form and *exo*-form. The *endo* form is that phenyl group and 6-methyl group are at the same side (*cis*), and *trans* for the *exo* form. Very low diastereoselectivities for **1** and **2** were observed from ^1H NMR spectra, two isomer ratios near to 1:1. Similar to the regioisomeric oxetanes formed from other BPs [9,10] their chemical shift of the proton H-1 ($\delta_{\text{H-1}}$) are in the range 4–6, and less $\delta_{\text{H-1}}$ for A-type oxetanes than B-type oxetanes. To investigate the effect of solvent on the regioselectivity, the photochemical reactions of DMT with MBP or other BPs were performed, and then measured by ^1H NMR spectroscopy directly on the crude product mixture in deuterated solvents.

The PB reaction of DMT and MBP has been performed in deuterated acetonitrile-water binary solvents in various ratios, and the regioselectivity (A-type/B-type) and the yield were listed in Table 1. Data show that the regioselectivity is strongly dependent on the ratio of two solvents. With increasing the proportion of water in solution, the proportion of B-type product fast increases, such as A:B = 44:56 for neat acetonitrile, and 7:93 for 1:3 (v/v) acetonitrile–water. As a comparison, using 4,4'-difluorobenzophenone (DFBP) and benzophenone (BP) instead of MBP, the experiments were also performed under the same condition. In contrast to large changes of the regioselectivity in the DMT–MBP system, small changes were observed, as 66:34 to 49:51 for DFBP–DMT system and 56:44 to 41:59 for BP–DMT system. This may relate to strong solvent effects of the lowest triplet of MBP [15].

Besides the decrease in the regioselectivity (A:B) for these three PB systems, the photochemical yields decrease largely especially in DFBP system, but only mass balance of DFBP system decrease remarkably, with increasing proportion of water in the binary solutions. Obvious side products, which may be formed via an electron transfer reaction from DMT to triplet DFBP, were observed in the solution containing high proportion of water, beginning at 3:2 acetonitrile–water, and increased with raising the proportion of water. The photoinduced electron-transfer reaction was observed in photochemical reaction of 4,4'-dicyanobenzophenone with DMT in acetonitrile [10].



Scheme 1.

Table 1

The regioselectivity in the photochemical reaction of DMT with MBP, DFBP and BP in acetonitrile–water binary solvent^a

Solvent, CD ₃ CN:D ₂ O	MBP ^b		DFBP ^c		BP ^d	
	1:2	Yield (mb ^e) %	A:B	Yield (mb ^e) %	A:B	Yield (mb ^e) %
5:0	44:56	96(98)	66:34	97(98)	56:44	63(97)
4:1	33:67	94(98)	58:42	96(97)	49:51	51(96)
3:2	28:72	89(96)	57:43	72(88)	47:53	47(95)
2:3	17:83	86(95)	49:51	60(63)	51:49	40(97)
1:3 ^f	7:93	28(97)	49:51	11(16)	41:59 ^g	36(98)
Benzene	32:68	100(98)	38:62	100(99)	42:58	82(98)

^a DMT:BP_s = 10:20 mM, 300 W high-pressure Hg lamp, 10 °C.^b Irradiation for 30 min.^c Irradiation for 8 min.^d Irradiation for 5 min.^e Mass balance.^f DMT:BP_s = 5:10 mM.^g CD₃CN:D₂O = 1:4.

Using Rehm–Weller equation [16,17], free energy changes (ΔG) for proposed electron-transfer reactions from DMT to triplet BPs, including 4,4'-dimethoxybenzophenone (DMBP), were estimated:

$$\Delta G \text{ (kJ mol}^{-1}\text{)} = 96.5[E_{\text{ox}}(D) - E_{\text{red}}(A) - \Delta E_{\text{coul}}] - \Delta E_{0,0} \quad (1)$$

$$\Delta E_{\text{coul}} \text{ (eV)} = \frac{e}{4\pi\epsilon_0 a} \left(\frac{1}{\epsilon} - \frac{2}{37.5} \right) \quad (2)$$

where E_{ox} of DMT in acetonitrile was 1.45 V versus Ag/AgCl [18], $e = 1.602 \times 10^{-19}$ C, $\epsilon_0 = 8.854 \times 10^{-12}$ C V⁻¹ m⁻¹, and $a = 7$ Å. The value of ϵ is known to be 2.28 in benzene, 37.5 in acetonitrile and 78.4 in water, thus the coulomb term ΔE_{coul} was +0.79 eV in benzene, -0.06 eV in acetonitrile and -0.12 eV in water. The change of $\Delta E_{0,0}$ in different solvents was not considered in the calculation, and data of ΔG were listed in Table 2. Because the energy level of T₁ (n, π^*) state would increase from non-polar solvent (methyltetrahydrofuran) [19] to polar solvents such as acetonitrile or water, ΔG value for DFBP–DMT in water is expected to be negative, if the change of $\Delta E_{0,0}$ was considered. Hence, the calculated result demonstrated that more side products in DFBP–DMT system were obtained from the electron-transfer reaction from DMT to triplet DFBP. The driving force (ΔG) of the reaction is enhanced with increasing water in the solution.

Besides the competitive reaction, electron transfer, the efficiency of the PB reaction depends on the nature of the lowest

Table 2

Calculated free energy changes for proposed electron transfer from DMT to triplet BPs

BPs	$\Delta E_{0,0}$ (kJ mol ⁻¹) ^a	$-E_{\text{red}}$ (V (SCE)) ^a	ΔG (kJ mol ⁻¹)	
			In CH ₃ CN	In water
DMBP	290	2.02	+37.1	+31.3
BP	289	1.83	+19.8	+14.0
DFBP	294	1.78	+10.0	+4.2

^a From Ref. [19].

triplet state, and the reactive state is n, π^* state. As the lowest triplet state of the aryl ketone is a “mixed state” of the π, π^* aromatic and n, π^* carbonyl state, a T₁ (π, π^*) state possesses some n, π^* character [20]. Two triplet levels of aryl ketones are strongly mixed when the energy difference is lower than 8 kJ mol⁻¹ [21,22]. The lowest triplet state of MBP has a pronounced n, π^* character in cyclohexane, while significant π, π^* character in 1:3 (v/v) acetonitrile–water [15]. The decrease of n, π^* character in the lowest triplet state may be responsible for the decrease in the efficiency. Control experimental data show that the efficiency in non-polar solvent such as benzene is the higher (Table 1). Hence, the efficiency of the PB reaction is determined by the proportion of n, π^* character in the T₁ state of aryl ketone. Another example supporting this proposal is that no reaction between DMT and 4-phenylbenzophenone with π, π^* character in polar solvent was observed, while B-type oxetane was obtained in benzene [23].

The frontier molecular orbital (FMO) interactions between two reactants can determine the regioselectivity of a cycloaddition. The values of ΔG can reflect the energy gaps between interacted FMOs. The triplet energy level of the active state (n, π^*) of PB reactions would be raised with increasing water in the solution, and leading to a decrease in the values of ΔG . The PB system with a less ΔG value reveals the lower A:B ratio in accord with our previous results from BPs with different substituents [10, 11].

According to the frontier molecular orbital (FMO) theory, the regioselectivity in the PB reactions without electron transfer involvement can be discussed [24,10]. The regioselectivity of a given cycloaddition can be attributable to the interacting manner of the paired FMOs (HOMO–LUMO) between two reactants. The triplet energy level of the active state (n, π^*) of BPs in PB reactions would be changed significantly with increasing water in the solution due to its stronger solvation than acetonitrile. The changes of FMO energy levels of triplet BPs, mainly two singly occupied molecular orbitals (SOMOs), would lead to changes of the energy gaps of the two interacting FMO orbitals, i.e., interaction between the higher SOMOs and two FMOs of DMT, HOMO and LUMO. The smaller the energy gap, the greater and more

favorable is the orbital interaction. The two pairs of interactions determined by two FMO energy gaps, which may be adjusted by the proportion of water in solution, lead to preferring to generate A-type oxetane or B-type oxetane, respectively, and control the regioselectivity of the ultimate cycloaddition products. The detailed mechanism warrants further investigation.

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