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Chemiluminescent decomposition of a dioxetane bearing a 3-(1-cyanoethenyl)phenyl moiety induced by Michael addition of an anion of malonate

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Abstract—A thermally stable dioxetane bearing a 3-(1-cyanoethenyl)phenyl group (**1**) was synthesized. Michael addition of an anion of malonate (**3a**,**b**) to a dioxetane (**1**) substituted with a 3-(1-cyanoethenyl)phenyl moiety took place to give an intermediary dioxetane bearing a benzylic anion, which decomposes rapidly with accompanying emission of crimson light. When an anion of chloromalonate (**3c**) was used as a base, intramolecular cyclopropanation of **3c** occurred concurrently with the Michael-addition-induced chemiluminescent decomposition.

Dioxetanes substituted with an aromatic electron donor such as an oxyanion of the hydroxyarene moiety undergo intramolecular charge-transfer (CT)-induced decomposition with accompanying luminescence.[1–4] The phenomenon has received much attention from the viewpoint of mechanistic interest related to bioluminescence and application to chemiluminescent bioassays.[5] In addition to such oxyanion of hydroxyarene, a benzylic carbanion has very recently been reported to play a role of an electron donor as well for the CT-induced chemiluminescent decomposition of a dioxetane.[6] This fact suggests that various reaction systems producing an intermediary benzylic anion should become an object to be investigated from a new viewpoint of CT-induced chemiluminescence. Thus, we attempted to design a dioxetane bearing a phenyl group substituted with an electron-deficient olefinic function, to which the addition of a nucleophile would lead to a benzylic anion causing the CT-induced chemiluminescent decomposition of the dioxetane.

The dioxetane designed was 5-*tert*-butyl-4,4-dimethyl-2,6,7-trioxabicyclo[3.2.0]heptane bearing a 3-(1-cyanoethenyl)phenyl group at the 1-position (**1**), of which the synthesis was effectively attained by means of singlet oxygenation. When a solution of 4-*tert*-butyl-5-[3-(1-cyanoethenyl)phenyl]-3,3-dimethyl-2,3-dihydrofuran (**2**) (140 mg) was irradiated together with a catalytic amount of tetraphenylporphin (TPP) in CH_2Cl_2 (10 mL) under O_2 atmosphere at −78 °C for 1 h, the desired dioxetane (**1**) was produced as pale yellow granules (mp 123.3–124.0 °C) in 73% yield after chromatographic purification [SiO_2/hexane–AcOEt (9:1)] followed by recrystallization (hexane–CH_2Cl_2). The structure of dioxetane (**1**) was determined by ^{1}H NMR, ^{13}C NMR, IR, Mass (EI), and HR Mass (ESI) spectral analysis.[7] Dioxetane (**1**) was quite stable enough to permit handling at room temperature though it polymerizes gradually by standing for a long period (Scheme 1).

First of all, dimethyl methylmalonate (**3a**) was chosen as a source of stable carbanion that would attack the 1-cyanoethenyl moiety attached to a phenyl in dioxetane (**1**).[8] A solution of an anion of ester (**3a**) (1.0×10^{-1} mol dm^{-3}) was prepared by dissolving a malonate (**3a**) together with an equimolar amount of 18-crown-6 and *t*-BuOK in benzene: an abbreviation $[K \subset (18\text{-crown-6})]^+(\mathbf{3a})^-$ is used here for this anionic system. When a solution of a dioxetane (**1**) in benzene (1.0×10^{-3} mol dm^{-3}, 1 mL) was added to a solution of $[K \subset 18\text{-crown-6})]^+(\mathbf{3a})^-$ in benzene (1.0×10^{-1} mol dm^{-3}, 2 mL) at 25 °C, the dioxetane (**1**) decomposed rapidly to emit flash crimson light (maximum wavelength $\lambda_{\max}^{CL} = 740$ nm, $\Phi^{CL} = 5.6 \times 10^{-6}$). This maximum wavelength

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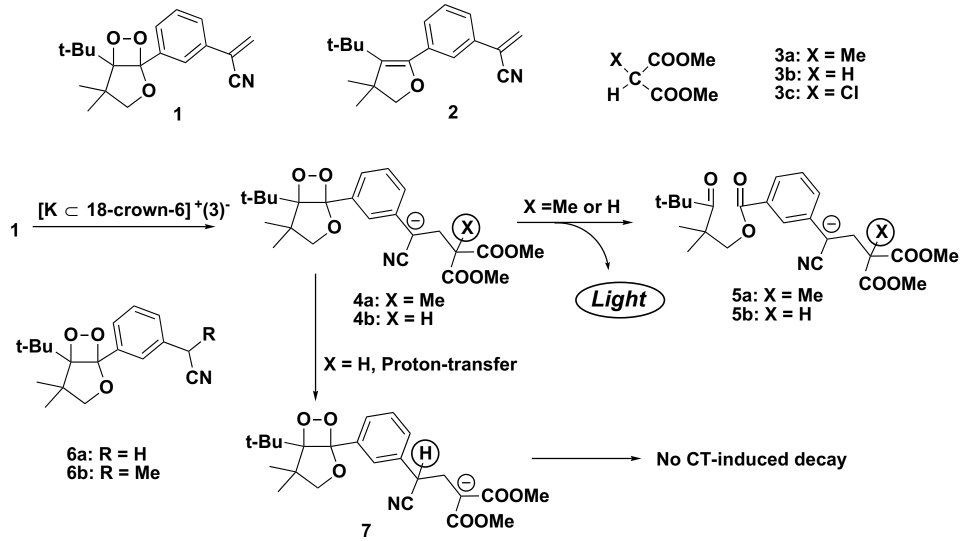


Scheme 1.

($\lambda_{\max}^{\mathrm{CL}}$) was considerably longer than that for a dioxetane bearing a 3-(cyanomethyl)phenyl moiety (**6a**) ($\lambda_{\max}^{\mathrm{CL}} = 702\,\mathrm{nm}$ in TBAF/DMSO),[6] while shorter than that for a dioxetane bearing the 3-(1-cyanoethyl)phenyl moiety (**6b**) ($\lambda_{\max}^{\mathrm{CL}} = 788\,\mathrm{nm}$), which was synthesized here. These differences in $\lambda_{\max}^{\mathrm{CL}}$ are presumably attributed to the inductive effect of a substitutent attached at a benzylic carbon of the (cyanomethyl)phenyl moiety.

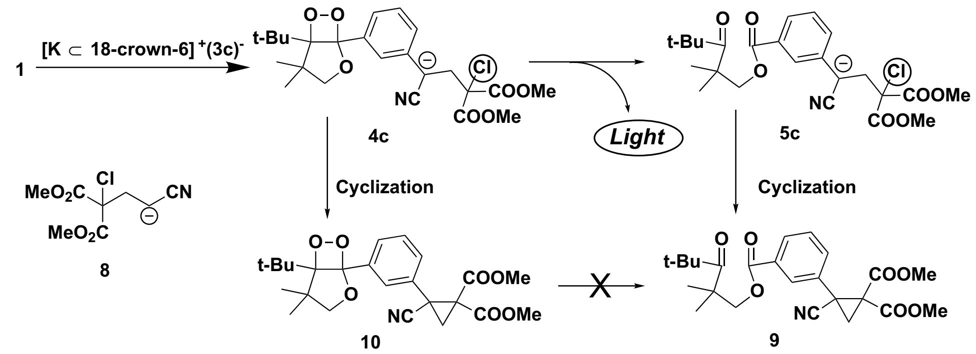
The spent reaction mixture of **1** with $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3a})^{-}$ after neutralization gave exclusively a ketoester (neutral form of **5a**); **5a** was presumably produced by the Michael addition of an anion of **3a** to **1** giving an anion (**4a**), which caused CT-induced chemiluminescent decomposition of a dioxetane ring successively. Thus, we prepared a dioxetane (neutral form of **4a**) bearing a phenyl substituted with a 1-cyano-3,3-bis(methoxycarbonyl)butyl group at the 3-position as a reference. On treatment with a *t*-butoxide anion, $[\mathrm{K} \subset (18\text{-crown-}6)]^{+}t\text{-BuO}^{-}$, in benzene ($1.0 \times 10^{-1}\,\mathrm{mol\,dm^{-3}}$, 2 mL) at 25 °C, a dioxetane (neutral form of **4a**) ($1.0 \times 10^{-3}\,\mathrm{mol\,dm^{-3}}$, 1 mL) underwent similarly the CT-induced decay to emit light with chemiluminescent properties: $\lambda_{\max}^{\mathrm{CL}} = 740\,\mathrm{nm}$, $\Phi^{\mathrm{CL}} = 5.7 \times 10^{-6}$, and the rate constant of the CT-induced decay $k = 3.5\,\mathrm{s^{-1}}$. The spent reaction mixture of a dioxetane (neutral form of **4a**) gave a ketoester (neutral form of **5a**) exclusively after neutralization. These results reveal that an emitter produced by the reaction of **1** with an anion of **3a** is undoubtedly a benzylic anion (**5a**). It should be noted here that the *t*-butoxide anion, $[\mathrm{K} \subset (18\text{-crown-}6)]^{+}$ $t\text{-BuO}^{-}$, induced also the chemiluminescent decomposition of **1**, though the $\lambda_{\max}^{\mathrm{CL}}$ of emission (706 nm) was shorter than that for the case of $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3a})^{-}$.[9]

Next, a reaction of **1** with a solution of an anion of dimethyl malonate (**3b**), $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3b})^{-}$, in place of $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3a})^{-}$, in benzene was carried out. This case also gave crimson light ($\lambda_{\max} = 737\,\mathrm{nm}$) as in the case of $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3a})^{-}$. However, the light yield ($\Phi^{\mathrm{CL}} = 1.5 \times 10^{-6}$) was considerably low ($\Phi^{\mathrm{CL}}$ for a reaction of **1** with **3a**:Φ^{CL} for a reaction of **1** with **3b** = 3.7:1), though both cases would lead to a very similar intermediary benzylic anion of dioxetane (**4a**) and (**4b**) as well as a very similar emitter (**5a**) and (**5b**), respectively.

The spent reaction mixture after the chemiluminescent decomposition of **1** with $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3b})^{-}$ gave the expected product (neutral form of **5b**) (28% yield) derived from Michael-addition of an anion of **3b** to **1** followed by CT-induced decay, along with a dioxetane (neutral form of **4b**) (39% yield), which was produced only by the Michael addition of an anion of **3b** to **1**. The formation of a dioxetane (neutral form of **4b**) reveals that a considerable quantity of an intermediary benzylic anion (**4b**), produced initially by the Michael addition of an anion of **3b** to **1**, would change into a more stable anion (**7**) before causing the CT-induced decay to **5b**. This means surely that an exchange of the benzylic anion into a malonate anion takes place as rapidly as the CT-induced decay for a benzylic anion (**4b**). These facts coincide with the decreased chemiluminescent efficiency in the case of **1** with $[\mathrm{K} \subset 18\text{-crown-}6]^{+}(\mathbf{3b})^{-}$.

The results described above suggested that the rate of the reaction, which occurs concurrently to extinguish the intermediary benzylic anion, can be estimated for the system of the Michael addition-induced chemiluminescent decomposition of a dioxetane (**1**). Thus, we attempted to examine such a reaction of benzylic anion (**4**) that leads to the CT-induced decay and/or a concurrent reaction to extinguish it without decay of the dioxetane ring.

Dimethyl chloromalonate (**3c**) has been reported to undergo base-induced reaction with an α,β-unsaturated nitrile to give a cyclopropanedicarboxylate.[10,11] The reaction proceeds through addition of an anion of **3c** to acrylonitrile giving an intermediary carbanion (**8**), of which the intramolecular nucleophilic attack to a carbon



Scheme 2.

bearing a chlorine furnishes a cyclopropanedicarboxylate. One mechanistically interesting point of this cyclopropanation is that the intramolecular nucleophilic attack of an anion of **3c** should be more rapid than the quenching of the anion by protonation, since the reaction proceeds effectively even under weak basic conditions where an anion (**8**) is hardly expected to form from a conjugate acid of **8**.

Thus, we carried out the reaction of a dioxetane (**1**) with an anion of dimethyl chloromalonate (**3c**). Similarly to the case of **4a**, when a dioxetane (**1**) was treated with an anion of dimethyl chloromalonate (**3c**), $[\mathrm{K} \subset 18\text{-crown-}6]^+(\mathbf{3c})^-$, in benzene, crimson light ($\lambda_{\max} = 710\,\mathrm{nm}$, $\Phi^{\mathrm{CL}} = 2.4 \times 10^{-6}$, $k = 4.5\,\mathrm{s}^{-1}$) was observed. After neutralization, the spent reaction mixture afforded a keto-ester (**9**) of a benzoic acid bearing a substituted cyclopropyl at the 3-position in 71% yield together with a cyclopropane derivative (**10**), in which the dioxetane ring remained intact in 29% yield[12] (Scheme 2).

A dioxetane (**10**) was stable and decomposed little into a ketoester (**9**) under the reaction conditions similar to the case of **1** with $[\mathrm{K} \subset 18\text{-crown-}6]^+(\mathbf{3c})^-$. Therefore, a reasonable explanation of the formation of **9** is that an intermediary benzylic anion (**4c**), produced by the Michael addition of an anion of **3c** to **1**, undergoes the CT-induced decay into a benzylic anion (**5c**) with accompanying light, and, thereafter, the anion (**5c**) is transformed into a cyclopropane (**9**) through intramolecular cyclization. According to this explanation, the rate of disappearance of **1** in the $[\mathrm{K} \subset 18\text{-crown-}6]^+(\mathbf{3c})^-$/benzene system[13] should be the sum of the rate for true CT-induced decomposition of **4c** and the rate for the reaction of **4c** leading to a dioxetane (**10**), since both paths leading to **9** through **5c** and to **10** through **4c** would be an intramolecular reaction. Therefore, referring to the ratio **9** versus **10** = 71:29, the rate constant of CT-induced decomposition of **4c** is estimated to be $3.2\,\mathrm{s}^{-1}$, while the rate for the reaction leading to **10** is estimated to be $1.3\,\mathrm{s}^{-1}$.

The results presented here show that the chemiluminescent decomposition of a dioxetane induced by Michael-type reaction with a nucleophile should provide a new probe to know a feature of an intramolecular reaction, which occurs concurrently with the CT-induced chemiluminescent decomposition of an intermediary dioxetane, though it would be limited to a reaction through a benzylic carbanion.

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References and notes

1. Schaap, A. P.; Chen, T.-S.; Handley, R. S.; DeSilva, R.; Giri, B. P. *Tetrahedron Lett.* **1987**, *28*, 1155.
2. McCapra, F. *J. Photochem. Photobiol., A: Chem.* **1990**, *15*, 21.
3. McCapra, F. Mechanism in Chemiluminescence and Bioluminescence-Unfinished Business. In *Bioluminescence and Chemiluminescence*; Hastings, J. W., Kricka, L. J., Stanley, P. E., Eds.; Wiley: NY, 1996; pp 7–15.
4. Recent reports: Watanabe, N.; Nagashima, Y.; Yamazaki, T.; Matsumoto, M. *Tetrahedron* **2003**, *59*, 4811–4819; Matsumoto, M.; Sakuma, T.; Watanabe, N. *Tetrahedron Lett.* **2002**, *43*, 8955–8958; Fujimori, K.; Wakasugi, K.; Matsumoto, M. *Chem. Lett.* **2002**, 762; Matsumoto, M.; Ito, Y.; Murakami, M.; Watanabe, N. *Luminescence* **2002**, *17*, 305.
5. Reviews: Beck, S.; Köster, H. *Anal. Chem.* **1990**, *62*, 2258–2270; Adam, W.; Reinhardt, D.; Saha-Möller, C. R. *Analyst* **1996**, *121*, 1527–1531; Matsumoto, M. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 595–604.
6. Matsumoto, M.; Mizuno, T.; Watanabe, N. *J. Chem. Soc., Chem. Commun.* **2003**, 483–484.
7. Selected data for **1**: ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$) δ_{H} 0.98 (s, 9H), 1.17 (s, 3H), 1.39 (s, 3H), 3.85 (d, $J = 8.2$ Hz, 1H), 4.60 (d, $J = 8.2$ Hz, 1H), 6.16 (s, 1H), 6.38 (s, 1H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.64 (d with fine coupling, $J = 7.8$ Hz, 1H), 7.68 (d with fine coupling, $J = 7.8$ Hz, 1H), 7.86 (s with fine coupling, 1H); ^{13}C NMR (125 MHz, $\mathrm{CDCl_3}$) δ_{C} 18.4 ($\mathrm{CH_3}$), 25.1 ($\mathrm{CH_3}$), 26.8 ($\mathrm{CH_3} \times 3$), 36.7 (C), 45.6 (C), 80.3 ($\mathrm{CH_2}$), 105.0 (C), 116.2 (C), 117.4 (C), 122.6 (C), 125.5 (CH), 127.0 (CH), 128.7 (CH), 128.8 ($\mathrm{CH_2}$), 129.8 (CH), 132.2 (C), 137.1 (C); IR (KBr) 2998, 2959, 2902, 2226 $\mathrm{cm^{-1}}$; Mass (m/z, %) 281 ($\mathrm{M^+} - 32$, 8), 258 (22), 256 (33), 230 (40), 228 (26), 174 (41), 157 (13), 156 (100), 85 (40), 57 (75); HRMS (ESI) 336.1593, calcd for $\mathrm{C_{19}H_{23}NO_3Na}$ ($\mathrm{M + Na^+}$) 336.1576; Anal. Calcd for $\mathrm{C_{19}H_{23}NO_3}$ Na: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.52; H, 7.80; N, 4.17.

8. Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179.
9. Neutralization of the spent reaction mixture of **1**/[K $\subset$ 18-crown-6]$^+$ *t*-BuO$^-$ system gave no expected ketoester, namely, 2,2,4,4-tetramethyl-3-oxopentyl 3-(2-*tert*-butoxy-1-cyanoethyl)benzoate, but 2,2,4,4-tetramethyl-3-oxopentyl 3-(1-cyanoethenyl)benzoate (14%) and a polymeric ketoester. In this case, an initially produced adduct of a *t*-butoxide to 1-cyanoethenyl moiety would remove easily a *t*-butoxide to regenerate a cyanoethenyl moiety.
10. Joucla, M.; Le Brun, J. *Tetrahedron Lett.* **1985**, *26*, 3001–3004.
11. Le Menn, J.-C.; Tallec, A.; Sarrazan, J. *Can. J. Chem.* **1991**, *69*, 761–767.
12. Few products other than **9** and **10** were observed.
13. The formal rate of CT-induced decomposition of **1** was estimated by measuring the time-dependency of the intensity of light emission. For the present system, the rate followed pseudo-first-order kinetics independent of the [K $\subset$ 18-crown-6]$^+$(**3**)$^-$ under the conditions using a large excess of the base as described here.