CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200800428

Photolysis of the Sulfonamide Bond of Metal Complexes of *N*-Dansyl-1,4,7,10-Tetraazacyclododecane in Aqueous Solution: A Mechanistic Study and Application to the Photorepair of *cis,syn*-Cyclobutane Thymine Photodimer

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Abstract: Sulfonamide constitutes a ubiquitous functional group that is frequently used in organic chemistry, analytical chemistry, and medicinal chemistry. We report herein on the photolysis of a dansylamide moiety of 1-dansyl-1,4,7,10-tetraazzacyclododecane (*N*-dansylcyclen, L^2) in the presence of a zinc(II) ion in aqueous solution. By potentiometric pH titrations, the complexation constant for the 1:1 complex of L^2 and Zn^{2+}, $\log K_s(ZnL^2)$, in aqueous solution at 25 °C with $I=0.1$ ($NaNO_3$) was determined to be 6.5 ± 0.1. The structure of the ZnL^2 complex was confirmed by single-crystal X-ray diffraction analysis. During fluorescence titrations of L^2 with Zn^{2+} (irradiation at 308 or 350 nm) in aqueous solution at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C, considerable enhancement in fluorescence emission of the Zn^{2+} complex of L^2 (ZnL^2) was observed, while metal-free L^2 exhibited only a negligible emission change upon UV irradiation. It was revealed that this emission enhancement arose from the photoinduced cleavage of a sulfonylamide moiety in ZnL^2, yielding the Zn^{2+}-cyclen complex and 5-dimethylaminonaphthalene-1-sulfinic acid, which has a greater quantum yield (Φ) for fluorescence emission than that of L^2 and ZnL^2. For comparison, the photolysis of *N*-(1-naphthalenesulfonyl)cyclen (L^3) and its Zn^{2+} complex (ZnL^3) under the same conditions (irradiation at 313 nm) gave the corresponding sulfonate (1-naphthylsulfonate). We also describe the results of a photoreversion reaction of *cis,syn*-cyclobutane thymine photodimer (T-[*c,s*]T) utilizing the photolysis of ZnL^2 and ZnL^3.

Keywords: DNA repair · macrocyclic ligands · photolysis · sulfonamides · zinc

Introduction

Sulfonamide is one of the representative functional groups used in organic synthesis, analytical chemistry, and medicinal chemistry.[1] For example, sulfonamides have been the starting materials for the synthesis of pharmaceutical agents having broad antibacterial spectrum and anticancer activities.[2] Sulfonamide groups have also been successfully utilized as protecting groups in areas of synthetic organic chemistry,[3] as important functionalities in asymmetric catalysts,[4] and even as aprotic organic solvents.[5]

One of the common reactions of sulfonamides and their derivatives is the photochemical cleavage of the S–N bond resulting in the release of the free amine.[1,2,3a] For example, it was reported by D'Souza and Day in 1968 that *N*-dansyl-L-alanine **1a** and *N*-dansyl-L-isoleucine **1b** underwent photolysis to give dansyl acid and the corresponding amino acids (Scheme 1).[6] It was also reported that the photolysis

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.200800428.

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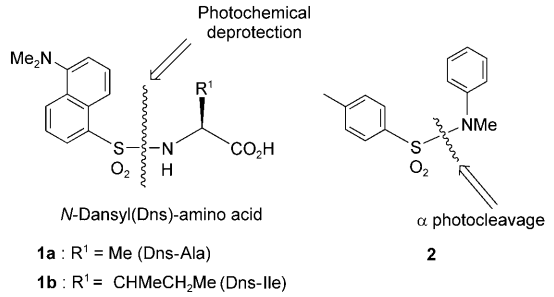
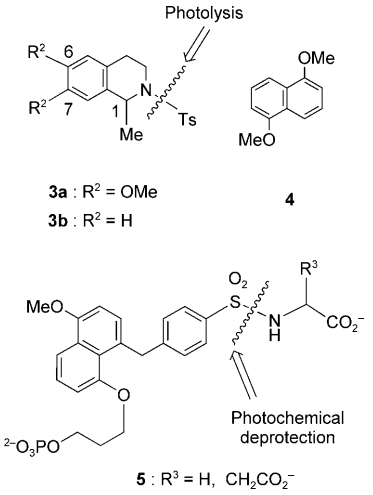


Scheme 1.

of **1** was much more efficient under acidic conditions than basic conditions.

Haas et al. reported that sulfonamides, such as **2**, undergo photolysis in Et_2O or MeOH to give an aniline derivative and a photo-Fries rearrangement-type product (Scheme 1).[7,8] They reported that S–N bond cleavage (α photocleavage) is a radical step that affords a radical pair, resulting in the formation of the aniline derivative. It was proposed that the α photocleavage of **2** proceeds via excited triplet states.

In 1969, Umezawa et al. reported the photolysis of 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline *N*-tosylate **3a** (Scheme 2).[9] It was postulated that this photolysis

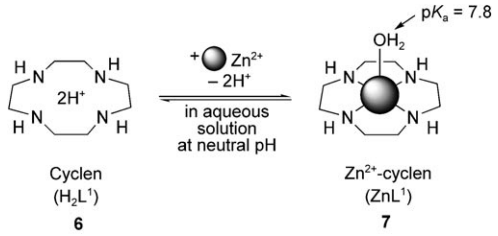


Scheme 2.

proceeded through the intramolecular formation of a donor–acceptor ion pair between the electron-donating dimethoxybenzene group (R^2) and the electron-withdrawing tosyl group. Yonemitsu's group subsequently reported that the photolysis of **3b**, which lacks methoxy groups on the 1,2,3,4-tetrahydroisoquinoline ring, is less efficient than that of **3a**, indicating that two methoxy groups in **3a** serve as electron donors to generate radical anion intermediates.[10] In addition, they showed the photolysis of **3b** in the presence of 1,5-dimethoxynaphthalene **4**, which donates an electron in an intermolecular fashion. In these papers, however, the products derived from the sulfonyl parts were not characterized.

In 1999, Corrie's group reported on the development of a photolabile protecting group for amino acids.[11] They found that photolysis of amino acids **5** having an electron-rich aromatic ring in the protecting group promoted deprotection, with the release of the corresponding free amino acids in moderate yields.[11,12]

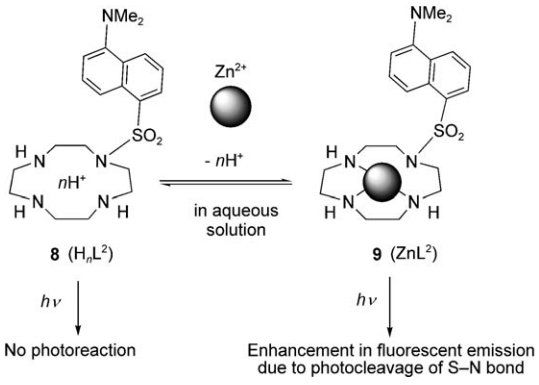
Meanwhile, we have been interested in the photochemical properties of metal complexes of functionalized macrocyclic polyamines such as 1,4,7,10-tetraazacyclododecane **6** (cyclen, L^1), which is a potent chelator of various metal ions in aqueous solution.[13,14] For example, a Zn^{2+} complex of cyclen **7** (ZnL^1) is thermodynamically stable and kinetically inert in aqueous solution (the K_d value is ca. 2 nM at pH 7.4; Scheme 3). We have reported on several cyclen-based Zn^{2+}



Scheme 3.

fluorophores equipped with fluorescent side chains[15–19] that fluorometrically respond to Zn^{2+} in sample solutions and living cells (apoptosis detection).[15b,c]

Based on this previous information, we synthesized *N*-dansylcyclen **8** (L^2) in an attempt to study the photochemical properties of a dansylamide moiety that is nearly fixed to Zn^{2+} or other metal cations (Scheme 4). We hypothesized



Scheme 4.

that the Lewis acidity of Zn^{2+} might have an effect on the photochemical (fluorescence) properties or photoreactivity of the dansylamide group in the 1:1 Zn^{2+} complex **9** (ZnL^2).[20]

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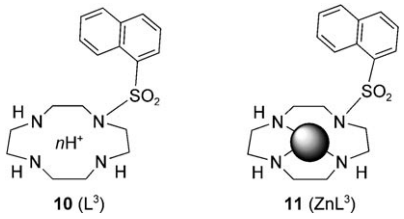
During fluorescent titrations of **8** with Zn^{2+} in aqueous solution at neutral pH to examine the Zn^{2+} complexation of **8**, we found that the fluorescence emission of the reaction mixture increased significantly. On the other hand, the emission of metal-free **8** exhibited only a negligible change under the same conditions. In this manuscript, we present evidence to show that the emission enhancement of **8** results from the photocleavage of the sulfonamide S–N bond of its Zn^{2+} complex **9** (ZnL^2). The photoreactivity of **9** was compared with that of the reference compounds *N*-(1-naphthalenesulfonyl)cyclen **10** (L^3) and its Zn^{2+} complex **11** (ZnL^3).



The results of photorepair reactions of *cis,syn*-cyclobutane thymine photodimer (T[*c,s*]T), which is one of the representative DNA photolesions,[21] utilizing photolysis of **9** and **11** will be described.

Results and Discussion

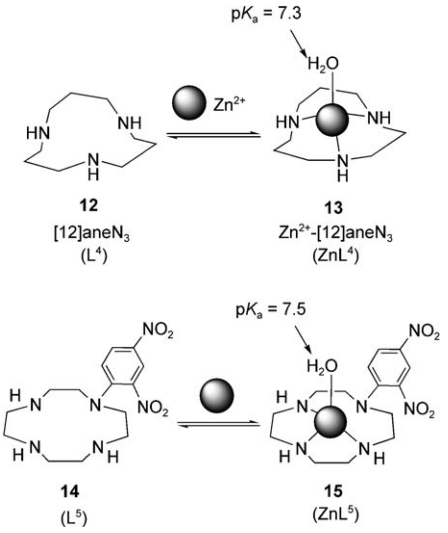
The pK_a Values of 8 (L^2) and 10 (L^3) and Their Complexation Constants with Zn^{2+}

The synthesis of **8** (L^2), **10** (L^3), and **9** (ZnL^2) was carried out via tris(*tert*-butyloxycarbonyl)-cyclen[22] as described in Scheme S1 in the Supporting Information (**8** and **10** were obtained as HCl salts ($L^2{\cdot}4HCl{\cdot}5H_2O$ and $L^3{\cdot}3HCl$)). The Zn^{2+} complex of L^2, **9**, was obtained as $ZnL^2{\cdot}Cl_2{\cdot}(H_2O)_3$. The deprotonation constants, pK_{ai} ($i=1$–4) of **8** (L^2) defined by Eq. (1) were examined by potentiometric pH titrations of a mixture of 1 mM H_4L^2 against 0.1 M NaOH with $I=0.1$ ($NaNO_3$) at 25 °C (Figure S1 in the Supporting Information). The titration data were analyzed for the acid–base equilibrium in Eq. (1) using the software program BEST[23] to give pK_{ai} values of <2, 3.51 ± 0.05, 6.44 ± 0.05, and 9.70 ± 0.05, respectively, as summarized in Table 1. The pK_{a1}, pK_{a3}, and pK_{a4} values of L^2 were assigned to the deprotonation constants of three secondary amines in a cyclen ring by analogy with the pK_a values for **12** (L^4, [12]aneN$_3$)[24] and **14** (L^5)[25] (Scheme 5), which were proven to be tridentate ligands for Zn^{2+} (see also Table 1). The pK_{a2} value of 3.5 for a dimethylamino moiety of dansyl group was confirmed by the ^{1}H NMR experiments in D_2O ($[L^2]=2$ mM), which showed a large shift of methyl signals of L^6 between pD $\approx$ 2 and pD 5 (Figure S2 in the Supporting Information).[26] Figures S3 and S4 in the Supporting Information show the change in UV and fluorescent emission of **8** (L^2) as a function of pH ($[L^2]=100$ or 10 μM), from which three pK_a values (3.5 ± 0.2, 6.5 ± 0.2, and 9.5 ± 0.2) were estimated. These three pK_a values are close to the pK_a values (3.5, 6.4, and 9.7) determined by potentiometric pH titrations.

Table 1. Deprotonation constants (pK_{ai}) and complexation constants of cyclen **6** (L^1), **8** (L^2), **10** (L^3), and **14** (L^5) with $I=0.1$ ($NaNO_3$) at 25 °C.[a]

	6 (L^1)[b]	**8** (L^2)[c]	**10** (L^3)[c]	**14** (L^5)[d]
pK_{a1}	<2	<2	<2	<3
pK_{a2}	<2	3.51[e]	6.81	7.3
pK_{a3}	9.9	6.44	10.19	10.1
pK_{a4}	11.0	9.70	–	–
log K_s(ZnL)[a]	16.2	6.5	6.5	7.9
log K_{app}(ZnL)[a,f] at pH 7.4	10.6	4.5	5.2	4.6
pK_a(ZnL)[g]	7.9	7.4	7.3	7.5

[a] For the definition of K_s(ZnL), K_{app}(ZnL), and pK_a(ZnL), see the text. [b] From reference [24]. [c] Determined in this work. [d] From reference [25]. [e] The pK_a value for the ArN^+HMe_2 group of L^2 assigned by ^{1}H NMR, UV, and fluorescence titrations. [f] Apparent complexation constants at pH 7.4 with $I=0.1$ ($NaNO_3$)). [g] Deprotonation constants of Zn^{2+}-bound water in ZnL.



Scheme 5.

$$H_nL^2 \rightleftharpoons H_{(n-1)}L^2 + H^+ : \quad K_{ai} = [H_{(n-1)}L^2]a_{H^+}/[H_nL^2] \ (n = 1-4,\ i = 5-n) \tag{1}$$

$$L^2 + Zn^{2+} \rightleftharpoons ZnL^2(H_2O) : \quad K_s(ZnL^2) = [ZnL^2(H_2O)]/[L^2][Zn^{2+}] \ (M^{-1}) \tag{2}$$

$$ZnL^2(H_2O) \rightleftharpoons ZnL^2(HO^-) + H^+ : \quad K_a(ZnL^2) = [ZnL^2(HO^-)]a_{H^+}/[ZnL^2(H_2O)] \tag{3}$$

$$K_{app}(ZnL^2) = [(ZnL^2(H_2O) + ZnL^2(HO^-))]/[L^2]_{free}[Zn^{2+}]_{free} \ \text{(at designated pH)} \ (M^{-1}) \tag{4}$$

$$[L^2]_{free} = [H_4L^2]_{free} + [H_3L^2]_{free} + [H_2L^2]_{free} + [HL^2]_{free} + [L^2]_{free} \tag{5}$$

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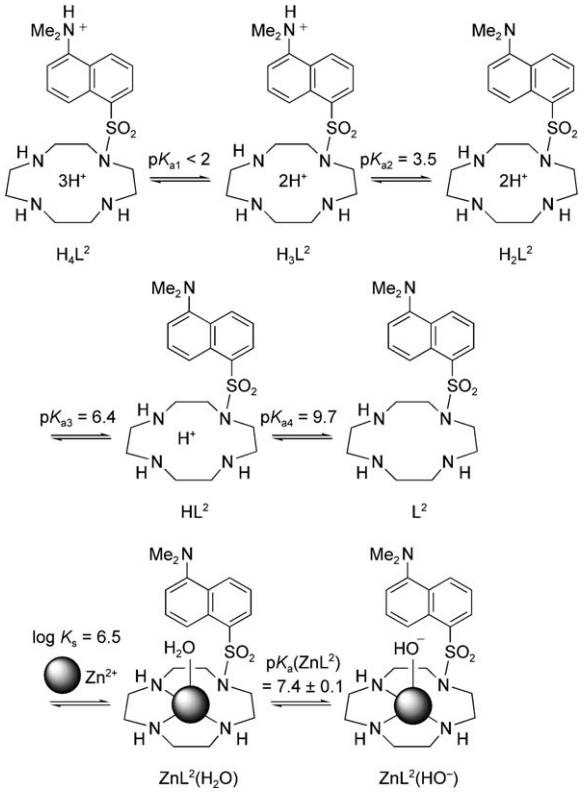
Analysis of a pH titration curve for a mixture of 1 mM H_4L^2 and 1 mM $ZnSO_4$ (Figure S1a in the Supporting Information) gave the intrinsic complexation constant of L^2 with Zn^{2+} ($K_s(ZnL^2)$ defined by Eq. (2)) of 6.5 ± 0.1. The pK_a value for Zn^{2+}-bound water of **8** (ZnL^2; $K_a(ZnL^2)$ defined by Eq. (3)) was 7.4 ± 0.1. This value is close to those for Zn^{2+}-**12** complex **13** (ZnL^4)[24] of 7.3 and Zn^{2+}-**14** complex **15** (ZnL^5)[25] of 7.5 (Scheme 5), indicating that three nitrogen atoms of a cyclen ring in L^2 coordinate to Zn^{2+}. From these values, the apparent complexation constant for **8** at pH 7.4 ($K_{app}(ZnL^2)$ defined by Eqs. (4)–(5)) was calculated to be 4.5 ± 0.1. Figure S1b in the Supporting Information presents a speciation diagram for a mixture of 1 mM H_4L^2 and 1 mM $ZnSO_4$ as a function of pH at 25 °C with $I=0.1$ ($NaNO_3$). The deprotonation and Zn^{2+} complexation behaviors of **8** (L^2) and **10** (L^3) are summarized in Scheme 6 and Table 1 in comparison with those of cyclen (L^1) and L^5.



Scheme 6.

X-ray Crystal Structure of 9 (ZnL^2)

Colorless crystals of **9** obtained as $ZnL^2{\cdot}Cl_2{\cdot}(H_2O)_3$ by recrystallization from an aqueous solution at pH 7.5 were subjected to single-crystal X-ray diffraction analysis. As shown in Figure 1, Zn^{2+} is coordinated by three secondary nitrogen atoms of the cyclen ring and a chloride anion. On the basis of our previous results, Zn^{2+}-bound Cl^- (Cl30) is replaced with a H_2O molecule in aqueous solution.[16,22,25] A hydrogen-bonding network including Zn^{2+}-bound Cl^- (Cl30), external chloride anion (Cl31), an amino group in the cyclen ring (N8), and water molecules (O33 and O34) was found.

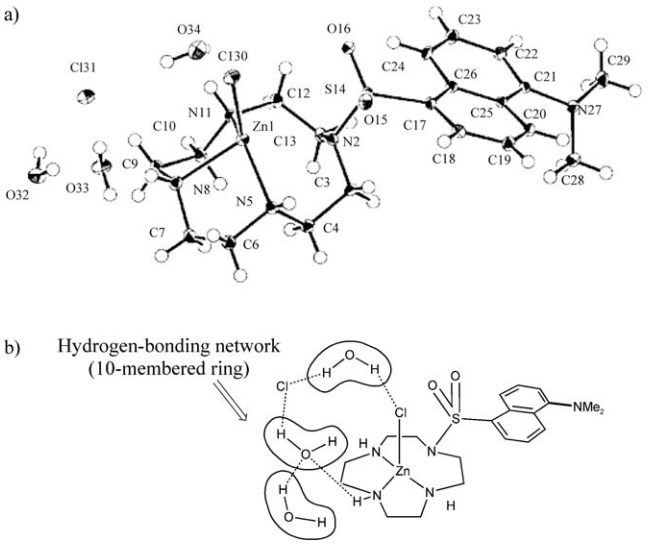


Figure 1. a) ORTEP drawing of **9** ($ZnL^2{\cdot}Cl_2{\cdot}(H_2O)_3$) and schematic drawing of hydrogen-bonding network including Zn^{2+}-bound Cl^-, a Cl^- counteranion, and three water molecules (50% probability ellipsoids). Selected bond lengths [Å]: Zn(1)-N(5) 2.08, Zn(1)-N(8) 2.15, Zn(1)-N(11) 2.06, Zn(1)-Cl(30) 2.21. b) Presentation of hydrogen-bonding network including Zn^{2+}, Cl^-, and water molecules.

UV Spectrophotometric and Fluorescence (Quick Scanning) Titrations of 8 (L^2) with Zn^{2+}

UV titration of **8** (100 μM) with Zn^{2+} was performed at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C. Metal-free **8** has absorption maxima at 243 nm and 332 nm ($\varepsilon_{243}=1.6\times10^4\,M^{-1}cm^{-1}$ and $\varepsilon_{332}=4.8\times10^3\,M^{-1}cm^{-1}$), as indicated with the dashed curve in Figure 2a. Upon addition of Zn^{2+}, the absorption maximum at 332 nm shifted to 338 nm. An increasing curve for absorbance at 380 nm (data not shown) gave the apparent 1:1 complexation constant for ZnL^2, $\log K_{app}(ZnL^2)$ of 4.2 ± 0.1, which agrees with the $\log K_{app}(ZnL^2)$ value obtained from potentiometric pH titrations described above (4.5 ± 0.1).

Fluorescence titration of **8** with Zn^{2+} was also carried out at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C (excitation at 338 nm). Metal-free **8** has an emission maximum (dashed curve in Figure 2b) at 558 nm. The quantum yield for fluorescence emission of **8** was $\Phi=3.5\times10^{-3}$ at 10 μM, which was much smaller than that of dansyl acid ($\Phi=8.8\times10^{-2}$ at 10 μM), implying that the emission of the dansyl group in **8** is considerably quenched by electron transfer from a cyclen ring.[27] As summarized in Figure 2b and its inset, the addition of Zn^{2+} gave a decreasing curve in the emission of **8**, from which the apparent complexation constant for **9** (ZnL^2), $\log K_{app}(ZnL^2)$, was determined to be 4.3 ± 0.1. Reproducible fluorescence spectra of **8** (or **10**) were obtained by a quick scanning of the emission wavelength (500~1000 nm min^{-1}), because **8** (or **10**) underwent a

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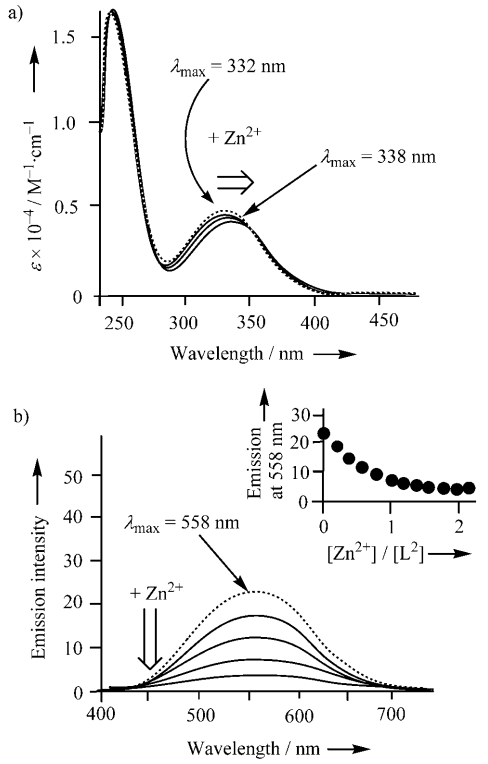

Figure 2. a) UV absorption spectral change of 100 μM **8** (L^2) upon the addition of Zn^{2+} at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C. Dashed curve is a UV spectrum of Zn^{2+}-free **8**. b) Change in fluorescent emission spectra of **7** (L^6; 100 μM) upon addition of Zn^{2+} at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C (excitation at 322 nm; obtained by quick scanning from 400 nm to 750 nm). The inset displays the decrease in emission of **8** (L^2) at 558 nm at the increasing concentrations of Zn^{2+}.

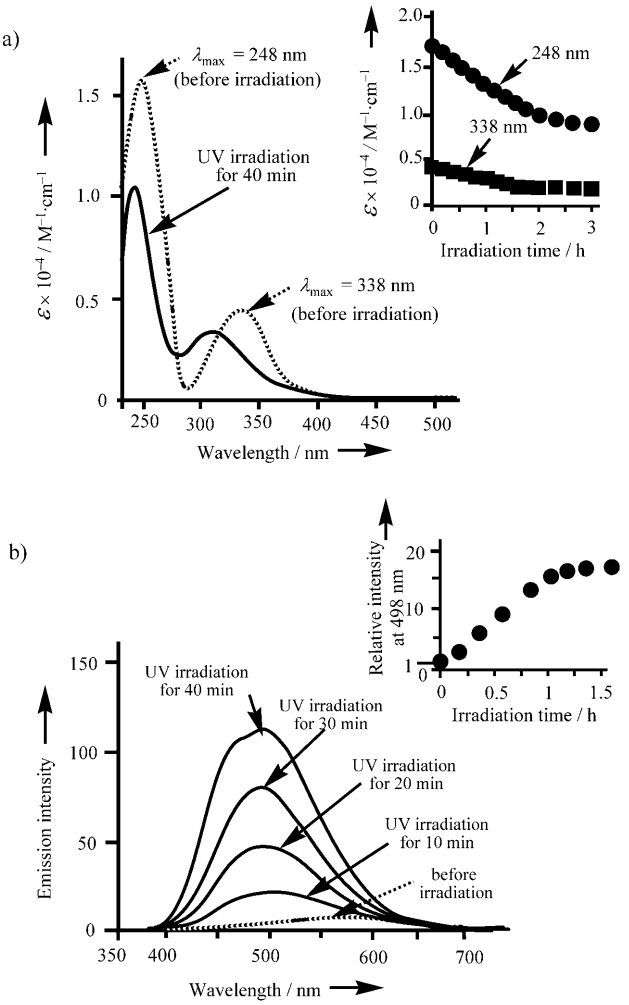

Figure 3. a) Change in UV absorption spectra of 100 μM **8** before (dashed curve) and after (solid curve) photoirradiation at 308 nm for 1 h in the presence of 300 μM $ZnSO_4$ at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C. The inset shows the change in the ε_{248} and ε_{338} values of **8** upon photoirradiation at 308 nm. b) Change in fluorescence emission spectra of **9** (ZnL^2; formed in situ from 100 μM L^2 and 300 μM $ZnSO_4$) before UV irradiation (dashed curve) and after photoirradiation at 338 nm for 10–40 min at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C. The inset shows the change in emission intensity of **9** at 498 nm upon UV irradiation at 308 nm (emission spectra obtained by excitation at 338 nm and quick scanning of emission wavelength).

photoreaction, resulting in an enhancement in emission in the presence of Zn^{2+}, as described below.

Accidental Finding of Enhancement in Fluorescent Emission of 8 (L^2) in the Presence of Zn^{2+}

During the fluorescence titrations of **8** with Zn^{2+}, we became aware that the emission of **8** exhibited considerable enhancement, with an emission maximum at 498 nm. After careful experiments, it was concluded that this emission enhancement is dependent on the duration of the UV exposure of **8** in the presence of Zn^{2+}. As displayed in Figure 3a, a UV absorption curve of a mixture of 0.1 mM **8** and 0.3 mM Zn^{2+}—these concentrations were chosen for a quantitative formation of **9** (ZnL^2) at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) based on the results of potentiometric pH titrations shown in Figure S1 in the Supporting Information—exhibited a blue-shift after photoirradiation at 308 nm for 30 min. As for fluorescence emission, photoirradiation at 308 nm facilitated considerable emission enhancement, as shown in Figure 3b and its inset. When stored in the dark, the emission spectra **9** exhibited only negligible change. In contrast, negligible change was observed in the UV spectra and fluorescence spectra of metal-free **8** after photoirradiation at 308 nm for 1 h, as shown in Figure S5 in the Supporting Information.

Photolysis of 9 (ZnL^2) Followed by ^1H NMR

The photoreaction of **9** (ZnL^2) in D_2O at pD 7.4 was monitored by ^1H NMR, as displayed in Figure 4. These photochemical reactions were carried out by photoirradiation at 350 nm (UV absorption maxima of **9**), which was found to promote photolysis faster than irradiation at 308 nm. Prior to the photoreactions, oxygen in the sample solutions was removed as much as possible by bubbling Ar through the reaction solution for 10 min or repeated freezing and melting

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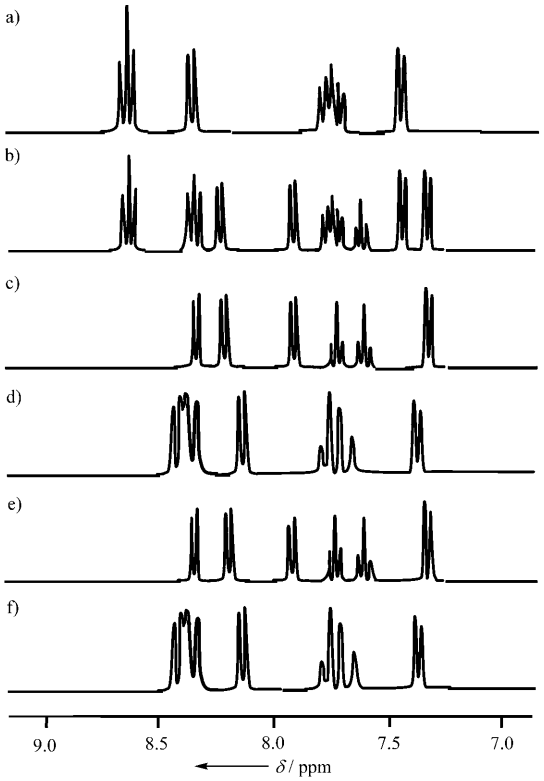
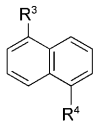


Figure 4. ^{1}H NMR spectra (aromatic regions) of a) a solution of 0.5 mM **9** (ZnL^2) (formed in situ from 0.5 mM **8** and 1.5 mM Zn^{2+}) in D_2O at pD 7.4 before UV irradiation, b) a solution of 0.5 mM **9** after UV irradiation at 350 nm for 0.5 h, c) a solution of 0.5 mM **9** after UV irradiation at 350 nm for 1 h, d) 0.5 mM dansyl acid **16a** at pD 7.4. e) 5-(dimethylamino)-1-naphthalensulfinate **16b**, and f) the solution from part (c) plus H_2O_2.

under reduced pressure. After UV irradiation for 0.5 and 1 h, the ^{1}H NMR spectra shown in Figure 4b,c were obtained. We initially suspected that the photoproduct produced from **9** would be dansyl acid (5-(dimethylamino)-1-naphthalenesulfonic acid (**16a**)). However, the ^{1}H NMR signals in Figure 4c did not agree with those of **16a** (Figure 4d) and showed a good coincidence with those of 5-(dimethylamino)-1-naphthalenesulfinic acid **16b** (Figure 4e), which was prepared from dansyl chloride and Na_2SO_3 according to a reported method.[28] ESI-MS spectra (negative mode) of a reaction mixture gave a mass peak at $m/z = 234$, which corresponded to **16b** (Figure S6a in the Supporting Information), thus providing support for the conclusion that the initial product of photolysis of **8** is **16b**. Moreover, the addition of an excess amount of H_2O_2 to the solution represented in Figure 4c gave the spectrum shown in Figure 4f, which showed good coincidence with Figure 4d (see also Figure S6b in the Supporting Information). Fries rearrangement-type products[8] were not observed to any extent.



16a ($R^3 = NMe_2$, $R^4 = SO_3^-$) : Dansyl acid (5-(dimethylamino)-1-naphthalenesulfonic acid)
16b ($R^3 = NMe_2$, $R^4 = SO_2^-$) : 5-(Dimethylamino)-1-naphthalenesulfinic acid
17a ($R^3 = H$, $R^4 = SO_3^-$) : 1-Naphthalenesulfonic acid
17b ($R^3 = H$, $R^4 = SO_2^-$) : 1-Naphthalenesulfinic acid

We also checked the aliphatic region of the ^{1}H NMR spectra of the photoreaction mixtures of **9** (1.0 mM) in D_2O at pD 7.4 and 25 °C (Figure S7 in the Supporting Information). Collectively considering the results displayed in Figure 4 and Figures S6 and S7,[30] we concluded that a sulfinic acid **16b** and Zn^{2+}-cyclen **7** are the initial products in the photolysis of **9**. As plotted in Figure S8 in the Supporting Information, the breakdown of **9** (ZnL^2) proceeded almost linearly as the photoirradiation time increased.

On the other hand, the photolysis of **11** (ZnL^3; a D_2O solution of **11** was irradiated at 313 nm, where molar absorption coefficient values (ε) of **9** and **11** were almost the same) gave 1-naphthalenesulfonate **17a** as the major product, not sulfinate **17b**[29] (Figure S9 in the Supporting Information). Interestingly, metal-free **10** also underwent photocleavage of the S–N bond to give **17a** and cyclen **6** (L^1; see Figure S10 in the Supporting Information), indicating that the mechanism of the photolysis of **10** and **11** is somewhat different from that of **9**. In addition, we discovered that the photolysis of 1.0 mM **11** in the presence of 4.0 mM *N,N,N*-triethanolamine (TEOA; $pK_a = 7.76$)[31] gave sulfinate **17b** as a major product. The discrepancy in the initial products in the photolysis of **9** and **11** is discussed below.

UV Absorbance and Fluorescent Emission Spectra of 5-(Dimethylamino)-1-naphthalenesulfinate (16b)

As described above, 5-(dimethylamino)-1-naphthalenesufinate **16b** was prepared by treating dansyl chloride with Na_2SO_3[28] and characterized. The dashed and solid curves in Figure S11a in the Supporting Information are UV absorption spectra of **16a** and **16b**, respectively ([**16a**] = [**16b**] = 100 μM). In Figure S11b in the Supporting Information, dashed and solid curves represent fluorescent emission spectra of **16a** and **16b** ([**16a**] = [**16b**] = 10 μM), in which the emission maxima of **16a** and **16b** are 502 nm and 495 nm, respectively.

Quantum yields (Φ) for the emission of **16a** and **16b** are 8.8×10^{-2} and 9.5×10^{-2} at 10 μM, implying that the emissions of these compounds are much greater than that of **9** (ZnL^2; $\Phi = 3.4 \times 10^{-3}$ at 10 μM). In addition, the emission maximum of **16b** (495 nm) showed a good coincidence with that of the photoreaction mixture of **9** (ZnL^2), as already shown in Figure 3. From these experimental results, we attributed the considerable enhancement in fluorescent emission after the photoirradiation of **9** (ZnL^2) to an S–N bond cleavage of **9**, resulting in the formation of 5-dimethylamino-1-naphthalenesulfinate (**16b**).

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Photoreaction of 8 (L^2) in the Presence of Various Metal Cations

We tested the effects of various metal cations on the photolysis of **8** at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C. Figure 5 shows the change in emission intensity at

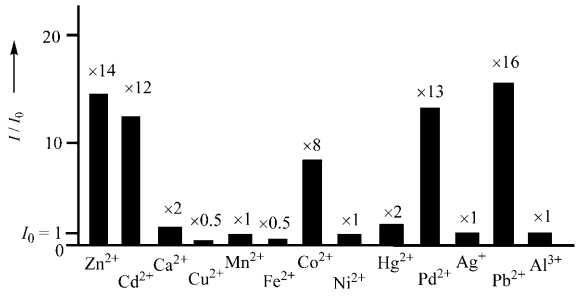


Figure 5. The change in emission intensity (I/I_0) of 0.1 mM **8** (excitation at 350 nm for fluorescence measurements) at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) and 25 °C after photoirradiation in comparison with those before UV irradiation in the presence of various metal cations (1 mM). The I_0 value is an emission intensity of metal-free **8** at 498 nm and I values are those after photoirradiation at 350 nm for 30 min in the presence of metal cations.

498 nm (I/I_0) of an aqueous solution of **8** (excitation at 350 nm for fluorescence measurements) after UV irradiation at 350 nm for 40 min to that before UV irradiation in the presence of the indicated metal cations. Considerable emission enhancement of **8** was observed in the presence of Zn^{2+}, Cd^{2+}, Co^{2+}, and Pb^{2+} (S–N bond cleavage was confirmed by ^1H NMR measurements), suggesting that the photolysis of **8** requires these Lewis acidic metal cations. The negligible photolysis of **8** in the presence of Cu^{2+} was confirmed by following changes in the UV spectrum.

Mechanisms Involved in Photolysis of 9 (ZnL^2) and 11 (ZnL^3)

The photoirradiation of metal-free **8** (L^2) at 350 nm under acidic conditions (pH 2–4) induced negligible S–N bond cleavage, and the photolysis of *N*-dansyl-L-proline in aqueous solution at pH 3 was much slower than that of **9**. It should also be noted that **9** (ZnL^2) underwent photolysis in aqueous solution without HEPES or other Good's buffers, suggesting that these buffer molecules are not appreciably effective as electron donors. In addition, the addition of electron donors such as triethylamine and 1,4-diazabicyclo-[2,2,2]octane (DABCO) had almost no effect on the photoreaction rates of **9**. Moreover, negligible acceleration of photocleavage of *N*-dansyl-glycine and *N*-dansyl-L-proline by Zn^{2+} was observed upon photoirradiation at 328 nm in MeCN/H_2O (1:1) solution at 25 °C.

To determine the effect of Zn^{2+}-bound H_2O on the photolysis of **9**, its photolysis was carried out at various pH values. The solid circles in Figure 6 indicate the pH-rate profile for the photolysis of 0.1 mM **9**, as followed by the change

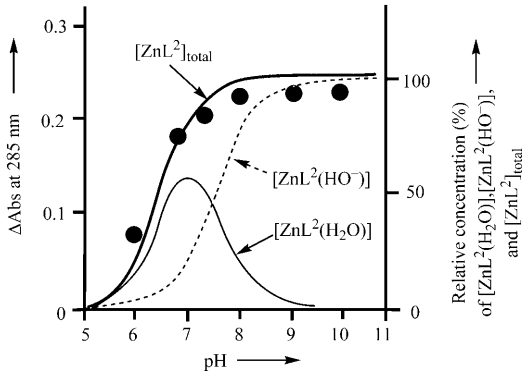
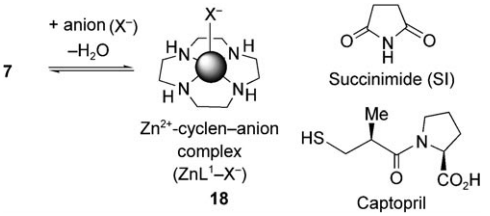


Figure 6. Comparison of pH-rate profile for photolysis (UV irradiation at 350 nm) of **8** and relative concentrations of ZnL^2 species. (**9** was formed in situ from **8** (0.1 mM) and Zn^{2+} (0.5–1.0 mM) for quantitative (>97%) complexation in 10 mM Good's buffer with $I=0.1$ ($NaNO_3$) and 25 °C. Photolysis of **9** was followed by UV spectra (ΔAbs at 285 nm obtained after photoirradiation for 30 min) and plotted with closed circles. Relative concentrations of $[ZnL^2(H_2O)]$, $[ZnL^2(HO^-)]$, and $[ZnL^2]_{total}$ (= $[ZnL^2(H_2O)]+[ZnL^2(HO^-)]$) calculated from the results of potentiometric pH titrations are displayed with a solid curve, a dashed curve, and a bold curve, respectively.

in the UV spectrum of **9** (ε_{285}). This suggests that the pH-dependent change in the photolysis rates of **9** is related to the total concentration of ZnL^2 ($[ZnL^2]_{total}$, equal to $[ZnL^2(H_2O)]+[ZnL^2(HO^-)]$), rather than the individual concentrations of $ZnL^2(H_2O)$ or $ZnL^2(HO^-)$ (for the structures of these species, see Scheme 6). These results indicated that photolysis of S–N bonds of **8** (L^2) requires a complexation with Zn^{2+} regardless of the deprotonation status of Zn^{2+}-bound water.

We next examined the effects of the anion-Zn^{2+} complexation on the photolysis of **9**. It has been confirmed that **7** forms 1:1 complexes **18** with anions (X^-) such as phosphate monoesters,[13,32] imidates (e.g., thymidine, uridine, and succinimide),[33,34] and thiolates[16,35] in aqueous solution (Scheme 7). By analysis of potentiometric pH titration curves of **9** and **11** with succinimide (SI) and captopril in aqueous solution with $I=0.1$ ($NaNO_3$) at 25 °C (data not shown), the affinity constants of these Zn^{2+} complexes with these anions (K_{app}(ZnL-X)), defined by Eqs. (6)–(9), were determined, and the results are summarized in Table 2.

$$ZnL(H_2O)+\text{anion}\ (X^-) \rightleftharpoons \text{ZnL-X}^-\ \text{complex}: \quad K_S(\text{ZnL-X}) = [\text{ZnL-X}^-]/[\text{ZnL}(H_2O)][X^-]\ (M^{-1}) \tag{6}$$



Scheme 7.

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Table 2. Apparent complexation constants ($\log K_{app}$(ZnL-X)) of **7** (ZnL^1), **9** (ZnL^2), and **11** (ZnL^3) with guest anions ($I=0.1$ ($NaNO_3$) at pH 7.4 and 25 °C).[a]

Anion (pK_a)[b]	**7** (ZnL^1)[c]	**9** (ZnL^2)	**11** (ZnL^3)
succinimide ($pK_a=9.6$)[b]	3.5[c]	4.1	3.7
captopril ($pK_a=3.6$, 10.0)[b]	4.5[c]	4.5	4.6

[a] The K_{app}(ZnL-X) values at pH 7.4 were calculated from K_S(ZnL-X) values. For the definition of K(ZnL-X) and K_{app}(ZnL-X), see the text. [b] pK_a values in parentheses are deprotonation constants of these guest molecules (taken from reference [16]). [c] The $\log K_{app}$(ZnL-X) values from reference [16].

$$K_{app}(\mathrm{ZnL\text{-}X}) = [\mathrm{ZnL\text{-}X^-}]/[\mathrm{ZnL}]_{free}[\mathrm{X}]_{free} \quad \text{(at designated pH)}\ (\mathrm{M^{-1}}) \tag{7}$$

$$[\mathrm{ZnL}]_{free} = [\mathrm{ZnL(H_2O)}]_{free} + [\mathrm{ZnL(HO^-)}]_{free} \tag{8}$$

$$[\mathrm{X}]_{free} = [\mathrm{H_nX}]_{free} + [\mathrm{H_{n-1}X}]_{free} + \cdots + [\mathrm{HX}]_{free} + [\mathrm{X^-}]_{free} \tag{9}$$

The photolysis of **9** (1.0 mM) was carried out in the presence of SI (1.5 mM) or captopril (1.5 mM) in D_2O at pD 9, where complexes of **9** and these anions were quantitatively (>98%) based on the results of potentiometric pH titrations (negligible dissociation of **9** was observed in ^{1}H NMR spectra). We found that photolysis of **9** was partially suppressed (29% and 45% inhibition by SI and captopril, respectively, after UV irradiation for 1 h), as evidenced by ^{1}H NMR (data not shown). Therefore, we assumed that Zn^{2+}-bound water plays a somewhat important role in the S–N bond cleavage of **9**.

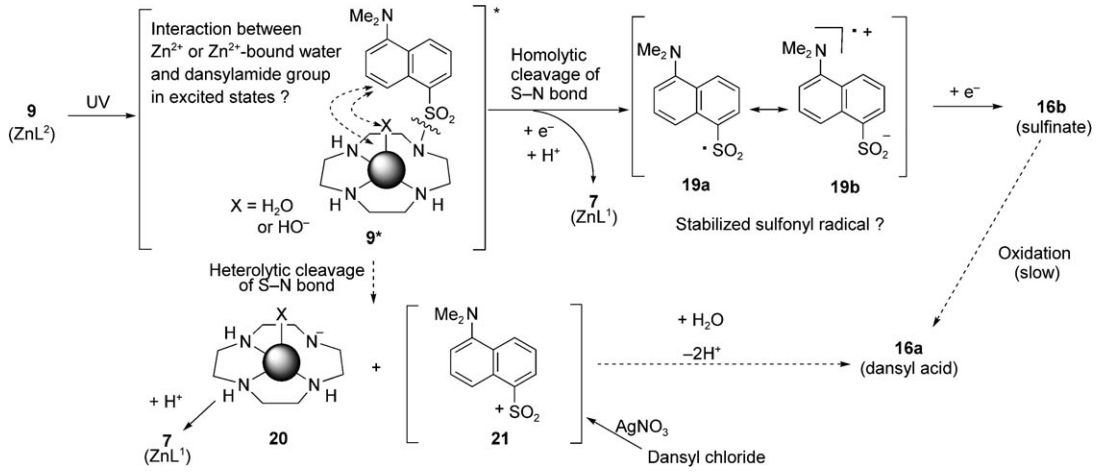
Based on these results, we hypothesized the reaction mechanisms as outlined in Scheme 8. Homolytic cleavage of the S–N bond in the excited states, in which there might be weak interaction between Zn^{2+} or Zn^{2+}-bound water and the dansylamide moiety, occurs to afford **19a**, which might be stabilized by the dimethylamino group (**19a**↔**19b**).[36] The addition of an electron to **19** gives sulfinate **16b**, as confirmed by the aforementioned ^{1}H NMR experiments.

Assuming heterolytic cleavage of the S–N bond in **9** as shown in the lower half of Scheme 8, **20** and **21** would be formed. The sulfonyl cation **21** should immediately react with water to give sulfonate **16a**. Indeed, a sulfonyl cation **21** that was generated from dansyl chloride with $AgNO_3$ in a CD_3CN/D_2O (at pD 7–8) solution was immediately converted into **16a**, as observed by ^{1}H NMR (Scheme 8, bottom). As described above, we observed the presence of the sulfinate species in ^{1}H NMR spectra during the photolysis of **9**. These results strongly support the scenario that the S–N bond of **9** is homolytically cleaved to give **16b** via **19**, resulting in the emission enhancement. We cannot exclude the possibility that Zn^{2+}-bound H_2O or HO^- functions as an electron donor to the photodecomposed Zn^{2+}-cyclen part to give **7** (ZnL^1).

As mentioned above, the initial photoproducts from **11** (ZnL^3) in the absence of an electron donor were **17a** and **7** (ZnL^1), and in the presence of an electron donor such as TEOA[31] were **17b** and **7**. This photolysis was facilitated by benzophenone sensitizing.[37,38] Considering these results together with the aforementioned mechanism proposed by Haas et al., we assume that the photolysis of **11** (and **10**) proceeds mainly via excited triplet states, in which its S–N bond is homolytically cleaved to yield **22**, as shown in Scheme 9. And it is likely that **22** is converted into a sulfonate **17a** in the absence of an electron donor or to a sulfinate **17b** in the presence of an electron donor. These results allowed us to hypothesize that the electron-donating dimethylamino group of **8** (L^2) prevents the sulfonamide cleavage and this effect is suppressed with Zn^{2+}.[36]

Attempts to Determine [Zn^{2+}] in an Aqueous Solution Utilizing Photolysis of 8

We attempted to measure [Zn^{2+}] in given sample solutions utilizing the photolysis of **8** at pH 7.4 (10 mM HEPES with $I=0.1$ ($NaNO_3$)) utilizing the working curve for the **16b**-dependent emission intensity. Aqueous solutions of 10 μM **8** with a given amount (0–10 μM) of Zn^{2+} (at pH 7, HEPES



Scheme 8.

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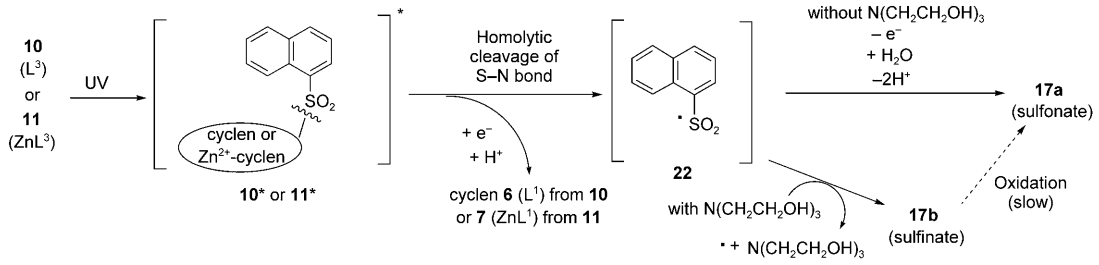


Scheme 9.

with $I=0.1$ ($NaNO_3$)) were irradiated with UV light at 350 nm for 30 min. However, the [Zn^{2+}] determined by this method was not reproducible. In addition, we attempted an indirect method for determining [Zn^{2+}], in which the initial photoproduct **16b** was converted into **16a** by oxidation with H_2O_2 or tBuO$_2$H. However, the emission of **16a** (and/or **16b**) was quenched considerably by these oxidizing agents, hampering the measurement of [Zn^{2+}] concentrations.

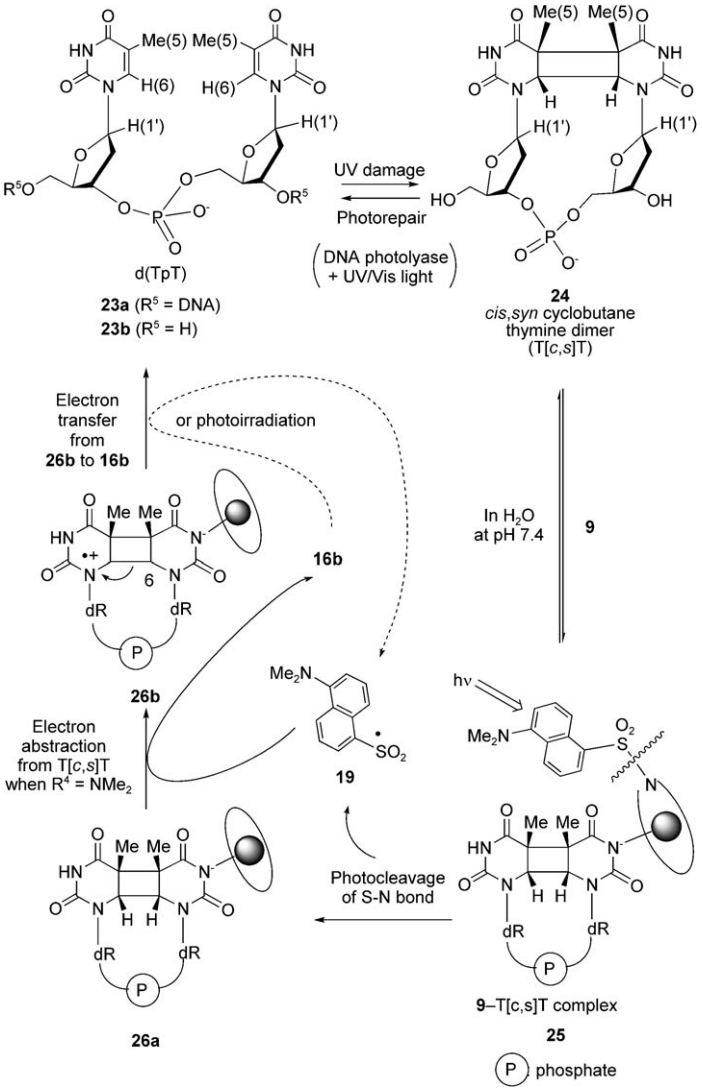
Photorepair of *cis,syn*-Cyclobutane-Type Thymine Photodimer (T[*c,s*]T) by 9 (ZnL^2)

To obtain supporting data concerning the difference in reaction intermediates in the photolysis of **9** and that of **11** described in Schemes 8 and 9, we have examined the photorepair of DNA photolesion in the presence of these Zn^{2+} complexes. The *cis,syn*-cyclobutane thymine photodimer **24** (T[*c,s*]T) is a representative photoproduct in DNA caused by a photo[2+2]cycloaddition reaction of two adjacent thymidine (d(TpT)) sites **23** (Scheme 10).[21] These DNA lesions may result in the misincorporation in DNA and RNA, the inhibition of DNA/RNA polymerases, cell damage, or the development of cancer. In nature, these photolesions are repaired by DNA photolyase with less toxic UV-A light ($\lambda >$ 320 nm).[39] Mechanistic studies of photolyases[39,40] and their model systems[41] have revealed that the reduced form of flavin adenosine dinucleotide (FAD, a sensitizing cofactor) donates one electron to a cyclobutane ring to promote its ring opening.

We previously reported that the photo[2+2]cycloaddition of **23** to **24** was effectively inhibited by dimeric Zn^{2+}-cyclen complexes.[42] In addition, it was discovered that the monomeric Zn^{2+}-cyclen complex accelerates photoreversion of **24** by irradiation with UV light of $\lambda < 300$ nm. A Zn^{2+}-cyclen complex having a tryptophan residue and a flavin unit was recently reported by us as a model compound for DNA photolyase.[43]

On the other hand, oxidative activation reactions, in which an electron is abstracted from T[*c,s*]T, have also been reported by several groups in some model systems,[44] in which the C6–C6' bond in a radical cation of a cyclobutane ring in T[*c,s*]T is weakened, resulting in cycloreversion to yield **23** (radical cation mechanism).

Based on our previous results,[42,43] it is highly likely that monomeric Zn^{2+}-cyclen **9** forms a 1:1 complex **25** with T-



Scheme 10.

[*c,s*]T in aqueous solution at neutral pH (Scheme 10). We then hypothesized that a radical species **19** ($ArSO_2$)$^{\cdot}$ formed by the homolytic photocleavage of the S–N bond of **9** would withdraw an electron from a cyclobutane ring of T[*c,s*]T to generate radical cation species **26b**, which would be repaired to give **23b**.

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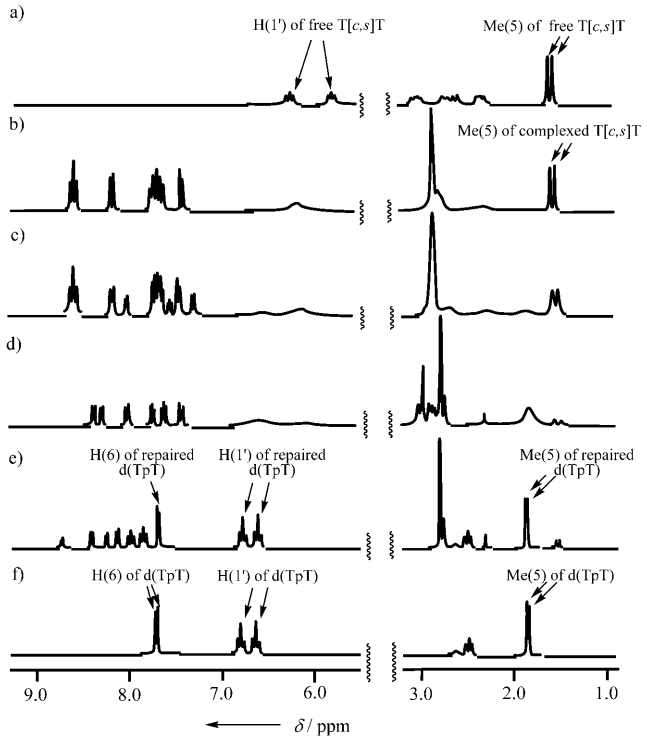

Figure 7. The results of photoreversion of **24** (1 mM) by photolysis of **9** (1 mM, prepared in situ from 1 mM **8**+2 mM Zn^{2+}) in D_2O at pD 7.4 and 25 °C (left: aromatic region, right: aliphatic region). a) 1 mM **24**; b) a mixture of 1 mM **24**+1 mM **9** before UV irradiation; c) a mixture of 1 mM **24**+1 mM **9** after UV irradiation for 1 h; d) after UV irradiation for 3 h; e) a spectrum obtained by addition of DCl to the solution in part (d) to dissociate Zn^{2+} complex; f) 1 mM **23b**.

The result for the photoreversion of **24** (1 mM) in the presence of **9** (1 mM) in D_2O at pD 7.4 followed by ^1H NMR is shown in Figure 7 (left: aromatic region, right: aliphatic region). Figures 7a and 7b are ^1H NMR spectra of 1 mM **24** and a mixture of 1 mM **24** and 1 mM **9**, respectively. Figures 7b and 7c are those of reaction mixtures after photoirradiation at 350 nm for 1 h and 3 h, respectively. The addition of DCl to the solution represented in Figure 7d for the dissociation of complexes gave the spectrum shown in Figure 7e, in which ^1H signals corresponding to the repaired **23b** (d(TpT); Figure 7f) was observed (for assignments, refer to the structure in Scheme 10). It should be noted that a sulfinate **16b** was formed from **9** as well as repaired **23b**. In addition, the negligible decomposition of **23b** was observed by photolysis of **9**.

The photoreversion of **24** with **9** was also followed by reversed-phase high-performance liquid chromatography (HPLC) analysis. As plotted in Figure 8, the photorepair of **24** (1.5 mM) proceeded in the presence of 1.5 mM **9** (closed circles) with photoirradiation at 350 nm. Interestingly, negligible cyclobutane ring opening of 1.5 mM **24** was observed upon photoirradiation in the presence of 1 equivalent of **11** (ZnL^3) in D_2O at pD 7.4±0.1 (closed squares in Figure 8) in the absence and presence of 5 mM TEOA (photoirradiation

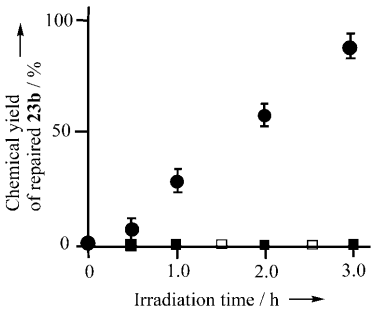

Figure 8. The photorepair reaction of **24** (1.5 mM) in D_2O at pD 7.5±0.2 and 25 °C in the presence of 1.5 mM **9** (closed circles), the reaction of **24** (1 mM) in the presence of 1 mM **11**+5 mM TEOA (closed squares), and the reaction of **24** (1 mM) in the presence of **16b** (1 mM)+ZnL^1 (2 mM; open squares). The photoirradiation wavelength was 350 nm for **9** and 313 nm for **11**.

at 313 nm), while the S–N bond of **11** was completely photocleaved. These facts suggest that the reactivity of the radical intermediates **19** and **22** is different.

In addition, the photoirradiation of **24** (1 mM) in the presence of a catalytic amount of **9** (0.3 mM) induced an almost quantitative photoreverstion of **24**, implying that this radical reaction is a catalytic reaction. Next, the photoirradiation of **24** in the presence of dansyl sulfinate **16b** and Zn^{2+}-cyclen (ZnL^1) scarcely promoted photoreversion of **24** (open squares in Figure 8). We therefore assume that radical species **19** (Schemes 8 and 10) formed by photolysis of **9** (ZnL^2) is a crucial reactive species for the photorepair of **24** and that sulfinate **16b** (or **22**) in Scheme 9 is not.

More interestingly, the photoreaction of **24** (1 mM) with the PbL^2 complex (1 mM) did not promote photoreversion of **24**, suggesting the possibility that Zn^{2+}-bound T[*c,s*]T (**25** or **26** in Scheme 10) is much more reactive, although the details are yet to be examined.

Conclusions

In this work, a Zn^{2+}-*N*-dansylcyclen complex **9** (ZnL^2) and Zn^{2+}-*N*-(1-naphthylsulfonyl)cyclen complex **11** (ZnL^3) were synthesized to examine the photochemical reactivity of a sulfonamide bond, which is closely fixed to Zn^{2+} ions. We accidentally discovered that **9** undergoes photolysis in aqueous solution at neutral pH, while its ligand **8** (L^2) is stable under the same conditions. It was revealed that the initial photoproducts from **9** are the corresponding sulfinate **16b** and Zn^{2+}-cyclen complex **7** (ZnL^1). On the other hand, the S–N bond of **10** (L^3) is photocleaved in the absence and presence of Zn^{2+} to give the corresponding sulfonate **17a** (and **6** or **7**), possibly by homolytic S–N bond cleavage in the excited triplet state. The photolysis of *N*-dansyl-L-glycine and *N*-dansyl-L-proline in the presence of an excess amount of Zn^{2+} was very slow. These data demonstrated the possibility that the Zn^{2+} ion and/or Zn^{2+}-bound water fixed near to the dansylamide group accelerates the homolytic photocleavage of its S–N bond.

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Although it was not possible to quantify the Zn^{2+} concentrations in solution and living cells, we have discovered the photorepair of T[*c,s*]T **24** utilizing the photocleavage of **9**, while the Zn^{2+} complex of *N*-(1-naphthylsulfonyl)cyclen **11** induced photoreversion only to a negligible extent, supporting the view that the mechanisms of photolysis of **9** and **11** are somewhat different. Very interestingly, the photolysis of a catalytic amount of **9** (ZnL^2) induced the nearly complete photoreversion of T[*c,s*]T, implying that radical intermediate **19** functions as a catalyst in the cycloreversion of T[*c,s*]T. These results will promise to open new routes to the design of photoreactions of metal complexes.

Experimental Section

General information: All reagents and solvents were purchased at the highest commercial quality and were used without further purification. $ZnSO_4{\cdot}7H_2O$, $3CdSO_4{\cdot}8H_2O$, $CuSO_4{\cdot}5H_2O$, $FeSO_4{\cdot}7H_2O$, $HgCl_2$, $Mn(CH_3COO)_2{\cdot}4H_2O$ and $AgNO_3$ were purchased from Kanto Chemical Co.; $NiSO_4{\cdot}6H_2O$ was purchased from Yoneyama Yakuhin Kogyo Co.; $Al(NO_3)_3{\cdot}9H_2O$, $CoSO_4{\cdot}7H_2O$, $Pb(NO_3)_2$ were purchased from Sigma-Aldrich Chemical Co. Anhydrous acetonitrile (CH_3CN) was obtained by distillation from calcium hydride. All aqueous solutions were prepared using deionized and distilled water. Buffer solutions (CAPS, pH 12.0, 11.5, 11.0, 10.5, and 10.0; CHES, pH 9.5 and 9.0; TAPS, pH 8.4 and 8.0; HEPES, pH 7.8, 7.6, 7.4, and 7.0; MES, pH 6.5 and 6.0) were used and the ionic strengths were adjusted with $NaNO_3$. The Good's buffer reagents (Dojindo) were commercially available: MOPS (3-(*N*-morpholino)propanesulfonic acid, $pK_a=7.2$), HEPES (*N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid, $pK_a=7.5$), EPPS (3-(4-(2-hydroxyethyl)-1-piperazinyl)propanesulfonic acid, $pK_a=8.0$), TAPS (*N*-(tris(hydroxymethyl)methylamino)-3-propanesulfonic acid, $pK_a=8.4$), CHES (2-(cyclohexylamino)ethanesulfonic acid, $pK_a=9.5$), CAPS (3-(cyclohexylamino)-propanesulfonic acid, $pK_a=10.4$). Melting points were measured on a Büchi 510 Melting Point Apparatus and are uncorrected. UV spectra were recorded on a Hitachi U-3500 spectrophotometer and JASCO UV/VIS spectrophotometer V-550, and fluorescence (excitation and emission) spectra were recorded on a Hitachi F-4500 fluorescence spectrophotometer and JASCO FP-6500 spectrofluorometer at 25 ± 0.1 °C. IR spectra were recorded on a Horiba FTIR-710 spectrophotometer at room temperature. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra at 35 ± 0.1 °C were recorded on a JEOL Lambda 400 spectrometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a JEOL Always 300 spectrometer. The chemical shifts (δ values) in D_2O were determined by use of external reference of [2-D_2,3-D_2]3-(trimethylsilyl)propionic acid (TSP) sodium salt (0 ppm for ^1H NMR) and 1,4-dioxane (67.2 ppm for ^{13}C NMR). The pD values in D_2O were corrected for a deuterium isotope effect using pD = (pH-meter reading)+0.40. Elemental analyses were performed on a Perkin–Elmer CHN 2400 analyzer. Thin-layer chromatography (TLC) and silica gel column chromatography were performed using a Merck 5554 (silica gel) TLC plate and Fuji Silysia Chemical FL-100D, respectively.

Crystallographic study of $\mathbf{9}{\cdot}Cl_2{\cdot}(H_2O)_3$ ($ZnL^2{\cdot}Cl_2{\cdot}(H_2O)_3$): $C_{20}H_{37}Cl_2N_5O_5SZn$, $M_r=585.89$, yellow needle, crystal size 0.10 mm × 0.08 mm × 0.02 mm, monoclinic, space group $P2_1/c$ (No. 14), $a=22.773(5)$ Å, $b=6.919(1)$ Å, $c=16.601(4)$ Å, $\beta=97.124(9)°$, $V=2595.7(9)$ Å^3, $Z=4$, $\rho_{calcd}=1.525$ g cm^{-3}, 31390 measured reflections, 7558 unique reflections ($R_{int}=0.035$), $2\theta_{max}=60.1°$, $R1=0.026$ ($I>2.00\sigma(I)$), $R=0.038$ ($I>-3.00\sigma(I)$), $wR2=0.059$ ($I/>-3.00\sigma(I)$). CCDC 708937 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

UV spectrophotometric and fluorescence titrations: UV spectra and fluorescence emission spectra were recorded on a Hitachi U-3500 spectrophotometer and JASCO fluorescence spectrophotometer, respectively, at 25.0 ± 0.1 °C. For fluorescence titrations, a sample solution in a 1.0 cm quartz cuvette was excited at the isosbestic point determined by UV titration. The obtained data for the UV titrations (changes in ε values at a given wavelength) and fluorescence titrations (increases in fluorescence emission intensity at a given wavelength) were analyzed for apparent complexation constants, K_{app}, using the Bind Works program (Calorimetry Sciences Corp). Quantum yields were determined by comparison of the integrated corrected emission spectrum of standard quinine sulfate, whose quantum yield (Φ) in 0.1 M H_2SO_4 was assumed to be 0.55 (excitation at 366 nm).[45]

Potentiometric pH titrations: The preparation of test solutions and the method of calibrating the electrode system (Potentiometric Automatic Titrator AT-400 and Auto Piston Buret APB-410, Kyoto Electronics Manufacturing (KEM), Co. Ltd. with KEM glass Electrode C-117) have been described earlier.[15–18,22,32,33] All the test solutions (50 mL) were kept under an argon (>99.999% purity) atmosphere. The potentiometric pH titrations were performed with $I=0.10$ ($NaNO_3$) at 25.0 ± 0.1 °C, and at least two independent titrations were performed (0.1 M aq. NaOH was used as a base). Deprotonation constants of Zn^{2+}-bound water K'_2 (= [HO^--bound species][H^+]/[H_2O-bound species]) were determined by means of the BEST program.[23] All the sigma fit values defined in the program were smaller than 0.1. The K_W ($=a_{H+}{\cdot}a_{OH-}$), K'_W ($=[H^+][OH^-]$) and f_{H+} values used at 25 °C are $10^{-14.00}$, $10^{-13.79}$, and 0.825. The corresponding mixed constants, K_2 ($=[HO^-$-bound species]a_{H+}/[H_2O-bound species]), were derived using $[H^+]=a_{H+}/f_{H+}$. The species distribution values (%) against pH ($=-\log[H^+]+0.084$) were obtained using the SPE program.[23]

Photoreaction of **8**–**11**): In a typical experiment, an aqueous solution (or a D_2O solution when photoreactions were followed by ^1H NMR) of substrate in a quartz cuvette with a soft rubber septum was purged with argon gas for at least 10 min. Photoirradiation of the cuvettes was performed at a given wavelength using a JASCO FP-6500 spectrofluorometer equipped with a 150 W xenon lamp with a band pass of 20 nm and a magnetic stirrer. The photolysis of **9** and **11** was followed by ^1H NMR, UV, fluorescent spectral measurements.

Photoreaction of T[*c,s*]T (**24**): The preparation of **24** was carried out according to the method of Murata et al.[46] In a typical experiment, an aqueous solution (or a D_2O solution when photoreactions were followed by ^1H NMR) of **24** in a quartz cuvette with a soft rubber septum was purged with argon gas for at least 10 min.[43] The photoirradiation of the cuvettes was performed at a given wavelength using a JASCO FP-6500 spectrofluorometer described in the text. The photoreversion of **23b** was followed by ^1H NMR and analyzed by reversed-phase HPLC as we previously reported.[43]

Acknowledgements

We are grateful to Prof. Atsushi Nishida of Faculty of the Pharmaceutical Sciences, Chiba University for helpful discussions. This work was supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (no. 18390009 and 19659026) and High-Tech Research Center Project for Private Universities (matching fund subsidy from MEXT). S.A. is grateful to grants from the Mitsubishi Chemical Corporation Fund (Tokyo), the Terumo Life Science Foundation (Kanagawa), the Mochida Memorial Foundation for Medical and Pharmaceutical Research (Tokyo), the Novartis Foundation (Tokyo, Japan), the Naito Foundation (Tokyo), and the Tokuyama Science Foundation (Tokyo).

[1] a) G. H. Whitham, *Organosulfur Chemistry*, Zeneca, Oxford, **1995**; b) W. M. Horspool in *The Chemistry of Sulphonic Acids, Esters and Their Derivatives* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1991**.

[2] a) R. Vardanyan, V. Hruby, *Synthesis of Essential Drugs*, Elsevier, Amsterdam, **2006**; b) J.-Y. Winum, J.-M. Dogné, An. Casini, X.

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deLeval, J.-L. Montero, A. Scozzafava, D. Vullo, A. Innocenti, C. T. Supuran, *J. Med. Chem.* **2005**, *48*, 2121–2125; c) A. Scozzafava, T. Owa, A. Mastrolorenzo, C. T. Supuran, *Curr. Med. Chem.* **2003**, *10*, 925–953; d) J. Drews, *Science* **2000**, *287*, 1960–1964; e) D. Leung, G. Abbenante, D. P. Fairlie, *J. Med. Chem.* **2000**, *43*, 305–341; f) M. Whittaker, C. D. Floyd, P. Brown, A. J. H. Gearing, *Chem. Rev.* **1999**, *99*, 2735–2776.

[3] a) V. N. Rajasekharan Pillali, *Org. Photochem.* **1987**, *9*, 225–323; b) P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis* 4th ed., Wiley, Hoboken, NJ, **2007**; c) T. Nishimura, K. Yamada, T. Takebe, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2008**, *10*, 2601–2604; d) T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353–359.

[4] a) K. Maruoka, *Org. Process Res. Dev.* **2008**, *12*, 679–6; b) T. Kano, Y. Hato, A. Yamamoto, K. Maruoka, *Tetrahedron* **2008**, *64*, 1197–1203; c) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079.

[5] H. G. Richey, Jr., J. Farkas, Jr., *J. Org. Chem.* **1987**, *52*, 479–483.

[6] a) L. D′Souza, R. A. Day, *Science* **1968**, *160*, 882–883; b) L. D′Souza, K. Bhatt, M. Madaiah, R. A. Day, *Arch. Biochem. Biophys.* **1970**, *141*, 690–693.

[7] B. Weiss, H. Dürr H. J. Haas, *Angew. Chem.* **1980**, *92*, 647–649; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 648–650.

[8] For the photo-Fries-type rearrangement reaction, see: a) H. Nozaki, T. Okada, R. Noyori, M. Kawanisi, *Tetrahedron* **1966**, *22*, 2177–2180; b) R. Nasielski-Hinkens, J. Maeck, M. Tenvoorde, *Tetrahedron* **1972**, *28*, 5025–5028; c) M. Z. A. Badr, M. M. Aly, A. M. Fahmy, *J. Org. Chem.* **1981**, *46*, 4784–4787.

[9] a) B. Umezawa, O. Hoshino, S. Sawaki, *Chem. Pharm. Bull.* **1969**, *17*, 1115–1119; b) B. Umezawa, O. Hoshino, S. Sawaki, *Chem. Pharm. Bull.* **1969**, *17*, 1120–1122.

[10] a) T. Hamada, A. Nishida, Y. Matsumoto, O. Yonemitsu, *J. Am. Chem. Soc.* **1980**, *102*, 3978–3980; b) T. Hamada, A. Nishida, O. Yonemitsu, *J. Am. Chem. Soc.* **1986**, *108*, 140–145.

[11] a) G. Papageorgiou, J. E. T. Corrie, *Tetrahedron* **1999**, *53*, 237–254; b) J. E. T. Corrie, G. Papageorgiou, *J. Chem. Soc. Perkin Trans. 1* **1996**, 1583–1592; c) J. A. Pincock, D. A. Jurgens, *Tetrahedron Lett.* **1979**, 1029–1030; d) M. Z. A. Badr, M. M. Aly, A. M. Fahmy, *J. Org. Chem.* **1981**, *46*, 4784–4787.

[12] For electrochemical cleavage of sulfonamides: a) R. Kossai, B. Emir, J. Simonet, G. Mousset, *J. Electroanal. Chem.* **1989**, *270*, 253–260; b) A. Lebouc, P. Martigny; R. Carlier, J. Simonet, *Tetrahedron* **1985**, *41*, 1251–1258; R. Carlier, J. Simonet, *Tetrahedron* **1985**, *41*, 1251–1258.

[13] a) E. Kimura, T. Koike, M. Shionoya in *Structure and Bonding: Metal Site in Proteins and Models*, *Vol. 89* (Eds.: J. P. Sadler), Springer, Berlin, **1997**, pp. 1–28; b) E. Kimura, T. Koike in *Comprehensive Supramolecular Chemistry*, *Vol. 10* (Ed.: D. N. Reinhoudt), Pergamon, Tokyo, **1996**, pp. 429–444; c) E. Kimura, T. Koike, *J. Chem. Soc. Chem. Commun.* **1998**, 1495–1500; d) E. Kimura, T. Koike in *Bioinorganic Catalysis* (Eds.: J. Reedijk, E. Bouwman), Marcel Dekkar, Inc, **1999**, pp. 33–54; e) S. Aoki, E. Kimura in *Comprehensive Coordination Chemistry II*, *Vol. 8.* (Eds.: L. Que, Jr., W. B. Tolman), Elsevier Ltd., **2004**, pp. 601–640.

[14] A. E. Martell, R. D. Hancock, *Metal Complexes in Aqueous Solutions*, Plenum, New York, **1996**.

[15] a) T. Koike, T. Watanabe, S. Aoki, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1996**, *118*, 12696–12703; b) E. Kimura, S. Aoki, E. Kikuta, T. Koike, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3731–3736; c) E. Kimura, R. Takasawa, S. Tanuma, S. Aoki, *Science STKE* **2004**, p. 7.

[16] S. Aoki, D. Kagata, M. Shiro, K. Takeda, E. Kimura, *J. Am. Chem. Soc.* **2004**, *126*, 13377–13390.

[17] S. Aoki, S. Kaido, H. Fujioka, E. Kimura, *Inorg. Chem.* **2003**, *42*, 1023–1030.

[18] a) S. Aoki, K. Sakurama, N. Matsuo, Y. Yamada, R. Takasawa, S. Tanuma, M. Shiro, K. Takeda, E. Kimura, *Chem. Eur. J.* **2006**, *12*, 9066–9080; b) S. Aoki, K. Sakurama, R. Ohshima, Y. Yamada, R. Takasawa, S. Tanuma, K. Takeda, E. Kimura, *Inorg. Chem.* **2008**, *47*, 2747–2754.

[19] For review of Zn^{2+} fluorophores: a) L. Prodi, F. Bolletta, M. Montalti, N. Zaccheroni, *Coord. Chem. Rev.* **2000**, *205*, 59–83; b) K. Kikuchi, K. Komatsu, T. Nagano, *Curr. Opin. Chem. Biol.* **2004**, *8*, 182–191; c) E. Kimura, *S. Afr. J. Chem.* **1997**, *50*, 240–248; d) E. Kimura, T. Koike, *Chem. Soc. Rev.* **1998**, *27*, 179–184; e) E. Kimura, S. Aoki, *BioMetals* **2001**, 14, 191–204.

[20] The same compound was synthesized by Wiest et al., independently. They have reported that **9** works as a probe of base flipping in DNA. However, they have not described the photoreaction of **9** itself; see: L. L. O'Neil, O. Wiest, *J. Am. Chem. Soc.* **2005**, *127*, 16800–16801.

[21] a) E. Friedberg, G. C. Walker, W. Siede, *DNA Repair and Mutagenesis*, American Society of Microbiology, Washington, **1995**; b) J. A. Nickoloff, M. F. Hoekstra, *DNA Damage and Repair*, *Vol. 1*, Humana, Totowa, **1998**; c) O. D. Schärer, *Angew. Chem.* **2003**, *115*, 3052–3082; *Angew. Chem. Int. Ed.* **2003**, *42*, 2946–2974; d) S. S. David, S. D. Williams, *Chem. Rev.* **1998**, *98*, 1221–1261; e) R. Beukers, A. P. M. Eker, P. H. M. Lohman, *DNA Repair* **2008**, *7*, 530–543.

[22] E. Kimura, S. Aoki, T. Koike, M. Shiro, *J. Am. Chem. Soc.* **1997**, *119*, 3068–3076.

[23] A. E. Martell, R. J. Motekaitis, *Determination and Use of Stability Constants*, *2nd ed.*, VCH, Weinheim, **1992**.

[24] a) E. Kimura, T. Shiota, T. Koike, M. Shiro, M. Kodama, *J. Am. Chem. Soc.* **1990**, *112*, 5805–5811; b) T. Koike, E. Kimura, I. Nakamura, Y. Hashimoto, M. Shiro, *J. Am. Chem. Soc.* **1992**, *114*, 7338–7345; c) X. Zhang, R. van Eldik, T. Koike, E. Kimura, *Inorg. Chem.* **1993**, *32*, 5749–5755.

[25] T. Koike, T. Gotoh, S. Aoki, E. Kimura, M. Shiro, *Inorg. Chim. Acta* **1998**, *270*, 424–432.

[26] S. Aoki, H. Kawatani, T. Goto, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 1123–1132.

[27] It should be noted that emission of metal-free **8** (L^2) and **10** (L^3) was quenched as their concentrations increased.

[28] a) J. F. Hartwig, P. M. Pil, S. J. Lippard, *J. Am. Chem. Soc.* **1992**, *114*, 8292–8293; b) F. E. Scully, J. P. Yang, K. Mazina, F. B. Daniel, *Environ. Sci. Technol.* **1984**, *18*, 787–792.

[29] M. P. Balfe, W. G. Wright, *J. Chem. Soc.* **1938**, 1490–1491.

[30] The ^{1}H NMR spectra obtained after photoreaction of **9** at pD 7.4 for 2 h (Figure S7b in the Supporting Information) showed a good agreement with the ^{1}H signals of **7** (Figure S7c). Upon addition of DCl to Figure S7b to decompose Zn^{2+} complexes, Figure S7d was obtained, in which a sharp singlet indicated by an open arrow corresponded to ^{1}H NMR signals of the cyclen·DCl salt (Figure S7e).

[31] D. R. Lide, *CRC Handbook of Chemistry & Physics*, *82nd ed.*, CRC Press/Taylor and Francis, Boca Raton, FL, **2007**.

[32] a) S. Aoki, E. Kimura, *Rev. Mol. Biotechnol.* **2002**, *90*, 129–155; b) S. Aoki, M. Shiro, T. Koike, E. Kimura, *J. Am. Chem. Soc.* **2000**, *122*, 576–584; c) S. Aoki, K. Iwaida, N. Hanamoto, M. Shiro, E. Kimura, *J. Am. Chem. Soc.* **2002**, *124*, 5256–5257; d) S. Aoki, A. Jikiba, K. Takeda, E. Kimura, *J. Phys. Org. Chem.* **2004**, *17*, 489–497; e) S. Aoki, M. Zulkefeli, M. Kohsako, M. Shiro, K. Takeda, E. Kimura, *J. Am. Chem. Soc.* **2005**, *127*, 9129–9139.

[33] a) M. Shionoya, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1993**, *115*, 6730–6737; b) M. Shionoya, T. Ikeda, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1994**, *116*, 3848–3859; c) E. Kimura, T. Ikeda, S. Aoki, M. Shionoya, *J. Biol. Inorg. Chem.* **1998**, *3*, 259–267; d) S. Aoki, Y. Honda, E. Kimura, *J. Am. Chem. Soc.* **1998**, *120*, 10018–10026; e) E. Kikuta, M. Murata, N. Katsube, T. Koike, E. Kimura, *J. Am. Chem. Soc.* **1999**, *121*, 5426–5436; f) S. Aoki, M. Shiro, T. Koike, E. Kimura, *J. Am. Chem. Soc.* **2000**, *122*, 576–584; g) E. Kikuta, S. Aoki, E. Kimura, *J. Am. Chem. Soc.* **2001**, *123*, 7911–7912; h) E. Kikuta, S. Aoki, E. Kimura, *J. Biol. Inorg. Chem.* **2002**, *7*, 473–482; i) E. Kimura, N. Katsube, T. Koike, M. Shiro, S. Aoki, *Supramol. Chem.* **2002**, *14*, 2002.

[34] For reviews: a) E. Kimura, E. Kikuta, *Prog. React. Kinet. Mech.* **2000**, *25*, 1–64; b) E. Kimura, E. Kikuta, *J. Biol. Inorg. Chem.* **2000**, *5*, 139–155; c) S. Aoki, E. Kimura, *Chem. Rev.* **2004**, *104*, 769–787.

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[35] a) S. Aoki, M. Shiro, E. Kimura, *Chem. Eur. J.* **2002**, *8*, 929–939; b) S. Aoki, M. Zulkefeli, M. Shiro, E. Kimura, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 4894–4899.

[36] We carried out the DFT calculation (UB3LYP/6-31+Gd) of **19** and **22**, which were speculated as initial products in the photolysis of **9** and **11**. As shown in Figure S12 in the Supporting Information, the SOMO of **19** (Figure S12a) around SO_2 is smaller than that of **22** (Figure S12b). These data may suggest the different chemical reactivity of **19** and **22**.

[37] N. J. Turro, *Modern Molecular Photochemistry*; University Science Books, Sausalito, CA, **1991**.

[38] A reaction mixture of 1.0 mM **11** and 5.0 mM benzophenone (BZ) in a 90:10 mixture of 10 mM HEPES (pH 7.4 with $I=0.1$ ($NaNO_3$)) and MeCN was irradiated at 360 nm, which is absorbed by only BZ. Under these conditions, **11** underwent ca. 65% photolysis after UV irradiation for 1 h, while negligible photolysis was observed without BZ.

[39] a) S. Weber, *Biochim. Biophys. Acta Bioenerg.* **2005**, *1707*, 1–23; b) C. B. Harrison, L. L. O'Neil, O. Wiest, *J. Phys. Chem. A* **2005**, *109*, 7001–7012; c) A. Sancar, *Adv. Protein Chem.* **2004**, *69*, 73–100; d) A. Sancar, *Chem. Rev.* **2003**, *103*, 2203–2237; e) T. Carrell, L. T. Burgdorf, L. M. Kundu, M. Cichon, *Curr. Opin. Chem. Biol.* **2001**, *5*, 491–498; f) J. Deisenhofer, *Mutat. Res.* **2000**, *460*, 143–149; g) T. Carell, R. Epple, *Eur. J. Org. Chem.* **1998**, 1245–1258; h) P. F. Heelis, R. F. Hartman, S. D. Rose, *Chem. Soc. Rev.* **1995**, *24*, 289–297; i) J.-S. Taylor, *Pure Appl. Chem.* **1995**, *67*, 183–190.

[40] a) H.-W. Park, S.-T. Kim, A. Sancar, J. Deisenhofer, *Science* **1995**, *268*, 1866–1872; b) T. Tamada, K. Kitadokoro, Y. Higuchi, K. Inaka, A. Yasui, P. E. de Ruiter, A. P. M. Eker, K. Miki, *Nat. Struct. Biol.* **1997**, *4*, 887–891; c) H. Komori, R. Masui, S. Kuramitsu, S. Yokoyama, T. Shibata, Y. Inoue, K. Miki, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 13560–16565; d) A. Mees, T. Klar, P. Gnau, U. Hennecke, A. P. M. Eker, T. Carell, L.-O. Essen, *Science* **2004**, *306*, 1789–1793.

[41] a) T. Carell, *Angew. Chem.* **1995**, *107*, 2697–2700; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2491–2494; b) A. A. Voityuk, M.-E. Michel-Beyerle, N. Rösch, *J. Am. Chem. Soc.* **1996**, *118*, 9750–9758; c) R. Epple, E.-U. Wallenborn, T. Carell, *J. Am. Chem. Soc.* **1997**, *119*, 7440–7451; d) C. Haas, K. Kräling, M. Cichon, N. Rahe, T. Carell, *Angew. Chem.* **2004**, *116*, 1878–1880; *Angew. Chem. Int. Ed.* **2004**, *43*, 1842–1844; e) F. Boussicault, M. Robert, *Chem. Rev.* **2008**, *108*, 2622–2645.

[42] S. Aoki, C. Sugimura, E. Kimura, *J. Am. Chem. Soc.* **1998**, *120*, 10094–10102.

[43] Y. Yamada, S. Aoki, *J. Biol. Inorg. Chem.* **2006**, *11*, 1007–1023.

[44] a) M. Pauvert, P. Laine, M. Jonas, O. Wiest, *J. Org. Chem.* **2004**, *69*, 543–548; b) P. J. Dandliker, R. E. Holmlin, J. K. Barton, *Science* **1997**, *275*, 1465–1468; c) M. Aida, M. Kaneko, M. Dupuis, *Int. J. Quantum Chem.* **1996**, *57*, 949–957; d) M. S. Goodman, S. D. Rose, *J. Org. Chem.* **1992**, *57*, 3268–3270; e) R. F. Hartman, S. D. Rose, *J. Org. Chem.* **1992**, *57*, 2302–2306; f) M. S. Jorns, *J. Am. Chem. Soc.* **1987**, *109*, 3133–3136; g) J. R. Van Camp, T. Young, R. F. Hartman, S. D. Rose, *Photochem. Photobiol.* **1987**, *45*, 365–370; h) S. E. Rokita, C. T. Walsh, *J. Am. Chem. Soc.* **1984**, *106*, 4589–4595.

[45] S. L. Murov, I. Carmichael, G. L. Hug, *Handbook of Photochemistry*, *2nd ed.*, VCH, Weinheim, **1992**.

[46] T. Murata, S. Iwai, E. Ohtsuka, *Nucleic Acids Res.* **1990**, *18*, 7279–7286.

Received: November 13, 2008
Published online: January 22, 2009

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