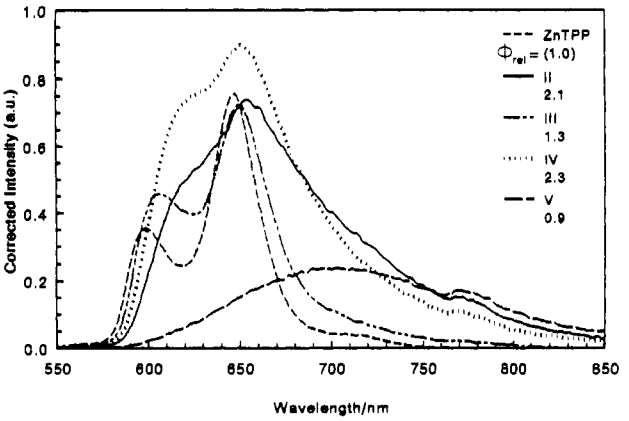


**Figure 2.** Emission spectra of ZnTPP, II, III, IV, and V in deaerated benzene for excitation at 400 nm. Spectra are scaled for excitation conditions and are corrected for emission wavelength[4] but not for instrument response; thus, the estimated quantum yields (relative to ZnTPP) indicated in the figure are somewhat low, especially for II and V. Major emission lifetimes (and relative amplitudes) are as follows: ZnTPP, 1.92 ns (>97%); II, 2.15 ns (>96%); III, 2.11 ns (>98%); IV, 2.31 ns (>97%); V, 1.42 ns (>97%). Picosecond laser excitation at 590 nm, emission at 650 nm.

reference porphyrin (ZnTPP) in the same solvents (Figure 2).

For further comparison of the emission spectra with the $\Delta G°$ of the CT state, we also synthesized a molecule analogous to IV in which, instead of an electron-donating methyl group, the distal aromatic ring of AQ carries an electron-withdrawing chloro group (i.e., V). The redox potential of the quinone in V is about 50 meV more positive than in II.[2] The spectrum of V differs markedly from the other spectra, displaying only a single, broad band with a maximum at ~670 nm, which is presumably due entirely to CT emission. However, none of the other spectra can be decomposed into simple CT and locally excited singlet (LES) components.

The emission-decay profiles can be interpreted in terms of a three-state model, in which a distribution of P–AQ dihedral angles gives rise to a distribution of short lifetimes that, in each case, relax to a single, longer lifetime (see caption below Figure 2). It seems likely that there are also distributions of spectral components (CT as well as LES), which would explain the complexity of the emission spectra. The dynamical behavior and, in particular, the temperature dependence of the lifetimes and spectra of these molecules are currently under investigation.

Despite the close proximity between the donor and acceptor groups, the fluorescence data for these molecules in a total of more than 50 solvents and binary mixtures are qualitatively consistent with the estimated solvent-dependent reaction energetics based on a two-sphere dielectric continuum model.[7] Specifically, the emission of each molecule becomes broader, more red-shifted, less intense, and shorter-lived as the solvent polarity is increased. Details of the solvent dependence will be discussed in a forthcoming publication.[8] In general, the spectroscopic properties of these molecules as functions of solvent and of the substituent on the AQ moiety are consistent with a recent theoretical treatment of CT emission in the Marcus inverted region.[9]

Because of their sensitivity to solvent polarity, these molecules should be useful as probes of local dielectric environments in media such as vesicles, microemulsions, and polymers. In addition, the existence of CT states in these dyad molecules suggests that multicomponent systems based on this simple architecture could be designed to maximize the fraction of excited-state energy that can ultimately be converted to stored redox energy. Thus, the CT state could be "tuned" to the dielectric constant and serve as a precursor to formation of a longer-lived, solvent-relaxed radical ion pair. Work along these lines is currently in progress.

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(7) Weller, A. *Z. Phys. Chem. (Neue Folge)* **1982**, *133*, 93-98.
(8) Kamioka, K.; Lutton, T. W.; Cormier, R. A.; Connolly, J. S. To be submitted.
(9) Marcus, R. A. *J. Phys. Chem.* **1989**, *93*, 3078-3086.

## Reactions of Magnesium Complexes of 1,2-Bis(methylene)cycloalkanes with Carboxylic Esters: The Formation of a Versatile Intermediate Capable of Generating Fused Rings or $\beta,\gamma$-Unsaturated Ketones

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Nontraditional organomagnesium compounds prepared from activated magnesium and 1,3-dienes constitute a relatively new branch of organomagnesium chemistry.[1] These unsaturated magnesium reagents contain two formal Mg–C bonds in one organic species and therefore can serve as bis-nucleophiles.[2,3] Recently, we have extended this chemistry to exocyclic conjugated dienes by using highly reactive magnesium,[4] providing a one-step method to spiro carbocycles.[5] In this paper, we report a facile method to synthesize fused carbocyclic enols by the reactions of 1,2-bis(methylene)cycloalkane–Mg reagents with carboxylic esters. Interestingly, these reactions can also be used to prepare $\beta,\gamma$-unsaturated ketones simply by controlling the reaction temperature.

In our earlier investigations, we found that treatment of the magnesium complex (**2a**) of 1,2-bis(methylene)cyclohexane (**1a**) with ethyl acetate at low temperature (−78 to −10 °C) and quenching of the reaction at −10 °C resulted in the formation of (2-methyl-1-cyclohexenyl)propan-2-one in 72% isolated yield. On the other hand, warming of the mixture to reflux followed by workup afforded a fused bicyclic enol, 2,3,4,5,6,7-hexahydro-2-methyl-1*H*-inden-2-ol, in excellent yield. These results initially led us to suspect that the adduct formed at low temperature was simply derived from the first attack by ethyl acetate at the 1-position of **2a**, producing an allylic Grignard reagent containing a carbonyl group. However, this suspicion was quickly ruled out by trapping of the intermediate with acetyl chloride. A detailed rationalization for the reaction of **2a** with ethyl acetate is given in Scheme I. It was found that treatment of **2a** with ethyl acetate at low temperature resulted in the formation of a magnesium salt

(1) For a recent review, see: Dzhemilev, U. M.; Ibragimov, A. G.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *406*, 1. For typical examples, see: (a) Ramsden, H. E. U.S. 3,388,179, 1968; *Chem. Abstr.* **1968**, *69*, 67563d. (b) Fujita, K.; Ohnuma, Y.; Yasuda, H.; Tani, H. *J. Organomet. Chem.* **1976**, *113*, 201. (c) Yang, M.; Yamamoto, K.; Otake, N.; Ando, M.; Takase, K. *Tetrahedron Lett.* **1970**, 3843. (d) Kai, Y.; Kanehisa, N.; Miki, K.; Kasai, N.; Mashima, K.; Yasuda, H.; Nakamura, A. *Chem. Lett.* **1982**, 1277. (e) Baker, R.; Cookson, R. C.; Saunders, A. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1815. (f) Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1976**, *98*, 7420.
(2) (a) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247. (b) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109.
(3) (a) Herberich, G. E.; Boveleth, W.; Hessner, B.; Hostalek, M.; Koeffer, D. P. J.; Ohst, H.; Soehnen, D. *Chem. Ber.* **1986**, *119*, 420. (b) Richter, W. J. *Chem. Ber.* **1983**, *116*, 3293. (c) Salomon, R. G. *J. Org. Chem.* **1974**, *39*, 3602. (d) Richter, W. J. *J. Organomet. Chem.* **1985**, *289*, 45.
(4) (a) Rieke, R. D.; Burns, T. P.; Wehmeyer, R. M.; Kahn, B. E. *High Energy Processes in Organometallic Chemistry*; Suslick, K. S., Ed.; American Chemical Society: Washington, DC, 1987; pp 223-245. (b) Rieke, R. D. *Science* **1989**, *246*, 1260.
(5) Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 5269.

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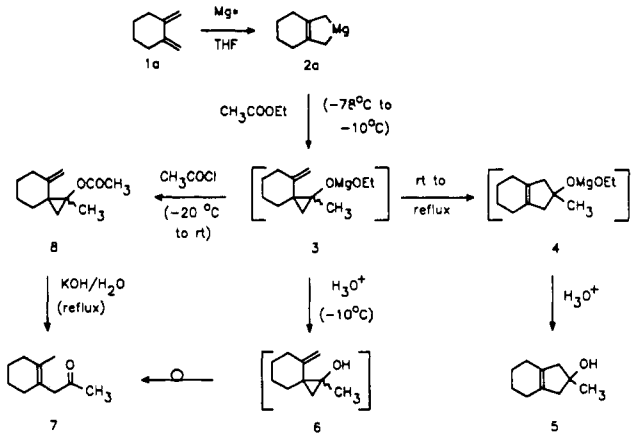
**Scheme I**



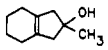
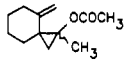
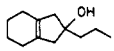
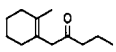
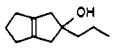
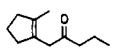
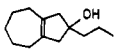
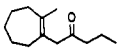
of a spiro enol containing a cyclopropane ring (**3**). This intermediate underwent ring expansion upon warming, giving the fused carbocyclic product (**5**). Alternatively, protonation of **3** at −10 °C yielded the corresponding spiro enol (**6**), which then rearranged in situ to the β,γ-unsaturated ketone (**7**). Addition of acetyl chloride to **3** at −20 °C and workup afforded 1-methyl-4-methylenespiro[2.5]oct-1-yl acetate (**8**) in a mixture of two stereoisomers (cis/trans = 90:10), establishing the identity of the initial adduct. Significantly, a basic hydrolysis of **8** also gave the enone (**7**), confirming again that the β,γ-unsaturated ketone (**7**) was formed from the rearrangement of the spiro enol (**6**).

It is important to point out that the ring enlargement from **3** to **4** involves a vinylcyclopropane–cyclopentene ring expansion, which has been observed for the lithium salts of 2-vinylcyclopropanol systems.[6] On the other hand, the rearrangement of **6** to **7** is formally a 2-vinylcyclopropanol ring opening. To our knowledge, this is the first report of such a rearrangement, although 1-vinylcyclopropanol–cyclobutanone rearrangements have been well documented.[7] The exact mechanistic aspects of the 2-vinylcyclopropanol ring opening are under investigation. The lack of five-membered-ring formation at low temperature suggests that the initial attack by ethyl acetate must have taken place at the 2-position of **2a**, and the subsequent intramolecular cyclization yielded the spiro intermediate (**3**).[8]

Table I contains some representative results for the reactions of **2a** with other carboxylic esters. This approach appears to be very general. Significantly, the method outlined in Scheme I can also be applied to the magnesium complexes of 1,2-bis(methylene)cyclopentane (**1b**) (Table I, entries 8 and 9) and 1,2-bis(methylene)cycloheptane (**1c**) (Table I, entries 10 and 11), making this a very general approach to fused carbocyclic enols or β,γ-unsaturated ketones. Several points here deserve comment. Firstly, it is necessary to keep the reaction temperature at or below −10 °C in order to obtain the enone product. On the other hand, the formation of the fused carbocycle was not completed without warming of the reaction mixture to reflux. Secondly, the reactions leading to β,γ-unsaturated ketones were found to be completely regioselective since no double-bond scrambling was observed. This feature should provide a new entry to the regioselective synthesis of β,γ-unsaturated ketones from 1,3-dienes.[9] Finally, the overall process from 1,2-bis(methylene)cycloalkanes to the corresponding fused carbocyclic enols represents a formal [4 + 1] annulation, which offers an easy access to the polyhydroindene, polyhydropentalene, and polyhydroazulene bicyclic systems.[10]

In summary, it has been demonstrated that fused bicyclic systems containing a substituted five-membered ring can be conveniently prepared by the reactions of the magnesium complexes of 1,2-bis(methylene)cycloalkanes with carboxylic esters. This reaction proceeds via a magnesium salt of a spiro enol

**Table I.** Reactions of Magnesium Complexes of 1,2-Bis(methylene)cycloalkanes with Carboxylic Esters

| Entry | Diene[a] | Ester | | Product[b] | % Yield[c] | Note[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | $CH_3COOEt$ | **5** |  | 91 | A |
| 2 | **1a** | $CH_3COOEt$ | **7** |  | 72 | B |
| 3 | **1a** | (1) $CH_3COOEt$<br>(2) $CH_3COCl$ | **8** |  <br>(cis/trans=90:10) | 75 | C |
| 4 | **1a** | $CH_3(CH_2)_2COOEt$ | **9** |  | 96 | A |
| 5 | **1a** | $CH_3(CH_2)_2COOEt$ | **10** |  | 81 | B |
| 6 | **1a** | PhCOOEt | **11** |  | 55 | A |
| 7 | **1a** | PhCOOEt | **12** |  | 62 | B |
| 8 | **1b** | $CH_3(CH_2)_2COOEt$ | **13** |  | 59 | A |
| 9 | **1b** | $CH_3(CH_2)_2COOEt$ | **14** |  | 76 | B |
| 10 | **1c** | $CH_3(CH_2)_2COOEt$ | **15** |  | 74 | A |
| 11 | **1c** | $CH_3(CH_2)_2COOEt$ | **16** |  | 84 | B |

[a] **1a**: 1,2-Bis(methylene)cyclohexane. **1b**: 1,2-Bis(methylene)cyclopentane. **1c**: 1,2-Bis(methylene)cycloheptane. [b] All new compounds have been fully characterized by $^1H$ NMR, $^{13}C$ NMR, FTIR, and mass spectra. [c] Isolated yields. [d] Ester was added to the magnesium–diene complex at −78 °C. After being stirred at −78 °C for 30 min, the reaction mixture was gradually warmed to the specified temperature. A: Fused bicyclic product was obtained at reflux. B: Quenching of the reaction at −10 °C gave β,γ-unsaturated ketone. C: Ethyl acetate was added to the magnesium complex of **1a** at −78 °C. The mixture was stirred at −78 °C for 30 min and then gradually warmed to −10 °C as usual. Addition of acetyl chloride at −20 °C afforded **8**.

(6) (a) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M., Jr. *J. Org. Chem.* **1980**, *45*, 1340. (b) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443.

(7) For a review, see: Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. For representative references, see: (a) Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375. (b) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556. (C) Ollivier, J.; Salaun, J. *Tetrahedron Lett.* **1984**, *25*, 1269. (d) Trost, B. M.; Mao, M. K. *J. Am. Chem. Soc.* **1983**, *105*, 6753.

(8) The chemistry for the reaction of **2a** with 1 equiv of acetyl chloride at −78 °C was found to be similar to that of **2a** with ethyl acetate, but acetyl chloride worked less satisfactorily than ethyl acetate for preparing **5** or **7**. On the other hand, treatment of **2a** with 2 equiv of acetyl chloride at −78 °C followed by warming to room temperature gave **8** in 88% isolated yield (cis/trans = 34:66).

(9) For typical references on preparing β,γ-unsaturated ketones, see: (a) Kachinsky, J. L. C.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 1393. (b) Marceau, P.; Gautreau, L.; Beguin, F.; Guillaumet, G. *J. Organomet. Chem.* **1991**, *403*, 21. (c) Hoffmann, H. M. R.; Tsushima, T. *J. Am. Chem. Soc.* **1977**, *99*, 6008. (d) Masson, S.; Saquet, M.; Thuillier, A. *Tetrahedron* **1977**, *33*, 2949. (e) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649. (f) Calas, R.; Dunogues, J.; Pillot, J. P.; Biran, C.; Pisciotti, F.; Arreguy, B. *J. Organomet. Chem.* **1975**, *85*, 149.

(10) (a) Mehta, G.; Krishnamurthy, N.; Karra, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 5765. (b) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. (c) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442. (d) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483. (e) Kozikowski, A. P.; Tuckmantel, W. *J. Org. Chem.* **1991**, *56*, 2826. (f) Binger, P.; Sternberg, E.; Wittig, U. *Chem. Ber.* **1987**, *120*, 1933.

containing a cyclopropane ring. Quenching of the intermediate at an appropriate temperature creates an alternative pathway for the reaction, leading to a regioselective synthesis of β,γ-unsaturated ketones. Efforts to extend the present approach to the other carbocycle-based conjugated dienes are currently underway.

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**Supplementary Material Available:** Experimental procedures for preparing **5** and **7**, characterization data for **8–16**, and $^1H$ and $^{13}C$ NMR spectra of **5** and **7–16** (30 pages). Ordering information is given on any current masthead page.

## Enzyme-like Activity of Albumins on the Thermal Back Reaction of a Photochromic Spirobenzopyran

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Recently there has been considerable interest in studies of photochromic molecules due to their potential applications to optical memory, photostimulated phase transition, photoregulation of various physical and chemical properties of polymers such as pH, polarity, and viscosity, surface wettability, potential and permeability of membranes, and so on.[2] Although control of the photochromic reaction itself is a subject of intensive research, little attention has been paid to control of thermal reactions. However, to achieve successful design of photochromic systems the thermal reaction has to be controlled as well.

Biomolecules such as antibodies, enzymes, and albumin are among the preferable matrices for controlling the thermal reaction, since they contain specific binding sites for organic molecules. Photoregulations of proteins are reported,[3] while systematic studies of the effects of biomolecules upon the properties of photochromic molecules, in particular upon the thermal reactions, have not yet been performed. In this paper we demonstrate enzyme-like activity of serum albumins toward a 6,8-dinitro-substituted spirobenzopyran.

6,8-Dinitro-1′,3′,3′-trimethylspiro[2*H*-1-benzopyran-2,2′-indoline] (6,8-dinitro-BIPS) was used (Scheme I) as a photochromic molecule.[4] Unlike most spirobenzopyrans, 6,8-dinitro-BIPS is stable in its merocyanine form (**1**). In solution the colored merocyanine (**1**) undergoes ring closure to the spiro form (**2**) when irradiated at λ = 500–600 nm. Ring opening proceeds thermally or by UV irradiation. Albumins were chosen as proteins because of their ability to bind and interact with various molecules and ions such as fatty acids, L-tryptophan, and $Ca^{2+}$, to mention a few.[5]

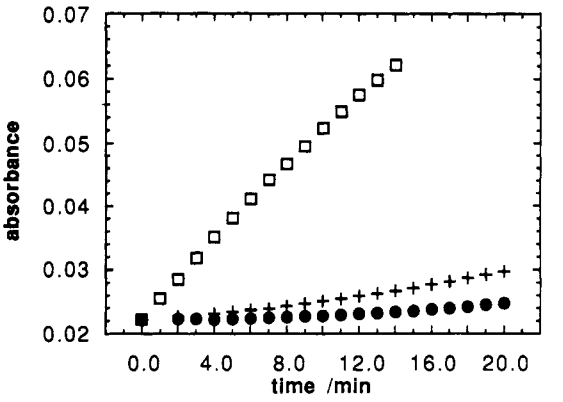
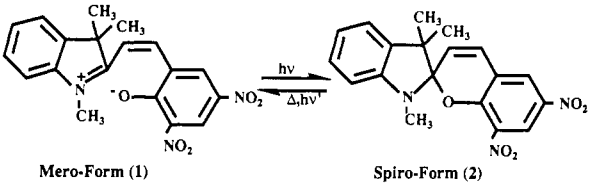



**Figure 1.** Thermal back reaction of the spiro form to the mero form of 6,8-dinitro-BIPS in the absence and presence of proteins: ●, without protein; □, with BSA; +, with BGG; 6,8-dinitro-BIPS, $1.82 \times 10^{-6}$ M; BSA, $5.04 \times 10^{-6}$ M; BGG, $4.29 \times 10^{-6}$ M; monitored at 480 nm; $T$ = 23.5 °C; path length = 5 cm.

**Scheme I**




The experiments were carried out as follows: the spiro form of 6,8-dinitro-BIPS was obtained by irradiating the merocyanine form in ethanol solution[6] with a Wacom super high pressure Hg lamp (500 W) for 5 min. GIF (Nikon) and Y50 (Toshiba) filters were used to select the excitation wavelength (λ = 500–600 nm). This solution was then added to phosphate-buffered saline (0.01 M PBS buffer pH 7.4, finally 2.9% (v/v) ethanol) containing human serum albumin (HSA), rabbit serum albumin (RSA), bovine serum albumin (BSA), BSA–palmitic acid (4.6 mol of palmitic acid/mol of BSA), or bovine γ globulin (BGG). Both HSA and BSA are essentially globulin and fatty acid free.[5a,7] The thermal back reaction was directly followed by measuring the absorption of the merocyanine at $\lambda_{max}$ = 480 nm.

The initial temporal behavior of 6,8-dinitro-BIPS in the presence and absence of the protein is shown for BSA and BGG in Figure 1. Without albumin, slow formation of the merocyanine was observed, whereas in the presence of BSA, HSA, or RSA, the thermal back reaction was accelerated markedly. On the contrary, BGG had only a small influence, indicating that the faster formation of the merocyanine is due to the presence of albumin and not to proteins in general. After 2.5 h all molecules were converted to the merocyanine in the presence of albumin. In contrast, only 30% of the final equilibrium concentration of **1** could be obtained in the absence of albumin.

† Department of Applied Physics, Osaka University, Suita, Osaka 565, Japan.

(1) Oct 1988–Sept 1993. After September 1993 all correspondence should be sent to the permanent address of H.M.

(2) Recent reviews: (a) Krongauz, V. A. In *Photochromism, Molecules and Systems*; Duerr, H., Bouas-Laurent, H., Eds., Elsevier: Amsterdam, 1990; pp 793–820. (b) Irie, M. *Adv. Polym. Sci.* **1990**, *94*, 27–67.

(3) (a) Willner, I.; Rubin, S.; Riklin, A. *J. Am. Chem. Soc.* **1991**, *113*, 3321–3325 and references cited therein. (b) Montagnoli, G.; Nannicini, L.; Giovannitti, M. P.; Riskri, M. G. *Photochem. Photobiol.* **1978**, *27*, 43–49. (c) Karube, I.; Nakamoto, Y.; Namba, K.; Suzuki, S. *Biochim. Biophys. Acta* **1976**, *429*, 975–981.

(4) The compound was synthesized according to the following: (a) Koelsch, C. F.; Workman, W. R. *J. Am. Chem. Soc.* **1952**, *74*, 6288–6289. The melting point (280 °C) and $\lambda_{max}$ = 514 nm in ethanol were consistent with the reported values; see: (b) Bertelson, R. C. In *Photochromism*; Brown, G. H., Ed.; Wiley-Interscience: New York, 1971; p 68

(5) See reviews: (a) Kragh-Hansen, U. *Dan. Med. Bull.* **1990**, *37*, 57–84. (b) Peters, T., Jr. *Adv. Protein Chem.* **1985**, *37*, 161–245.

(6) 6,8-Dinitro-BIPS is reported to be very insoluble in most organic solvents, as stated in the following: (a) Guglielmetti, R. In *Photochromism, Molecules and Systems*; Duerr, H.; Bouas-Laurent, H., Eds.; Elsevier: Amsterdam, **1990**; p 423. (b) Hinnen, A.; Audic, C.; Gautron, R. *Bull. Soc. Chim. Fr.* **1968**, 2066–2074. We confirmed that 6,8-dinitro-BIPS was soluble in ethanol, acetonitrile, or dioxane in the range of $5 \times 10^{-5}$ M; $2 \times 10^{-6}$ M solutions in PBS buffer containing 2.9% (v/v) ethanol, acetonitrile, or dioxane could be prepared as well. The Lambert–Beer law held for $(0.5–3.5) \times 10^{-6}$ M, indicating no formation of aggregates.

(7) Fatty acids can bind to several binding sites of albumin: (a) Droege, J. H. M.; Janssen, L. H. M.; Wilting, J. *Biochem. J.* **1988**, *250*, 443–446. (b) Reynolds, J.; Herbert, S.; Steinhardt, J. *Biochemistry* **1968**, *7*, 1357–1361. To minimize the possibility that the observed catalytic activity of albumins is due to an unknown contamination, the catalytic activity of BSA (Sigma, BSA A-0281, less than 0.005% fatty acids, less than 1% globulin) was compared to the catalytic activity of BSA from other markers (Nacalai tesque, BSA ultrapure; Armour subdivision, BSA-CRC-7, less than 0.02% fatty acids). The results obtained from the products of Sigma and Nacalai were similar within the experimental error, while the crude product (Armour subdivision) showed less activity.

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