Acidity Control by On/Off Switching of an Intramolecular NH···O Hydrogen Bond by E/Z Photoisomerization of Cinnamate Framework

Takashi Matsuhira,[1] Hitoshi Yamamoto,*[1] and Taka-aki Okamura[2]
[1]*Department for the Administration of Safety and Hygiene (DASH), Osaka University, 1-1 Yamadaoka, Suita, Osaka 565-0871*
[2]*Department of Macromolecular Science, Graduate School of Science, Osaka University, 1-1 Machikaneyama-cho, Toyonaka, Osaka 560-0043*

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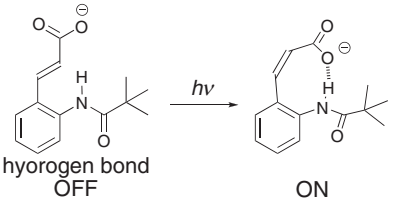
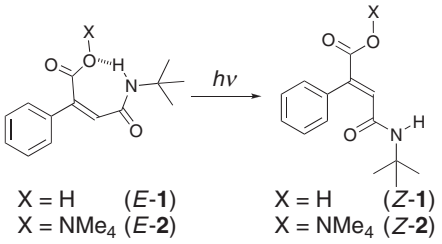
Acidity control by photoswitching of intramolecular NH···O hydrogen bond using E/Z photoisomerization of cinnamate framework was achieved. According to the photoisomerization, the distance between amide NH and carboxylic oxygen was disgregated, and an intramolecular NH···O hydrogen bond formed in E carboxylate was interrupted in Z compound in DMSO-d_6 solution. The pK_a value of Z carboxylic acid was increased in E compound in DMSO solution.

Native hydrolytic proteins rearrange the intramolecular hydrogen bonds to carboxylate oxygens, to control the activity of oxy-anions in their reaction center. They induce dynamic switching of the overall protein structure triggered by external stimulation to rearrange the hydrogen-bond network.[1] We propose that the switching of intramolecular hydrogen bonding will achieve control of the chemical properties of oxy-anion accompanied minimal conformation change by controlling the distance between hydrogen-bond donors and acceptors in small molecules.[2] Photoisomerization, considered to be a promising strategies for stimulating these compounds, effectively facilitates the control of molecular structures. There have been many investigations using photoisomerization for photoswitching devices.[3] For example, the effects of intramolecular OH···O, NH···N, and NH···O hydrogen bonds in Z configuration on photoreactivity,[4] as well as the pK_a change of phenol or carboxylic acid derivatives by the switching of conjugation through photoisomerization[5] have been investigated. Hence we have applied photoisomerization to design hydrogen bond switching devices.[2] In a previous study, the authors showed the OFF to ON one-way switching of an intramolecular NH···O hydrogen bond accompanying the E to Z photoisomerization of a cinnamate framework (Scheme 1), and found that NH···O hydrogen bonds formed in Z configuration lowered the pK_a value of the Z carboxylic acid derivative.[2b] The authors conceived an idea that introduction of a carboxylic acid derivative into a cinnamate framework, and interruption of an intramolecular NH···O hydrogen bond by photoisomerization (ON to OFF switching), will increase the pK_a value of the corresponding carboxylic acid. Following this strategy, we designed ON → OFF type compounds (*E*-**1**/*Z*-**1** and *E*-**2**/*Z*-**2**) that interrupt intramolecular NH···O hydrogen bonding through one-way E/Z photoisomerization of a cinnamate framework (Scheme 2). The formation of intramolecular NH···O hydrogen bonding in E carboxylate ON → OFF compounds showed promise in a previous investigation of a similar maleic amide skeleton.[6]



Scheme 1. OFF → ON one-way switching of an intramolecular NH···O hydrogen bond by E to Z photoisomerization of cinnamate framework.[2b]



Scheme 2. ON → OFF (*E*-**1**, *Z*-**1**, *E*-**2**, and *Z*-**2**) switching of intramolecular NH···O hydrogen bond by E to Z photoisomerization of cinnamate framework.

E-**1** was synthesized through coupling of phenylmaleic anhydride and *tert*-butylamine. *Z*-**1** was isolated from a photoreaction mixture through addition of hydrochloric acid. *E*-**2** and *Z*-**2** were synthesized through a counter cation exchange reaction of corresponding acids.[7]

E/Z photoisomerization was followed by UV–vis spectra (Figure 1). Each E compound was isomerized and reached a photostationary state (PSS) at 313 nm irradiation. The absorbances of E isomers decreased in accordance with a two state transition upon irradiation, indicating that only the corresponding Z isomers were formed without any side reactions. The E/Z ratios in PSS were 15/85 (*E*-**1**/*Z*-**1**) and 16/84 (*E*-**2**/*Z*-**2**) respectively.

^{1}H NMR spectra of carboxylates (*E*-**2** and *Z*-**2**) in DMSO-d_6 are shown in Figure 2. E/Z configurations were confirmed based on NOE correlated spectroscopy (NOESY).[7] NOE correlation between olefin and phenyl protons were observed in *E*-**2**, whereas correlation between *tert*-butyl and phenyl protons were observed in *Z*-**2**. These correlations evidently confirm the configuration around the allene. The amide NH chemical shift was 9.22 ppm in *E*-**2** and 6.64 ppm in *Z*-**2** at 303 K, and the temperature dependency of the amide NH chemical shift of *Z*-**2** was -9.0 ppb K^{-1}, whereas that of *E*-**2** was -0.5 ppb K^{-1} in the range of 303 to 333 K. The upfield shift ($\Delta\delta = 2.58$) and the increase of temperature coefficient suggest that an intramolecular NH···O hydrogen bond formed in *E*-**2** was interrupted in *Z*-**2**.

An attempt was made to measure pK_a values of *E*-**1** and *Z*-**1** by potentiometric titration in a 10% Triton X-100 aqueous mi-

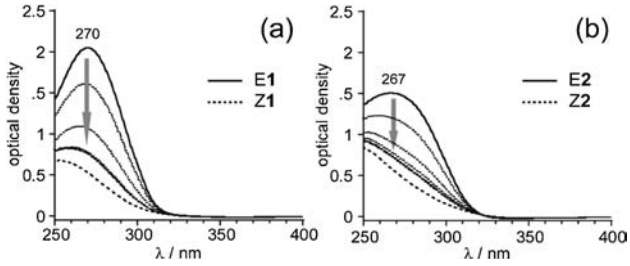


Figure 1. Time course UV–vis spectra changes of (a) *E*-**1**, (b) *E*-**2**, toward 313 nm photoirradiation (dotted lines), 1 mM in DMSO at 293 K. Solid lines are those taken before irradiation, and the broken lines are isolated Z compounds.

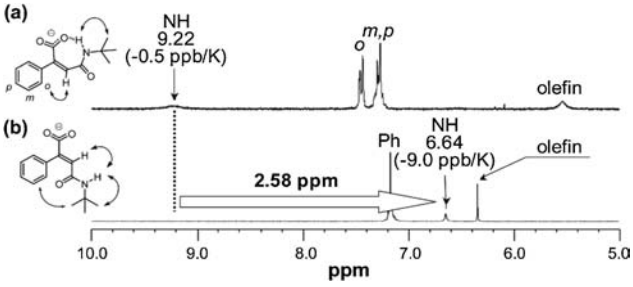


Figure 2. ^{1}H NMR spectra of isolated carboxylate derivatives a) *E*-**2**, b) *Z*-**2**, 5 mM in DMSO-d_6 at 303 K.

cellar solution at 298 K. The pK_a value of *Z*-**1** was obtained as 4.3, but that of *E*-**1** was not obtained accurately because of hydrolysis of the amide bond in aqueous micellar conditions.[7] This hydrolysis reaction does not proceed in organic solvents like DMSO. Thus, we approached determination of relative acidity in such an organic solvent. The differences of pK_a values in organic solvent was obtained in accordance with a previous report on related compounds.[2b] The counter cation exchange reaction between two acids was examined, and the differences of pK_a values in organic solvent were obtained from the deprotonation ratio of two acids $[A^-]/[AH]$ and $[BH]/[B^-]$, from following equations.

$$AH + B^- \overset{K_{eq}}{\rightleftharpoons} A^- + BH \quad (1)$$

$$K_{eq} = \frac{[A^-][BH]}{[AH][B^-]} = \frac{[A^-][H^+]}{[AH]} \times \frac{[BH]}{[H^+][B^-]} = \frac{K_a(1)}{K_a(2)} \quad (2)$$

Carboxylic acid *E*-**2** and carboxylate *Z*-**1** were mixed in DMSO-d_6 solution and the equilibrium constant was confirmed from the chemical shift of ^{1}H NMR spectra.[7] It was estimated that 75% of the E compound was deprotonated, and 73% of the Z compound was protonated, by comparing the chemical shifts with the isolated carboxylic acids and carboxylates. This result indicates that the E compound has a pK_a 0.92 unit lower than the Z compound in DMSO solution. We propose that the interruption of intramolecular NH···O hydrogen bonding in Z carboxylate discourages the deprotonation and increases the pK_a value of the corresponding carboxylic acid *Z*-**1**. Estimating in a uniform manner, the Z configured OFF → ON compound has 1.63 unit lower pK_a value than the E compound,[2b] and the Z isomer has a 0.39 unit lower pK_a value than *Z*-**1**, in DMSO solution.[7] Figure 3 shows the pK_a differences in DMSO solution as a straight line. Depending on photoisomerization, the pK_a value of the carboxylic acid was lowered

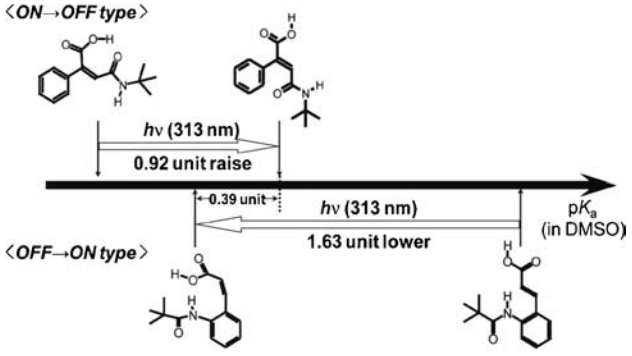


Figure 3. pK_a differences of OFF → ON and ON → OFF type carboxylic acids in DMSO solution on straight line, obtained from ^{1}H NMR analysis of ion-exchange reaction.

in OFF → ON compounds, and raised in ON → OFF compounds, and the acidity was reversed after photoisomerization.

In conclusion, ON → OFF photoswitching of an intramolecular NH···O hydrogen bond by using E to Z photoisomerization of a cinnamic acid framework was achieved. *E*-**2** forms an intramolecular NH···O hydrogen bond in DMSO-d_6 solution, and that hydrogen bond is interrupted in *Z*-**2**, as a result of photoisomerization of the cinnamate framework. Consequently, the acidity of the carboxylic acid was controlled arbitrarily by photoswitching the intramolecular NH···O distances. Carboxylic acid compounds that change chemical properties in response to external stimulation could allow reactivity control by small molecules.

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7 The detail procedures of the synthesis, NOESY spectra, hydrolysis of *E*-**1**, and the details of counter cation exchange reactions are described in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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