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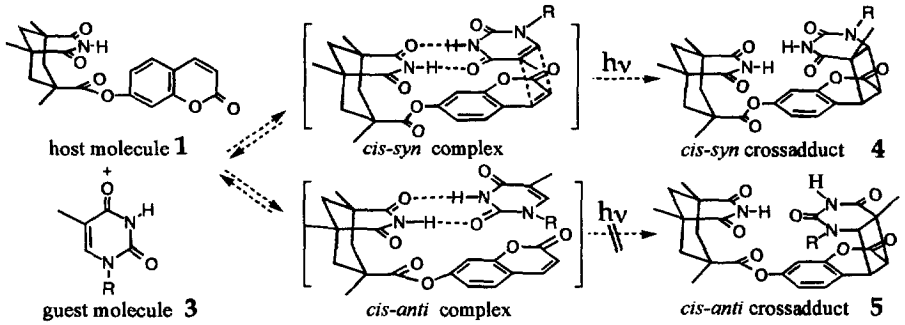
Highly Regio- and Stereoselective Photocycloaddition between Coumarin and Thymine by Molecular Recognition

Keiji Mori, Osamu Murai, Shigeki Hashimoto, and Yushin Nakamura*

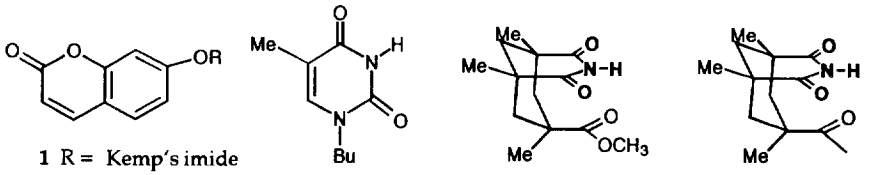
Department of Biological Science and Technology, Science University of Tokyo,
Yamazaki, Noda 278, Japan

Abstract: The photoreaction of Kemp's imide-linked coumarin **1** and thymine **3** gave two crossadducts, *cis-syn* **4** and *cis-anti* **5**. The yield and ratio of **4**/**5** in benzene solution remarkably increased by factors of 4.2 and 10 than those in acetonitrile solution, respectively. On the other hand, the reaction of acetoxycoumarin **2** and **3** gave only the *cis-anti* crossadduct in each solution.

Molecular recognition is central to enzyme reactions, immunological reactions and gene expression in biology, to stereoselective reactions such as asymmetric synthesis in organic chemistry, and to host-guest complexations and catalytic reactions in biomimetic chemistry.[1] Rebek. Jr.[2] and Hamilton[3] have reported molecular recognitions for host-guest complexations between adenine and Kemp's imide, and thymine and 2,6-diamino-pyridine derivatives. Psoralens, furocoumarin derivatives, are used in the phototherapy of psoriasis[4] and in the mapping of chromatin in view of there ability in covalent bonding and cross-linking formation with DNA or RNA.[5] The photoaddition of psoralen to the thymine of DNA proceeds with cross-linking in both the double bond sites of the furan and lactone rings with highly regio- and stereoselective *cis-syn* formations due to its intercalation into A-T and T-A base pairs. On the other hand, irradiation of psoralens or coumarins with thymines in solution or in the solid does not give such stereo-controlled products.[6] We designed a reaction control by the molecular recognition of the photocycloaddition of coumarin and thymine. Our reaction strategy is shown in Scheme 1. We chose Kemp's imide as the host molecule, which is linked with the coumarin moiety. CAChe molecular mechanics calculations for the complimentary formation of the host molecule **1** and guest one **3** exhibit two types, *cis-syn* and *cis-anti*, of



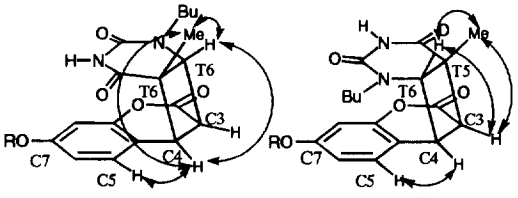
Scheme 1 Strategy of stereoselective photocycloaddition of coumarin **1** and **3** by molecular recognition



1 R = Kemp's imide
2 R = $-COCH_3$
3
7
Kemp's imide

stable complexes based on the hydrogen bonding formation.[7] We assumed that for the photocycloaddition, the *cis-syn* complex should be preferable to the *cis-anti* complex because of the more attractive overlapping with respect to the direction and distance of the two double bonds of coumarin and thymine (Scheme 1).

The host compound **1** was prepared according to the method of Rebek, Jr.[2] Acethoxycoumarin **2** as a comparative compound to **1** and 1-butyl thymine **3** as a guest molecule were used. The photoreaction of **1** (18 mmol cm^{-3}) and **3** (90 mmol cm^{-3}) in acetonitrile solution in a Pyrex tube occurred with irradiation under a 400 W high pressure Hg lamp in an argon atmosphere at 15 °C for 8 h to give two crossadducts, **4** and **5**, in 15 and 8 % isolated yields, respectively.[8] Under the same conditions, the reaction with **2** only gave **6** (21 %).[8] The MS, UV and ^1H NMR spectra of **4**, **5** and **6** exhibited the characteristics of crossadducts with a cyclobutane ring between the coumarin and thymine.[9] The results of the NOESY spectra of **4** and **5** as shown in Fig. 1 indicate that the stereochemistry on the cyclobutane ring of **4** and **5** should be *cis* configurations. Moreover, the regiochemistry of **4** and **5** should be *syn* and *anti* configurations, respectively, based on the observations of NOE between C-4-H at δ 3.56 (doublet) and C-5-H at δ 7.13 (doublet) of **4** and between C-4-H at δ 3.93 (quartet) and C-5-H at δ 6.85 (doublet) of **5**. The structure of **6** was determined to have the same *cis-anti* configuration as **5** based on the similarity of the NMR spectra of **5** and **6**. It, furthermore, was confirmed by the following chemical experiments. The hydrolysis of **5** with 1N LiOH gave a phenol derivative that was converted to **6** for the acetylation.



cis-syn **4** *cis-anti* **5**

Fig. 1 Observed NOE of **4** and **5** in NOESY spectra

The photocrossadduct yields of the reactions in acetonitrile and benzene solutions were determined by HPLC.[10] As shown in Fig. 2, the results indicate that i) the rates of reactions with **1** in acetonitrile and, especially, in benzene were higher than those with **2**; ii) the yields of the crossadducts, **4** and **5**, in benzene after irradiation for 2 h increased by a factor of 4.2 than that in acetonitrile; iii) the ratio of *cis-syn* **4** / *cis-anti* **5** (96:4) in benzene remarkably increased by a factor of 10 than that (68:32) in acetonitrile;[11] and iv) the *cis-syn* crossadduct in the reaction of acetoxycoumarin **2** with **3** was not observed in each solution. These results strongly suggest that the *cis-syn* crossadduct **4** is formed through molecular recognition.

The host-guest complexations between **1** or **7** and **3** were ascertained by means of the NMR experiments. As shown in Table 1, downfield shifts of the imide N-H resonances of **1** or **7** and **3** in the mixture show a complexation between the host and guest molecules that reflects the hydrogen bonding formation.[2]

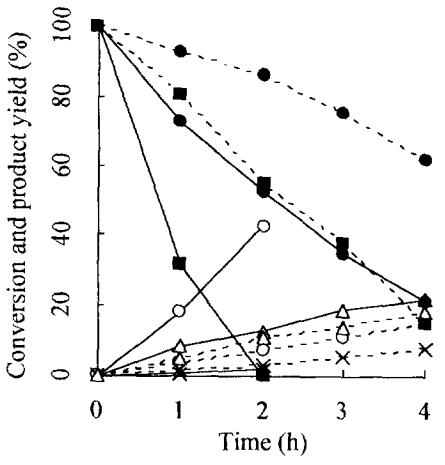


Fig. 2 Quantitative analysis and time course of photoreactions of **1** or **2** and **3**: ----- in acetonitrile, —— in benzene, compound; ■ **1**, ● **2**, ○ **4**, × **5**, △ **6**

Table 1 Chemical shifts of imide-H in the mixture of **1** or **7** and **3** in NMR spectra (C_6D_6)

Compound	Imide-H (δ)	Imide-H of mixture (δ)	⊿ δ
1	7.72	8.31	0.59
3	8.63	8.80	0.17
7	7.36	7.75	0.39
3	8.63	8.86	0.23

Furthermore, the greater downfield shift of the N-H resonance of **1** compared to that of **7** in each mixture indicates that the complex between **1** and **3** due to the additional π-π stacking formation should be more stable than that of **7** and **3**. The observation of the smaller downfield shift of N-H of **3** in the complex with **1** versus that with **7** can be explained by the following fact. The N-H of **3** in the complex with **1** is situated on the aromatic ring of coumarin in both the *cis-syn* and *cis-anti* stable complexes as shown by the CAChe calculations (Scheme 1), and hence the N-H of **3** is shielded by the aromatic ring, but that of **1** in the complex is not.

In conclusion, we have demonstrated that the highly regio- and stereoselective photocycloaddition of coumarin and thymine was successful in a very simple system by molecular recognition based on hydrogen bonding and π-π stacking forces.

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7. There are two conformations in each *cis-syn* and *cis-anti* complex with hydrogen bonding between 2(CO), 3(NH) or 3(NH), 4(CO) of thymine **3** and Kemp's imide of **1**. CAChe MM calculations exhibited -246 or -232 kJ mol^{-1} for the *syn* complexes and -246 or -257 kJ mol^{-1} for the *anti* complexes, respectively.
8. Both reactions gave the polymer and other unknown compounds which were not the other crossoadduct based on the NMR spectra. All new compounds were characterized based on their microanalyses, UV, MS, and COSY and NOESY ^1H NMR spectra.
9. Selected data for **1**: mp 251-252 °C; UV (EtOH) λ_{max} 275, 310 nm (ε 11000, 8800 dm^{-3} mol^{-1} cm^{-1}); ^1H NMR (400 MHz, ($CDCl_3$) δ 1.27-1.33 (8H, m, K(Kemp's H)-4,6-Hb overlapped with 1.30, s, K-1,3-Me), 1.43-1.46 (4H, m, K-2-Hb overlapped with 1.45, s, K-5-Me), 2.06 (1H, d, J=14.0 Hz, K-2-Ha), 2.81 (2H, d, J=13.6 Hz, K-4,6-Ha), 6.24 (1H, d, J=9.6 Hz, C (coumarin)-3-H), 6.99 (1H, dd, J=2.0, 8.4 Hz, C-6-H), 7.08 (1H, d, J=2 Hz, C-8-H), 7.43 (1H, d, J=8 Hz, C-5-H), 7.65 (1H, d, J=9.6 Hz, C-4-H), 7.92 (1H, s, NH); MS m/z 383 (M^+); *Anal.* Calcd. for $C_{21}H_{21}NO_6$; C, 65.79; H, 5.52; N, 3.65, Found; C, 65.72; H, 5.49; N, 3.62.

   For **4**: mp 290-292 °C; UV (EtOH) λ_{max} 240 nm (ε 5980 dm^{-3} mol^{-1} cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD=3:1) δ 0.96 (3H, t, J=7.2, Bu-4-H), 1.27-1.37 (10H, m, K-4,6-Hb, Bu-2-H overlapped with 1.29, s, K-1,3-Me), 1.39-1.44 (4H, m, K-2-Hb overlapped with 1.40, s, K-5-Me), 1.63 (3H, s, T (thymine)-5-Me), 1.56-1.63 (2H, m, Bu-2-H), 2.04 (1H, d, J=13.6 Hz, K-2-Ha), 2.35 (2H, bs, N-H), 2.77 (2 H, dd, J=14.4, 1.6 Hz, K-4,6-Ha), 3.02-3.09 (1H, m, Bu-1-Ha), 3.56 (1H, d, J=8.0 Hz, C-4-H), 3.79 (1H, q, J=9.6, 8.8 Hz, C-3-H), 3.87-3.94 (1H, m, Bu-1-Hb), 4.18 (1H, d, J=8.8 Hz, T-6-H), 6.80 (1H, d, J=2.4 Hz, C-8-H), 6.88 (1H, dd, J=8.4, 2.4 Hz, C-6-H), 7.13 (1H, d, J=8.4 Hz, C-4-H); MS (FAB) m/z 566 (M+1); *Anal.* Calcd. for $C_{30}H_{35}N_3O_8$; C, 63.69; H, 6.24; N, 7.43, Found; C, 63.51; H, 6.19; N, 7.12.

   For **5**: mp >300 °C; UV (EtOH) λ_{max} 240 nm (ε 6340 dm^{-3} mol^{-1} cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD=3:1) δ 0.98 (3H, t, J=7.6, Bu-4-H), 1.26-1.30 (8H, m, K-4,6-Hb overlapped with 1.28, s, K-1,3-Me), 1.36-1.45 (6H, m, K-2-Hb, Bu-3-H overlapped with 1.40, s, K-5-Me), 1.60-1.67 (5H, m, Bu-2-H overlapped with 1.62, s, T-5-Me), 2.04 (1H, d, J=13.2 Hz, K-2-Ha), 2.40 (2H, bs, N-H), 2.75 (2H, dd, J=14.0, 1.4 Hz, K-4,6-Ha), 2.86-2.92 (1H, m, Bu-1-Ha), 3.35 (1H, d, J=8.0 Hz, C-3-H or T-6-H), 3.93 (1H, q, J=8.4, 7.2 Hz, C-4-H), 4.00-4.08 (2H, m, Bu-1-Hb overlapped with 4.04, d, J=7.2, C-3-H or T-6-H), 6.84 (1H, d, J=2.4 Hz,C- 8-H), 6.85 (1H, d, J=8.4 Hz, C-5-H), 6.94 (1H, dd, J=8.1, 2.4 HZ, C-6-H); MS (FAB) m/z 566 (M+1); *Anal.* Calcd. for $C_{30}H_{35}N_3O_8$; C, 63.69; H, 6.24; N, 7.43, Found; C, 63.71; H, 6.41; N, 7.28.

   For **6**: mp 240-242 °C; UV (EtOH) λ_{max} 240 nm (ε 5440 dm^{-3} mol^{-1} cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, J=7.2 Hz, Bu-4-H), 1.35-1.44 (2H, m, Bu-3-H), 1.61-1.65 (2H, m, Bu-2-H), 1.65 (3H, s, T-5-Me), 2.29 (3H, s, -$COCH_3$), 2.88-2.95 (1H, m, Bu-1-Ha), 3.37 (1H, d, J=8.4 Hz, C-3-H or T-6-H), 3.95 (1H, q, J=8.4, 6.8 Hz, C-4-H), 4.02-4.09 (2H, m, Bu-1-Hb overlapped with 4.05, d, J=6.8 Hz, C-3-H or T-6-H), 6.84 (1H, d, J=2.0 Hz, C-8-H), 6.88 (1H, d, J=8.4 Hz, C-5-H), 6.92 (1H, dd. J=8.4, 2.0 Hz, C-6-H), 7.06 (1H, bs, NH); MS (FAB) m/z 387 (M+1); *Anal.* Calcd. for $C_{20}H_{22}N_2O_6$; C, 62.17; H, 5.74; N, 7.25, Found; C, 62.22; H, 5.69; N, 7.20.
10. HPLC conditions: C18 column (150 x 4.6 mm); particle size 5 μm; eluent CH_3CN - H_2O (44 : 56 →32 : 68, 15 min), detection at 240 nm for **4** ,**5** and **6** or 360 nm for **1** and **2**. The compounds were separated and quantitatively determined by HPLC under these conditions.
11. Benzene as solvent would be preferable for hydrogen bonding formation to acetonitrile due to its small dielectric constant.

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