STEREO- AND REGIOSELECTIVE PHOTOCYCLOADDITION OF COUMARIN AND THYMINE DERIVATIVES USING MOLECULAR RECOGNITION CATALYST

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Abstract The photocycloaddition of coumarin and thymine derivatives in the presence of molecular recognition catalyst in acetonitrile solution afforded two crossadducts *cis-syn* and *cis-anti*. Remarkably, the ratio of *cis-syn* and *cis-anti* crossadducts was greater by a factor of 12.5 than that of the adducts formed in the reaction using 18-crown-6-ether as the catalyst.

Molecular recognition is essential 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). We have recently reported on the highly stereo- and regioselective photocycloaddition between coumarin and thymine derivatives by molecular recognition based on hydrogen bonding and π–π stacking interactions (2). Herein we report on the stereo- and regioselective photocycloaddition of the coumarin and thymine derivatives using a molecular recognition catalyst. We have designed catalyst **1** to feature two molecular recognition sites, using 2,6-diaminopyridine and crown ether moieties to provide hydrogen bond formation and cation binding interaction, respectively. Coumarin tethered alkylammonium salt **2** and N-butylthymine **3** were selected as the recognition partners of catalyst **1**. Our strategy for the photoreaction of **2** and **3** in the presence of catalyst **1** is illustrated in Fig. 1. Molecular mechanics calculations of the complimentary formation of substrates **2** and **3** with catalyst **1** exhibited two types of stable complexes, *cic-syn* and *cis-anti*, based on the hydrogen bonding and π–π stacking interactions (3). However, we assumed that, for photocycloaddition, the *cis-syn* complex would be preferable over the *cis-anti* complex because of the more attractive overlapping of the two double bonds of the coumarin and thymine moieties, as shown in Fig. 1.

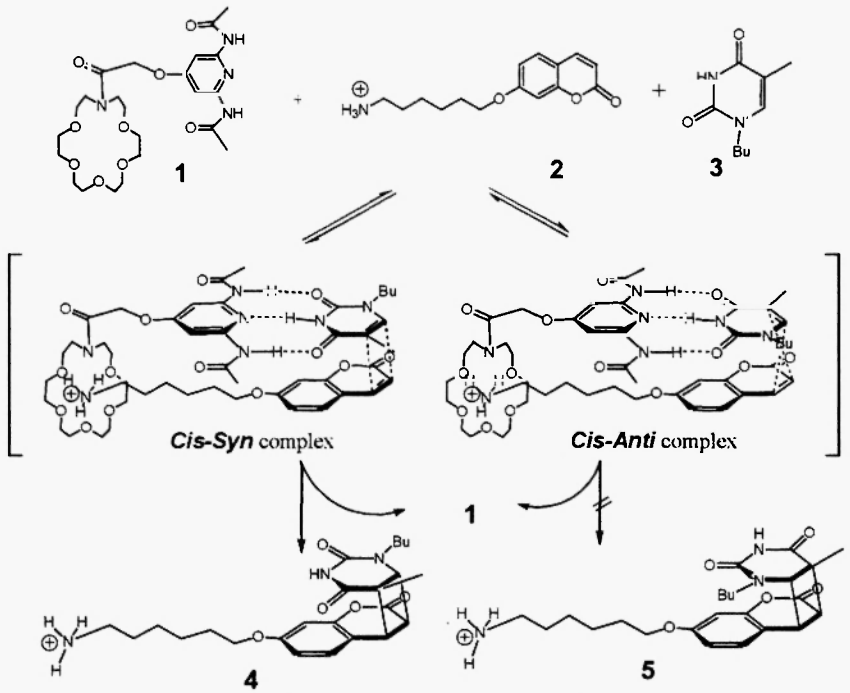


Fig. 1 Strategy of photoreaction of coumarin **2** and thymine **3** using catalyst **1**

Catalyst **1** and substrate **2** were prepared according to the scheme as shown in Fig. 2 (4). The photoreaction of **2** (0.23 mmol cm^{-3}) and **3** (2.3 mmol cm^{-3}) with **1** (0.23mmol cm^{-3}) in acetonitrile was carried out in a Pyrex tube under an argon atmosphere at 20 ℃. Irradiation using a 400 W high pressure Hg lamp for 2 h afforded two crossadducts, **4** and **5** in 8.5 and 3.4 % yields, respectively. Under similar conditions using 18-crown-6-ether instead of **1**, the reaction afforded **4** and **5** in 2.6 and 12.3 % yields, respectively (5). The MS, UV, and ^{1}H-NMR data of **4a** and **5a**, the acetates of **4** and 5, exhibited characteristics of the crossadducts with a cyclobutane ring formed between the coumarin and thymine (6). Moreover, based on the similarity of the cyclobutane ring protons in the NMR spectra we have previously reported (7), the structures of *cis-syn* **4a** and *cis-anti* **5a** were determined to be similar to *cis-syn* **12** and *cis-anti* **13**, respectively, as shown in Table 1. Remarkably, the results of the photoreactions, in the presence of the catalyst **1**, indicate that the ratio of *cis-syn* **4** / *cis-anti* **5** increased by a factor of 12.5 than that in the presence of 18-crown-6-ether.

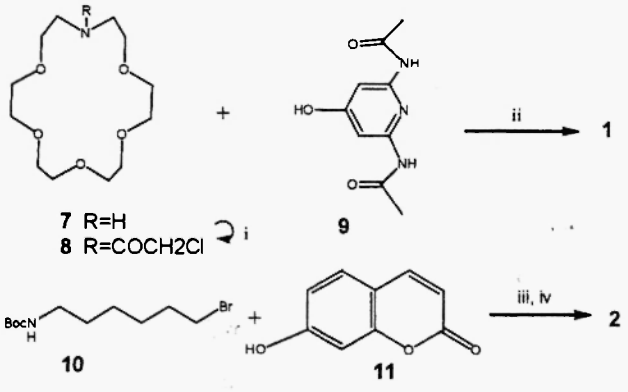


Fig. 2 Preparation of **1** and **2**. Reagents: i $ClCOCH_2Cl$. CH_2Cl_2, ii K_2CO_3. DMSO. iii K_2CO_3.2-butanon. iv HCl.EtOH

Table 1. Chemical shifts from the NMR spectra of the cyclobutane ring of crossadducts **4a** and **5a**, with **12** and **13**.[a)]

H	**4a**		**12**		**5a**		**13**	
	ppm	Hz	ppm	Hz	ppm	Hz	ppm	Hz
6'-H	4.15	d, J=8.8	4.18	d, J=8.8	3.99	d, J=6.8	4.04	d, J=7.6
3-H	3.80	t, J=9.0	3.79	t, J=8.4	3.34	d, J=7.6	3.35	d, J=8.0
4-H	3.53	d, J=9.2	3.56	d, J=8.4	3.90	t, J=7.2	3.93	t , J=7.6

a) The coupling constants of the triplets (t) were apparently of those which could be observed in the NMR spectra.

As shown in Table 2, complexation between **1** and **3** was confirmed by NMR studies, in which downfield shifts of the amide or imide N-H signals of **1** and **3** in the mixture indicate the formation of hydrogen bonding, and hence complexation between both molecules. Although the complexations of **1**, **2** and **3** were not ascertained by NMR experiments because of their insolubilities, these results strongly suggest that the *cis-syn* crossadduct of **4** was formed through molecular recognition.

Table 2 Chemical shifts from the NMR spectra of amide- and imide-H in the mixture of **1** and **3** in $CDCl_3$ solution

Compound	Amide- or imide-H (δ)	Amide- or imide-H of mixture (δ)	⊿δ
1	8.29	9.96	1.67
3	9.05	11.75	2.70

In conclusion, we have demonstrated successful stereo- and regioselective photocycloaddition of in a simple system of coumarin and thymine in the presence of a molecular recognition catalyst that is based on hydrogen bond formation and π–π stacking forces.

REFERRENCES AND NOTES

(1) A. D. Buckingham, A. C. Legon, S. M. Roberts, *Principles of Molecular Recognition*, Bracket A & P, Glasgow, 1993; H. Dugas, *Bioorganic Chemistry*, Springer New York, 1996; J. M. Lehn, *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 89.

(2) K. Mori, O. Murai, S. Hashimoto, and Y. Nakamura, *Tetrahedron Letters*, **37**, 8523, 1996.

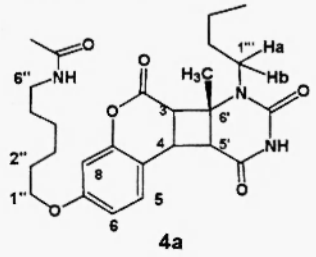
(3) These models were obtained through optimization of the hybrid of **1**, **2** and **3** by AMBER* force field in chloroform set by using MacroModel version 6.0. The calculations exhibited –1369.00 kJ mol^{-1} for the *cis-syn* complex and –1369.78 kJ mol^{-1} for the *cis-anti* complex, respectively.

(4) All new compounds were characterized based on their microanalyses, UV, MS, NMR spectra. Selected data for **1**: $C_{23}H_{36}N_4O_9$, MW 512.56, MS m/z 512 [M^+]; ^{1}HNMR ($CDCl_3$) ppm, 8.32 (s, 2H, NH), 7.48 (s. 2H ArH), 4.96 (s, 2H, -$COCH_2O$)-, 3.65 (m, 24H -OCH_2CH_2O-), 2.11 (s, 3H –$COCH_3$). For **2**:

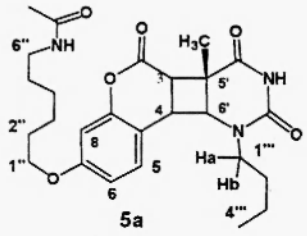
$C_{15}H_{20}NO_3Cl$, MW 297.8, MS m/z 261 $[M-HCl]^+$; ^{1}HNMR (DMSO-d_6) ppm, 8.01 (m, 4H, NH3,), 7.61 (d, 1H, J=8.8 Hz, CH), 6.97 (d, 1H, J=5 Hz), 6.93 (d, 1H, J=5 Hz), 6.27 (d, 1H, J=8.8 Hz), 4.08 (t, 2H, J=6.4 Hz), 2.77 (t, 2H, J=7.5 Hz), 1.75 (t, 2H, J=6.4 Hz), 1.60 (t, 2H,J=7.6 Hz), 1.41 (m, 4H).

(5) The ratio of the adducts **4** and **5** was determined by HPLC after conversion into the acetates **4a** and **5a** by treatment of the reaction mixture with Ac2O/pyridine. In this reaction, the other crossadduct or thymine dimmer was not observed except polymers.

(6) Selected data for **4a**: $C_{26}H_{32}N_3O_6$, MW 482, MS m/z 483 $[M+H]^+$, UV λmax 277 (ω = 1668), ^{1}HNMR ($CDCl_3$) ppm, 7.40 (1H, d, J=8.4 Hz, C5-H), 6.68 (1H, dd, J=8.4, 2.4 Hz, C6-H), 6.50 (1H, d, J=2.4 Hz, C8-H), 4.15 (1H, d, J=8.8 Hz, C6'-H), 3.97-3.90 (3H, m, C1" -H_2,C1"-Ha), 3.85 (1H, t, J=9.0 Hz, C3-H), 3.53 (1H, d, J=9.2 Hz, C4-H), 3.27-3.22 (2H, m, C6"-H_2), 3.09-3.04 (1H, m, C1'"-Hb), 2.02 (3H, s, NHCO-CH_3), 1.80-1.72 (2H, m, C2"-H_2), 1.65 (3H, s, C5'-CH_3), 1.59-1.32 (10H, -CH2-), 0.96 (3H, t, J=7.2 Hz, C4'"-H_3) ; for **5a**: $C_{26}H_{32}N_3O_6$, MW 482, MS m/z 483 $[M+H]^+$, UV λ max 277 (ω =1368), ^{1}HNMR ($CDCl_3$) ppm, 6.76 (1H, d, J=8.8 HZ, C5-H), 6.68 (1H, dd, J=8.8, 2.4 Hz, C6-H), 6.55 (1H, d, J=2.4 Hz, C8-H), 4.o6-4.00 (1H, m, C1'"=Ha), 3.99 (1H, d, J=6.8 Hz, C6'-H), 3.90 (1H, t, J=7.2 Hz, C4-H), 3.28-3.23 (2H, m, C6"-H_2), 2.92-2.88 (1H, m, C1'"-Hb), 1.98 (3H, s, $NHCOCH_3$), 1.78-1.75 (2H, m, C2"-H_2), 1.65 (3H, s, C5'-CH_3), 1.55-1.38 (10H, m, -CH_2-), 0.99 (3H, s, C4'"-H_3).

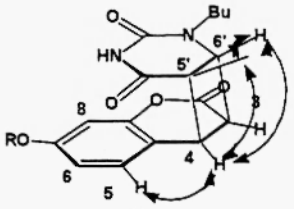


4a



5a

(7) See the reference 2 and the structures of **12** and **13** with the observed NOE are shown below.



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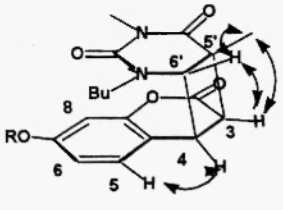

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