

Template-Assisted Preferential Formation of a Syn Photodimer in a Pyrophosphate-Induced Self-Assembly of a Thymine-Functionalized Isothiouronium Receptor

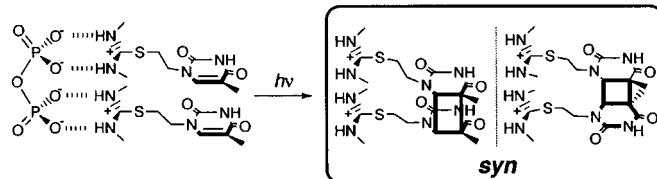
Yuichi Kato, Seiichi Nishizawa, and Norio Teramae*

Department of Chemistry, Graduate School of Science, Tohoku University,
Aoba-ku, Sendai 980-8578, Japan

teram@anal.chem.tohoku.ac.jp

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ABSTRACT



The effect of anion templation is investigated for the photodimerization of a thymine-functionalized isothiouronium receptor. The receptor forms a photodimer at the thymine moiety in methanol upon UV irradiation, while the isothiouronium moiety works as an oxoanion binding site via a two-point hydrogen-bonding motif. As compared to the case of a free receptor, the presence of pyrophosphate (PPi) resulted in the preferential formation of the syn-type photodimer, which would be desirable for recognizing the templated PPi.

Studies on the chemistry of anion recognition have drawn great interest over the past decade.^{1,2} In particular, use of anions as templates to synthesize a supramolecular array or self-assembly is now becoming one of the central topics in this field.^{3,4} Most of these anion-templated assemblies have been achieved by metallomacrocycles³ such as the metal-

polypyridine double helicates by Lehn and co-workers^{3a,b} and the cages or nanotubes by Fujita and co-workers.^{3c,d} In these self-assembling receptors,³ the anion is essential in the control of the assembling process, and the reversible coordination to metal ions has been utilized for the linking of building blocks.

On the other hand, considerably less progress has been made using the anion-templated supramolecular assembly based on the reversible formation of covalent bonds.^{5–7} A variety of photoinduced reactions such as [2 + 2] cyclization

(1) For recent reviews: (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, 97, 1609. (b) Beer, P. D. *Acc. Chem. Res.* **1998**, 31, 71. (c) Snowden, T. S.; Anslyn, E. V. *Curr. Opin. Chem. Biol.* **1999**, 3, 740. (d) Beer P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, 40, 486.

(2) For recent topics: (a) Aoki, S.; Iwaida, K.; Hanamoto, N.; Shiro, M.; Kimura, E. *J. Am. Chem. Soc.* **2002**, 124, 5256. (b) Ojida, A.; Mitooka, Y.; Inoue, M.; Hamachi, I. *J. Am. Chem. Soc.* **2002**, 124, 6256. (c) Shigemori, K.; Nishizawa, S.; Yokobori, T.; Shioya, T.; Teramae, N. *New J. Chem.* **2002**, 26, 1102.

(3) (a) Hasenknopf, B.; Lehn, J.-M.; Kneisel, B. O.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed.* **1996**, 35, 1838. (b) Hasenknopf, B.; Lehn, J.-M.; Boumediene, N.; Dupont-Gervais, A.; Van Dorsselaer, A.; Kneisel, B.; Fenske, D. *J. Am. Chem. Soc.* **1997**, 119, 10956. (c) Fujita, M.; Nagao, S.; Ogura, K. *J. Am. Chem. Soc.* **1995**, 117, 1649. (d) Aoyagi, M.; Biradha, K.; Fujita, M. *J. Am. Chem. Soc.* **1999**, 121, 7457. For other recent examples, see: (e) Vilar, R.; Minges, D. M. P.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **1998**, 37, 1258. (f) Fleming, J. S.; Mann, K. L. V.; Carraz, J.-A.; Psillakis, E.; Jeffery, J. C.; McCleverty, J. A.; Ward, M. D. *Angew. Chem., Int. Ed.* **1998**, 37, 1279. (g) Campos-Fernández, C. S.; Clérac, R.; Dunbar, K. R. *Angew. Chem., Int. Ed.* **1999**, 38, 3477. (h) Campos-Fernández, C. S.; Clérac, R.; Koomen, J. M.; Russell, D. H.; Dunbar, K. R. *J. Am. Chem. Soc.* **2001**, 123, 773.

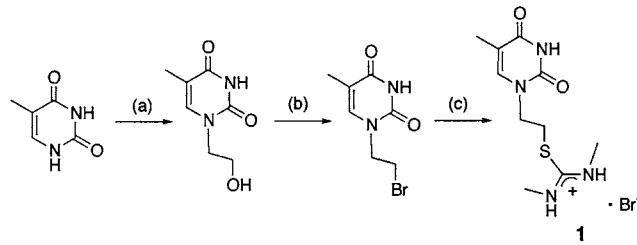
(4) For examples of anion-templated self-assembly in the absence of metal ions for the linking of building blocks: (a) Nishizawa, S.; Kato, Y.; Teramae, N. *J. Am. Chem. Soc.* **1999**, 121, 9463. (b) Lam, C.-K.; Mak, T. C. W. *Chem. Commun.* **2001**, 1568.

(5) For the synthesis of rotaxanes by anion complexation: Seel, C.; Vögtle, F. *Chem. Eur. J.* **2000**, 6, 21, and references therein.

should be suitable for fixing the structure of self-assembly organized by anion templation. Using light to trigger photoreactions has an advantage in the convenience of control for the reversible formation of a self-assembly, and it offers a novel approach to synthesizing supramolecular receptors that can be isolated without a templated anion. It is expected that this type of self-assembling receptor thus prepared is highly selective for the templated anion and can be used in various applications such as sensing and separation. Even though the methodological drawback concerning the purification process should be improved, it is important to show the new possibility of the templated-assisted synthesis of molecular architectures.

As the first step in the development of such a novel type of self-assembling receptor based on the anion-templated photochemical synthesis, we here report the effect of anion templation on the photodimerization of thymine-functionalized isothiouronium receptor **1** (cf. Scheme 1) in MeOH.

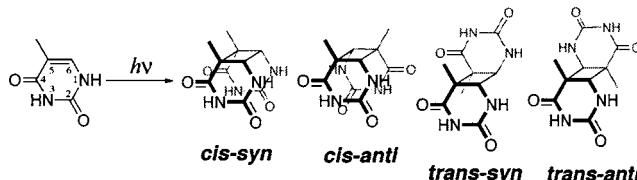
Scheme 1^a



^a Conditions: (a) ethylene carbonate, NaOH(trace), DMF; (b) CBr₄, PPh₃, THF; (c) dimethylthiourea, dry EtOH.

Receptor **1** is able to form the cyclobutane-type photodimer at the thymine moiety by UV irradiation (Scheme 2),⁸ while

Scheme 2



the isothiouronium moiety works as an oxoanion binding site via a two-point hydrogen-bonding motif.^{9,10} In the present

(6) The first templated photochemical synthesis of a uracil (neutral substrate) receptor has recently been reported: Bassani, D. M.; Sallenave, X.; Darcos, V.; Desvergne, J.-P. *Chem. Commun.* **2001**, 1446.

(7) Target molecule templation has been successfully utilized for the synthesis of molecular imprinted polymers (MIPs): (a) Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1812. (b) Kriz, D.; Ramstrom, O.; Mosbach, K. *Anal. Chem.* **1997**, 368, 345A. For other recent examples, see: (c) Matsui, J.; Higashi, M.; Takeuchi, T. *J. Am. Chem. Soc.* **2000**, 122, 5218. (d) Hishiya, T.; Asanuma, H.; Komiyama, M. *J. Am. Chem. Soc.* **2002**, 124, 570.

(8) Fisher, G. J.; Johns, H. E. In *Photochemistry and Photobiology of Nucleic Acids*; Wang, S.-Y., Ed.: Academic Press: New York, 1976; Vol. 1, Chapter 5.

study, the significant role of anion templation in the photodimer formation of **1** is demonstrated on the basis of the results obtained by UV-vis and ¹H NMR measurements.

Receptor **1** was synthesized in three steps starting from thymine (Scheme 1). The N-alkylation with ethylene carbonate and NaOH in DMF gave 1-(2-hydroxyethyl)thymine, and then the bromination was performed with CBr₄/PPh₃ in THF. The resulting 1-(2-bromoethyl)thymine was reacted with 1,3-dimethylthiourea in dry EtOH, giving **1** as a bromide salt.¹¹

As shown in Figure 1, receptor **1** has an absorption band at 267 nm ($\epsilon = 9.8 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$) in MeOH, and there

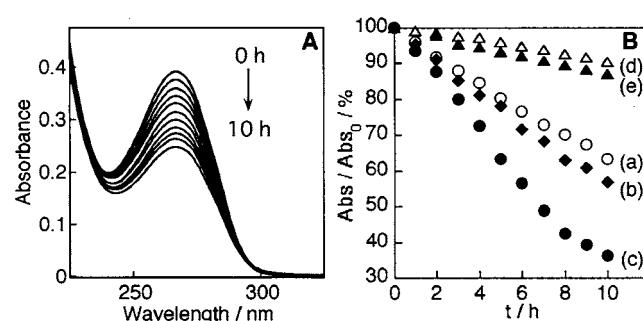


Figure 1. (A) UV-vis absorption spectra of **1** (0.4 mM) in MeOH during the continuous irradiation of monochromatized light at 270 nm. Cell length: 1 mm. (B) Time course of the absorbance ratio Abs/Abs₀ (%; Abs₀ and Abs are the absorbances before and after the UV irradiation at 270 nm, respectively) at 267 nm of **1** or 1-methylthymine in MeOH. (a) **1**; (b) **1** + KH₂PO₄; (c) **1** + K₄PPi (K₄P₂O₇); (d) 1-methylthymine; (e) 1-methylthymine + K₄PPi. [1] = [1-methylthymine] = 0.4 mM. [Anion] = 0.3 mM. 18-Crown-6 (4.0 mM) was added to dissolve K⁺ salts.

are no marked differences when compared with the spectrum of 1-methylthymine ($\lambda_{\text{max}} = 271 \text{ nm}$; $\epsilon = 9.3 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$). This indicates that there is no significant interaction between thymine and isothiouronium moieties in the ground state. Upon photoirradiation (excitation wavelength = 270 nm), a decrease in the absorbance at 267 nm is observed, indicating that the photodimerization does take place at the thymine moiety of **1**.⁸ Indeed, after photoirradiation for 20 h, new signals appear at 3.7 and 1.4 ppm in the ¹H NMR spectrum of **1**, which can be ascribed, respectively, to the C⁶-H and C⁵-CH₃ protons of the thymine moiety. As has been well demonstrated previously,⁸ this is a characteristic feature of the cyclobutane ring formation between two thymines.

(9) (a) Yeo, W.-S.; Hong, J.-I. *Tetrahedron Lett.* **1998**, 39, 3769. (b) Yeo, W.-S.; Hong, J.-I. *Tetrahedron Lett.* **1998**, 39, 8137. (c) Kubo, Y.; Tsukahara, M.; Ishihara, S.; Tokita, S. *Chem. Commun.* **2000**, 653. (d) Kubo, Y.; Ishihara, S.; Tsukahara, M.; Tokita, S. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1455.

(10) Nishizawa, S.; Cui, Y.-Y.; Minagawa, M.; Morita, K.; Kato, Y.; Taniguchi, S.; Kato, R.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **2002**, 866.

(11) Identifying data for **1**: ¹H NMR (270 MHz, in DMSO-*d*₆) δ 11.37 (br, 1H, N³H), 9.12 (br, 2H, NH-CH₃), 7.54 (d, *J* = 1.4 Hz, 1H, C⁶H), 3.92 (t, *J* = 6.1 Hz, 2H, S-CH₂-), 3.54 (t, *J* = 6.1 Hz, 2H, ar-CH₂-), 2.94 (s, 3H, NH-CH₃), 2.85 (s, 3H, NH-CH₃), 1.75 (s, 3H, ar-CH₃); FAB-MS (*m/z*) 257 [M - Br]⁺.

Interestingly, receptor **1** can form the photodimer more easily than a control compound 1-methylthymine does (Figure 1B). While the decrease in the absorbance is only 10% for 1-methylthymine (curve d), the absorbance is reduced by as much as 40% for **1** (curve a) when the irradiation is performed for 10 h. It is well recognized that the triplet state is the precursor of virtually all of the thymine dimers formed in solutions below 1 mM, and thus triplet sensitizers such as acetone and acetophenone can accelerate the dimerization of thymine derivatives.⁸ In the present case, it seems likely that a heavy-atom effect from the bromide ion causes the efficiency of intersystem crossing from the singlet to the triplet state to be large.¹²

The effect of anions (H_2PO_4^- and $\text{P}_2\text{O}_7^{4-}$; PPi) on the photodimerization of **1** was examined in MeOH (Figure 1B). For comparison, the control compound, 1-methylthymine, which has no anion binding sites, was also examined. As shown in curve b, the decrease in the absorbance at 267 nm of **1** is somewhat larger in the presence of H_2PO_4^- than in the absence of anions (curve a), indicating that H_2PO_4^- has only a small effect on the photodimerization. By contrast, a significant decrease in the absorbance of **1** is observed for PPi. In the presence of PPi (curve c), the absorbance at 267 nm decreases to 36% (photoirradiation time = 10 h), which corresponds to approximately half the value observed in the free receptor (63%, curve a). Obviously, the photodimerization of **1** is accelerated in the presence of PPi. Since a slight effect by PPi on the photodimerization is observed for 1-methylthymine (curves d and e), the binding of PPi at the isothiouronium moiety of **1** should be responsible for the acceleration of the photodimer formation.

^1H NMR binding studies indicate that the contrast in effects of H_2PO_4^- and PPi reflects the large differences in the binding affinity with receptor **1**. In the case of H_2PO_4^- , no obvious changes are observed in ^1H NMR spectra of **1**, indicating a low stability of the complex between H_2PO_4^- and **1** in $\text{MeOH}-d_4$.¹³ On the other hand, addition of PPi results in remarkable changes in ^1H NMR spectra of **1**, indicating that **1** can bind PPi in $\text{MeOH}-d_4$. As shown in Figure 2, the chemical shifts of the C^5-CH_3 and $\text{S}-\text{CH}_2-$ protons in the presence of 1.08 mM PPi (spectrum e) are smaller by 0.015 and 0.192 ppm, respectively, than in free **1** (spectrum a), while a downfield shift by 0.022 ppm is observed for the C^6-H proton. Furthermore, as indicated by the open circles, appearance of new signals is observed at the PPi concentrations below 0.90 mM (spectrum b–d). These three signals can be assigned to C^6-H , $\text{S}-\text{CH}_2-$, and C^5-CH_3 on the basis of $^1\text{H}-^1\text{H}$ COSY measurements. Receptor **1** thus shows two sets of NMR signals, which are distinguished on the NMR time scale, upon the complexation with PPi. The integrated intensities of these new signals increase and reach the maximum at the PPi concentration of approximately 0.5 equiv relative to the receptor concentra-

(12) For a report on the heavy-atom effect of the bromide on intersystem crossing: (a) Plummer, B. F.; Singleton, S. F. *J. Phys. Chem.* **1989**, *93*, 5515. (b) Gunnlaugsson, T.; Bichell, B.; Nolan, C. *Tetrahedron Lett.* **2002**, *43*, 4989.

(13) Similar results were recently obtained in the binding of H_2PO_4^- with a naphthalene-functionalized monoisothiouronium receptor.¹⁰

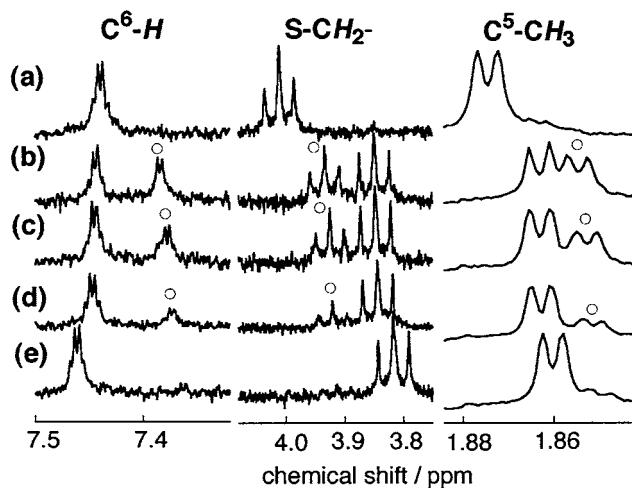
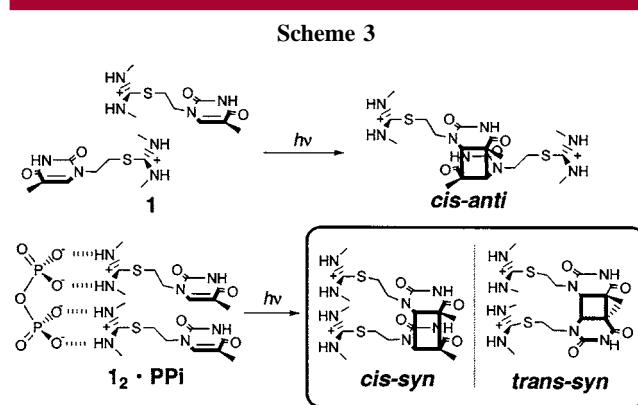


Figure 2. ^1H NMR spectra of **1** (0.80 mM) in $\text{MeOH}-d_4$ in the presence of (a) 0 mM, (b) 0.36 mM, (c) 0.45 mM, (d) 0.54 mM, and (e) 1.08 mM of TBAPPi ($\text{TBA}_4\text{P}_2\text{O}_7$; tetrabutylammonium pyrophosphate).

tion; this increase is accompanied by decreased intensities of the original signals. The reverse change is observed upon further addition of PPi, and the new signals completely disappear in the presence of excess PPi. These results strongly indicate that two kinds of complexes are formed between **1** and PPi, 1:1 and 2:1 host-to-guest complexes. Therefore, the PPi-induced acceleration of the photodimerization of **1** is due to the formation of the 2:1 complex, where two thymine moieties are oriented so as to place an excited thymine in proximity to another thymine with the correct orientation for photochemical reactions (cf. Scheme 3). For



such a stacked ground-state dimer, the photodimer might arise from the singlet as well as the triplet state as in the case of aggregates of thymine, giving the higher overall quantum yield for photodimer formation. Indeed, in accordance with the above consideration, the effect of PPi on the photodimer structure of **1** is significant.

As shown in Scheme 2, there are four isomeric photodimers of thymine, i.e., cis-syn, trans-syn, cis-anti, and

trans-anti. These isomers can be distinguished by the order in the chemical shifts of the C^5-CH_3 protons; the chemical shift of the C^5-CH_3 of the thymine photodimer is larger in the order of cis-anti > cis-syn > trans-anti > trans-syn.¹⁴ The structures of photodimers of **1** were therefore assigned on the basis of the chemical shifts of the C^5-CH_3 protons (Figure 3).

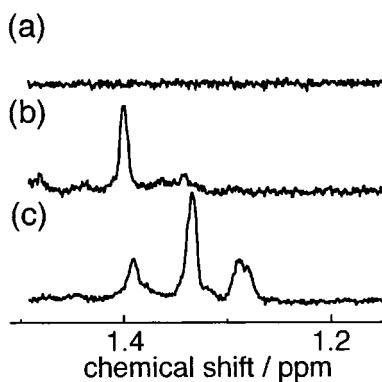


Figure 3. ^1H NMR spectra of **1** (0.8 mM) in D_2O in the C^5-CH_3 proton region; (a) before photoirradiation; (b): after photoirradiation in the absence of anion templates; (c): after photoirradiation in the presence of 0.6 mM of K_4PPi ($\text{K}_4\text{P}_2\text{O}_7$).

In the absence of PPi, the photodimer of **1** shows only one signal at 1.40 ppm (spectrum b in Figure 3), which can be assigned to a cis-anti-type photodimer where the isothiouronium moieties are oriented in the opposite direction as illustrated in Scheme 3. The preferential formation of the anti-type photodimer, such as found in 1-(2-carboxyethyl)-thymine,^{14c} is explained by the charge repulsion between the positively charged binding sites. On the other hand, the

(14) (a) Kita, Y.; Inaki, Y.; Takemoto, K. *J. Polym. Sci. Polym. Chem. Ed.* **1980**, *18*, 427. (b) Cadet, J.; Voituriez, L.; Hruska, F. E.; Kan, L.-S.; de Leeuw, F. A. A. M.; Altona, C. *Can. J. Chem.* **1985**, *63*, 2861. (c) Moghaddam, M. J.; Hozumi, S.; Inaki, Y.; Takemoto, K. *J. Polym. Sci. Polym. Chem. Ed.* **1987**, *26*, 3297.

presence of PPi results in the predominant formation of syn-type (cis-syn and trans-syn) photodimer (spectrum c in Figure 3), where the binding sites are oriented in the same direction; the distribution of the photoproducts is in the order of cis-syn (55%; 1.33 ppm) > trans-syn (25%; 1.29 ppm),¹⁵ cis-anti (20%; 1.39 ppm). In the presence of a large excess of PPi where a 1:1 complex is predominant, such a preferential formation of the syn-type photodimer is not observed (cis-anti, 48%; cis-syn, 52%). It is highly evident that PPi does work as a template to organize the binding sites of receptor **1**, as schematically illustrated in Scheme 3.

In summary, we have shown that anion templation can be utilized to control the photodimer structure of **1**. While only the formation of the anti-type photodimer was observed in the case of the free receptor, the presence of PPi resulted in the preferential formation of the syn-type photodimer, which would be desirable for recognizing the templated PPi. Even though the present system demonstrated here is very simple, the anion-templated photochemical synthesis would offer a novel approach for constructing more sophisticated self-assembling receptors; such work is now in progress in our laboratory.

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Supporting Information Available: $^1\text{H}-^1\text{H}$ COSY spectrum of **1** upon addition of PPi. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) A control experiment revealed that 1-methylthymine gave mainly three types of photodimers (cis-anti, 39%; cis-syn, 29%; trans-anti, 5%; trans-syn, 27%) in MeOH. The signal at 1.29 ppm was therefore assigned to trans-syn not to trans-anti.