Novel Photoadditions Involving 1,4-Transfer of Cyano Group. Photoreaction of 6-Cyanouracils with Alkenes and Alkynes[1]

Isao Saito,* Koji Shimozono, and Teruo Matsuura

Contribution from the Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606, Japan. *Received July 30, 1982*

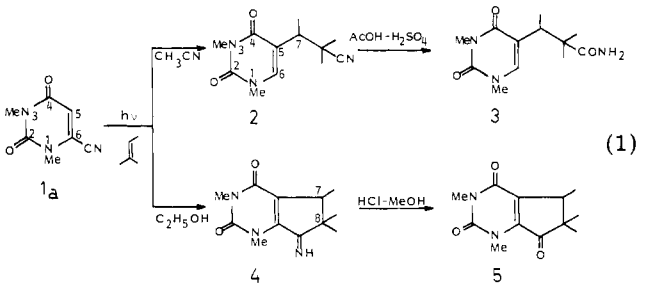
Abstract: A novel photoaddition of 6-cyano-1,3-dimethyluracil (**1a**) to olefins involving 1,4-transfer of a cyano group has been described. Irradiation of **1a** with 2-methyl-2-butene in acetonitrile gave 1,2,3,4-tetrahydro-α,α,β,1,3-pentamethyl-2,4-dioxo-5-pyrimidinepropanenitrile (**2**) as a sole isolable product. Similarly, irradiation of **1a** and cyclopentene afforded 2-(1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)cyclopentanecarbonitrile (**6a**) but in competition with the formation of the corresponding [2 + 2] cycloadduct **7a**, whereas the same irradiation in protic solvents gave [3 + 2] cycloadduct **8b** together with **7a**. The yield of **6a** and **8b** increased at the expense of [2 + 2] cycloadduct **7a** as the reaction temperature was raised. Labeling experiments using C-5-deuterated compound established that 1,2-deuterium shift and C-5 deuterium loss occur competitively during the course of cyano migration. Involvement of carbene intermediate as a precursor of **6a** was suggested by the labeling experiments and the trapping reaction with 1-propanethiol. On the basis of these experimental observations, mechanistic aspects of the photoaddition are discussed. Synthetic applications of this novel photoaddition were also described. Thus, irradiation of 6-cyanouracil derivatives in the presence of alkenes or alkynes gave the corresponding 5-substituted uracils in one step, providing a useful synthetic route to 5-substituted uracil and uridine derivatives.

Photochemical cycloaddition involving 1,4-biradical intermediates has been the subject of a great number of synthetic and mechanistic investigations.[2] The major reactions generally observed in the photoreaction of cyclic enones with olefins are [2 + 2] cyclocyclization and the formation of ene products.[3] Anomalous photoadditions involving rearrangement of 1,4-biradical intermediates are rarely observed.[4] Recently, Agosta et al.[5] have demonstrated novel examples in which unusual photochemical transformations are promoted by thermal activations of intermediate biradicals in certain intramolecular photoadditions. In our studies to explore the chemical basis of photoinduced nucleic acid–protein cross-links,[6] we encountered an interesting observation that 6-cyanouracil derivatives undergo anomalous photoaddition with alkenes resulting in 1,4-transfer of cyano group or the formation of [3 + 2] cycloadducts by interception of biradical intermediates by the cyano groups in competition with normal [2 + 2] cyclocyclization.[7] These photochemical transformations showed a striking dependency on reaction temperature and solvent, thus providing an interesting mechanistic probe on diverse modes of reaction of biradical intermediates. It has been observed that this novel type of [3 + 2] photocyclization can occur in several other cyano-substituted chromophores such as 2-cyanopyridine,[8] 3-cyanocyclohexenone[9] and 2-cyanochromone.[10] The present reaction also offers a useful synthetic method for appending functionalized carbon chains to the C-5 positions of uracil and uridine derivatives, since irradiation of readily available 6-cyanouracil derivatives with alkenes and alkynes gave the corresponding 5-substituted uracils in one step.[7a]

In the present paper, we describe the details of mechanistic and synthetic aspects of this novel type of photoaddition. Previously, acetone-sensitized photoaddition of pyrimidine bases, including uracil and thymine, to olefins has been reported to give [2 + 2] cycloadducts with little regioselectivity.[11] Thereafter, Swenton et al.[12] have demonstrated a remarkable effect of α substituents in controlling the regioselectivity of the photoaddition of uracils and cycloalkenones to olefins. In our expectation of a more powerful effect of β-electron-withdrawing substituents,[3,13] we initiated the study of photoreaction of 6-cyano-1,3-dimethyluracil in the presence of olefins.

Results and Discussion

Photoaddition of 6-Cyano-1,3-dimethyluracil to Olefins. 6-Cyano-1,3-dimethyluracil (**1a**) is readily available from 5-bromo-1,3-dimethyluracil by treatment with potassium cyanide in dimethylformamide.[14] Irradiation of **1a** (λ_{max} 289 nm, log ϵ 3.89) with Pyrex-filtered light (>290 nm) in the presence of 2-methyl-2-butene (20-equiv excess) in acetonitrile at ambient temperature produced a single photoproduct, **2**, in 65% yield. No



(1)

other products such as cyclobutane-type adducts were detected

(1) Photoinduced Reactions. 145.
(2) Turro, N. J. "Modern Molecular Photochemistry"; Benjamin/Cummings: Menlo Park, CA, 1978; p 414.
(3) (a) Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50. (b) Bauslaugh, P. G. *Synthesis* **1970**, 287. (c) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. (d) Dilling, W. L. *Photochem. Photobiol.* **1977**, *25*, 605. (e) Kossanyi, J. *Pure Appl. Chem.* **1979**, *51*, 181. (f) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559 and references therein.
(4) For recent examples of anomalous photoadditions, see: (a) Barany, F.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1946. (b) Wagner, P. J.; Lin, K-C.; Noguchi, Y. *Ibid.* **1981**, *103*, 3837. (c) Hussain, S.; Agosta, W. C. *Tetrahedron* **1981**, *37*, 3301.
(5) Wolff, S.; Barany, F.; Agosta, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2378.
(6) (a) Saito, I.; Ito, S.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 2901. (b) Saito, I.; Ito, S.; Matsuura, T. *Tetrahedron Lett.* **1978**, 2585. (c) Ito, S.; Saito, I.; Nakata, A.; Matsuura, T. *Photochem. Photobiol.* **1980**, *32*, 683. (d) Ito, S.; Saito, I.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, *102*, 7535. (e) Saito, I.; Ito, S.; Matsuura, T.; Helene, C. *Photochem. Photobiol.* **1981**, *33*, 15. (f) Saito, I.; Sugiyama, H.; Ito, S.; Furukawa, N.; Matsuura, T. *J. Am. Chem. Soc.* **1981**, *103*, 1598. (g) Saito, I.; Sugiyama, H.; Furukawa, N.; Matsuura, T. *Tetrahedron Lett.* **1981**, *22*, 3265.
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(8) Saito, I.; Kanehira, K.; Shimozono, K.; Matsuura, T. *Tetrahedron Lett.* **1980**, *21*, 2737.
(9) Saito, I.; Shimozono, K.; Matsuura, T. *J. Org. Chem.* **1982**, *47*, 4356.
(10) Saito, I.; Shimozono, K.; Matsuura, T. *Tetrahedron Lett.* **1982**, *23*, 5439.
(11) Wexler, A. J.; Hyatt, J. A.; Roynold, P. W.; Cottrell, C.; Swenton, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 512 and references therein.
(12) (a) Wexler, A. J.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 1602. (b) Greenlee, M. L.; Fritzen, E. L., Jr.; Swenton, J. S. *J. Org. Chem.* **1978**, *43*, 4512. (c) Swenton, J. C.; Fritzen, E. L., Jr. *Tetrahedron Lett.* **1979**, 1951.
(13) For references to β-substituted enones, see: (a) Cantrell, T. S. *Tetrahedron* **1971**, *27*, 1227 and references therein. (b) Kaneko, C.; Shimomura, N. *Tetrahedron Lett.* **1982**, *23*, 2571.
(14) (a) Inoue, H.; Ueda, T. *Chem. Pharm. Bull.* **1971**, *19*, 1743. (b) Senda, S.; Hirota, K.; Asao, T. *J. Org. Chem.* **1975**, *40*, 353.

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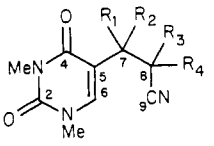
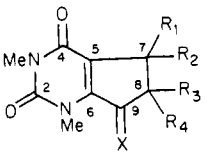
Table I. ^{13}C NMR Chemical Shifts (δ, $CDCl_3$) for the Photoproducts



2, $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$
6a, $R_1 = R_4 = H$; R_2-R_3 = -$(CH_2)_3$-

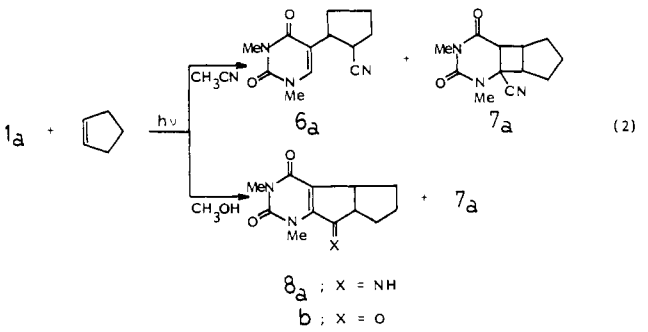


4, X = NH; $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$
5, X = O; $R_1 = H$; $R_2 = R_3 = R_4 = CH_3$
8b, X = O; $R_1 = R_4 = H$, R_2-R_3 = -$(CH_2)_3$-

	carbon							
compd	2	4	5	6	7	8	9	others
2	150.9 (s)	163.5 (s)	114.1 (s)	140.3 (d)	36.4 (d)	38.5 (s)	123.6 (s)	37.0, 28.1, 25.8, 25.1, 16.6
6a	151.2 (s)	163.1 (s)	111.1 (s)	139.4 (d)	34.0 (d)	40.4 (d)	121.0 (s)	36.8, 29.7, 27.7, 27.2, 22.2
4	152.8 (s)	161.2 (s)	126.5 (s)	144.3 (s)	42.2 (d)	46.8 (s)	186.0 (s)	31.3, 28.3, 28.0, 20.8, 15.1
5	152.1 (s)	161.3 (s)	133.8 (s)	141.1 (s)	40.5 (d)	48.7 (s)	205.2 (s)	30.0, 28.1, 26.6, 19.7, 14.8
8b	152.0 (s)	161.1 (s)	134.4 (s)	143.4 (s)	38.2 (d)	51.6 (d)	203.9 (s)	30.3, 29.7, 28.9, 28.2, 24.1

on TLC. The structure of **2** was assigned on the basis of spectral data and confirmed by converting it to amide **3**. The orientation of C-5 side chain is evident from the existence of allylic coupling (J = 0.5 Hz) between C-7 methine and C-6 olefinic protons in the ^1H NMR. Irradiation in benzene gave a similar result, but an entirely different product was obtained in the photoreaction in alcoholic solvents. Thus, irradiation of **1a** with 2-methyl-2-butene in ethanol gave rise to [3 + 2]-cycloadduct **4** as the sole isolable product in 80% yield. The imine **4** was readily converted to **5** by hydrolysis. The orientation of the adduct **4** was deduced from the ^{13}C NMR chemical shifts of C-8 (δ 46.8, s) and C-7 carbons (δ 42.2, d) in comparison with those of model compounds (Table I).

Irradiation of **1a** with other olefins under similar conditions gave the corresponding rearranged adducts but in competition with the formation of [2 + 2] cycloadducts. For example, irradiation of **1a** and cyclopentene in acetonitrile at room temperature produced **6a** (43%) and **7a** (26%), whereas [3 + 2]-cycloadduct **8b**, presumably formed via **8a**, was obtained as the major product together with a minor amount of **7a** upon irradiation in methanol.



(2)

8a ; X = NH
b ; X = O

The structures of these products were assigned on the basis of spectral data, including ^1H and ^{13}C NMR in a similar manner (Table I). The ring junction of the cyclobutane **7a** is presumed to be cis since no change in the ^1H NMR was observed upon treatment with base.[15] A similar type of anomalous photoaddition leading to 1,4-transfer of a cyano group has been observed in the photoadditions of **1a** with other olefins and alkynes (vide infra).

One of the most striking features of these unusual photoadditions is the remarkable temperature effect on the product ratio. Irradiation of **1a** and cyclopentene in acetone at −78 °C gave no **6a**; the cyclobutane **7a** was formed exclusively (Table II). The yield of rearranged adduct **6a** increased as the reaction temperature was raised. A paralleling temperature dependency has been observed in the formation of [3 + 2]-cycloadduct **8b** in the photoreaction of **1a** with cyclopentene in methanol, as indicated in Table II. These results suggest that **6a** and **8b** are derived from

(15) Corey, E. J.; Le Mahieu, R.; Bass, J. D.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

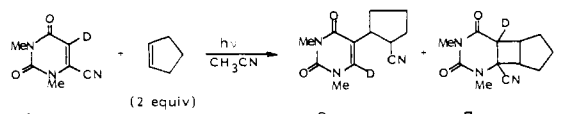
Table II. Product Distribution in the Photoreaction of 1a with Cyclopentene at Various Temperatures[a]

	product yield, %			
	in acetonitrile		in methanol	
temp, °C	6a[b]	7a[b]	8b[c]	7a[c]
−78	0	75[d]	8	72
−20	15	56		
0	39	39	41	28
18	43	26	50	20
65			77	5
81	81	0		

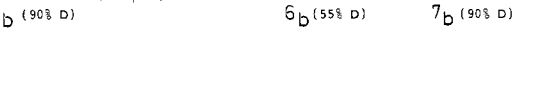
[a] [1a] = 10 mM, [cyclopentene] = 0.2 M. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Acetone was used as solvent.

a common intermediate. These photoadditions were sensitized by xanthone in acetonitrile at ambient temperature, and the products **6a** and **7a** were formed approximately in the same ratio upon sensitized and direct irradiations. Furthermore, addition of piperylene greatly retarded the rate of product formation but did not change the product ratio significantly. These observations indicate that all of the photoproducts (**6a**, **7a**, **8b**) are originated from the reaction of a single excited state of **1a**, most likely its lowest triplet state, with cyclopentene.

Deuterium-Labeling Experiments. In order to get further insight into the reaction mechanism of the cyano migration, we have carried out the photoreaction of 6-cyano-1,3-dimethyluracil-5-d_1 (**1b**)[14b] containing 90% deuterium at the C-5 position in the presence of cyclopentene in acetonitrile at ambient temperature. Irradiation of **1b** and 2 equiv of cyclopentene in a sealed tube produced **6b** (55% D) together with **7b** (90% D). However, a



(3)



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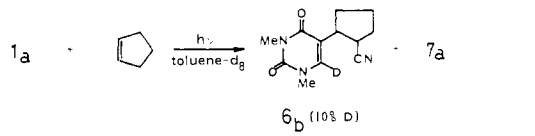


(5)

considerable amount of the deuterium was lost during the conversion to **6b**, with the deuterium of **7b** being completely retained

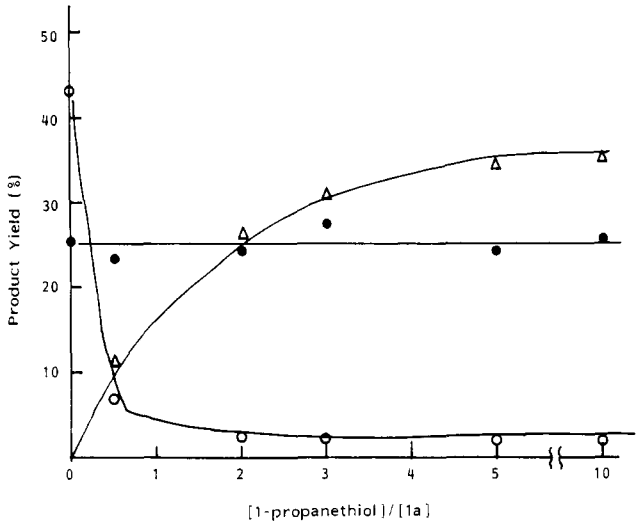
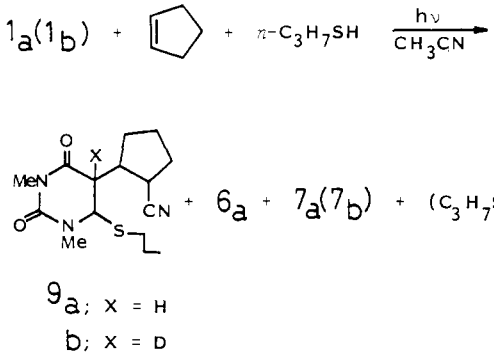


Figure 1. Dependence of the yields of **6a** (○), **7a** (●), and **9a** (△) on the concentration of 1-propanethiol. A mixture of **1a** (10 mM) and cyclopentene (50 mM) in acetonitrile was irradiated in the presence of different concentrations of 1-propanethiol.

on the C-5 position. Under these conditions, the deuterium of the recovered **1b** was not lost at all during this irradiation. Surprisingly, irradiation of **1b** in the presence of a large excess of cyclopentene (more than 20-equiv excess) in acetonitrile resulted in a complete loss of the deuterium in **6a** with the retention of the deuterium in cyclobutane **7b**. A similar result has been obtained in the photoreaction in carbon tetrachloride. These observations imply that a 1,2-deuterium shift and the process leading to deuterium loss occur competitively for the formation of **6b**. In the presence of large excess of cyclopentene as hydrogen donor, hydrogen abstraction by a radical intermediate and subsequent C-5 deuterium loss would occur to result in the formation **6a** having no deuterium. In support of this, irradiation of **1a** with cyclopentene (2 equiv) in toluene-d_8 afforded the C-6-deuterated product **6b** (10% D), indicating actual incorporation of the deuterium into the C-6 position of **6b** by deuterium abstraction of a radical intermediate from the solvent.

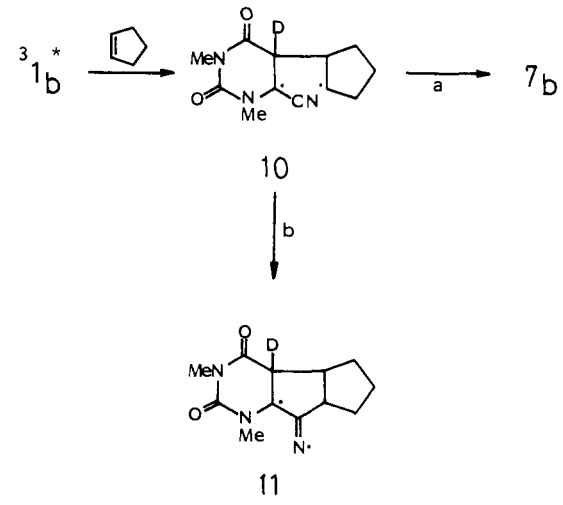
Trapping of the Intermediate with Mercaptan. In attempts to intercept the intermediate responsible for **6a**, we carried out the photoreaction of **1a** and cyclopentene (5 equiv) in the presence of excess 1-propanethiol. Irradiation in acetonitrile followed by chromatographic separation afforded **9a** together with **6a**, **7a**, and di-*n*-propyl disulfide. The structure of **9a** is obvious from its



(6)

spectral data and was confirmed by converting it to **6a** with conventional oxidation to sulfoxide followed by elimination. As shown in Figure 1, the yield of **9a** increased with increasing concentration of 1-propanethiol at the expense of **6a**, whereas the yield of cyclobutane **7a** was unchanged by addition of 1-propanethiol. Under these conditions, neither direct nor acetone-sensitized irradiation of **6a** in the presence of 1-propanethiol produced any detectable amount of **9a**. The result clearly indicates that the precursor of **6a** is intercepted by 1-propanethiol to result in the formation of **9a**. When the 5-deuterated compound **1b** was

Scheme I



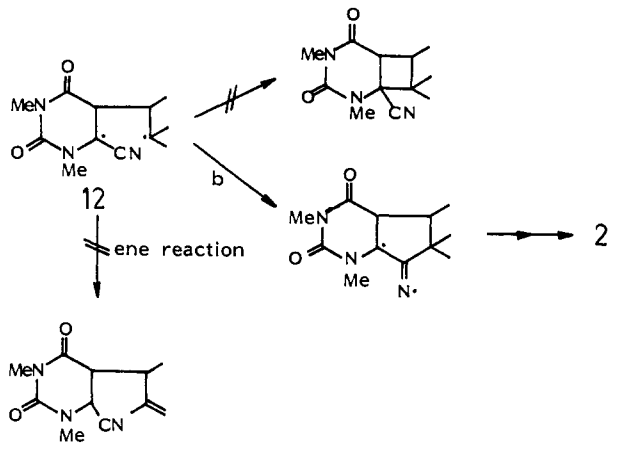
irradiated in the presence of cyclopentene and 1-propanethiol, the deuterium was completely retained on the C-5 position of **9b**: there was no indication of deuterium scrambling. These observations suggest that the process of deuterium loss observed in the photoaddition without mercaptan must occur after completion of the cyano migration.

Mechanistic Aspects. When the formation of unusual photoproducts **6a** and **8a** are being accounted for, the following experimental results should be taken into consideration: (i) All of the photoproducts (**6a**, **7a**, **8b**) originate from the reaction of triplet **1a** with cyclopentene. (ii) Formation of anomalous adducts such as **6a** and **8a** becomes predominant as the reaction temperature is raised. (iii) The loss of the C-5 deuterium competes with a 1,2-deuterium shift for the formation of the rearranged adduct **6b** from **1b**. (iv) Mercaptan can intercept the intermediate for **6a** but not for the cyclobutane **7a**. (v) C-5-deuterium loss must occur after completion of the cyano migration.

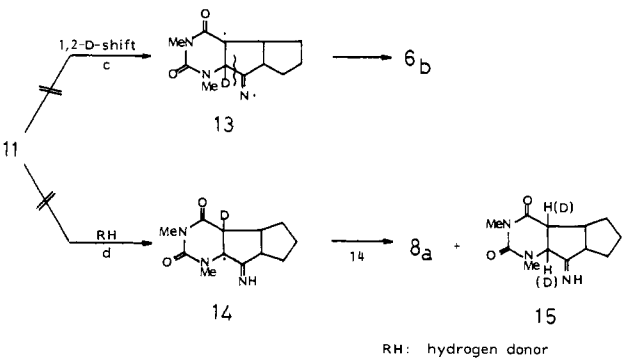
With these observations in mind, we propose the mechanism given in Scheme I, using an example of the reaction of deuterated compound **1b** and cyclopentene. The first step may involve formation of the triplet 1,4-biradical **10**, which is probably formed from collapse of the complex between triplet **1a** and cyclopentene as was proposed in the case of triplet uracils and olefins,[11] while lacking in direct evidence for triplet-exciplex formation. It is worthwhile to mention here that no ground-state charge-transfer-type interaction between **1a** and cyclopentene was observed, as evidenced by UV absorption spectra. The biradical **10** may then close to cyclobutane **7b** after spin inversion in the usual way (path a). While mercaptans proved to be excellent biradical scavengers,[16] the biradical **10** does not seem to be intercepted by 1-propanethiol in the present case, since addition of excess 1-propanethiol did not inhibit the cyclobutane formation. An alternative route for the reaction of biradical **10** is the cyclization at the carbon of the cyano group to furnish the five-membered-ring iminyl radical **11** (path b) as depicted in Scheme I. In the case of the more congested bis(tertiary) biradical derived from 2-methyl-2-butene and triplet **1b**, this process (path b) occurs exclusively because of the reluctance of two teritary radicals to couple on steric grounds. Notably, in none of these cases was the ene-type product observed. It has been pointed out that bis(tertiary) biradicals tend to prefer disproportionation rather than coupling.[17] In the present case, however, the urea moiety of the 1,4-biradical **12** would compel the six-membered ring to maintain its planarity so that **12** cannot achieve a proper conformation for disproportionation, as already pointed out by Swenton et al.[11] in the case of 5-substituted uracils. As a result of the rigidity of the ring

(16) For example, see: Enicinas, M. V.; Wagner, P. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 1357.
(17) (a) Schneider, R. A.; Meinwald, J. *J. Am. Chem. Soc.* **1967**, *89*, 2023. (b) Greenlee, M. L.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1978**, *43*, 4512.

Scheme II



Scheme III

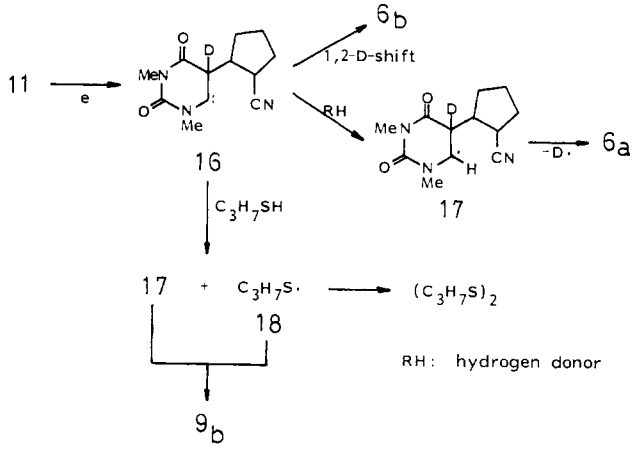


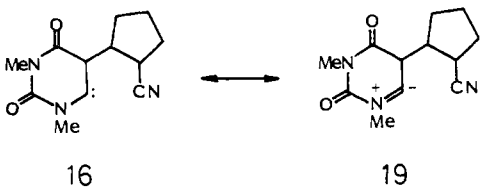
system coupled with the reluctance of two tertiary radicals to combine, only path b would be available for the reaction with 2-methyl-2-butene (Scheme II).

Raising the reaction temperature provides more activation energy for the formation of the iminyl radical species such as **11** and results in an increased yield of **6b** as observed with cyclopentene. In addition, conformational change of the 1,4-biradical **10** induced by increasing the temperature would also be responsible for the enhancement of **6a** at higher temperatures. A similar type of addition of alkyl monoradicals to cyano groups has reasonable precedents in free radical chemistry.[18] For example, cyclization of 4-cyanobutyl radical to cyclopentiminyl radical has been demonstrated to be temperature dependent.[19] Furthermore, a similar temperature-dependent photochemical transformation that can compete with [2 + 2] cycloaddition has previously been observed by Agosta and Wolff in the photorearrangement of geranonitrile at elevated temperatures.[5,20,21] We also noted a temperature-dependent [3 + 2] cycloaddition of 3-cyano-5,5-dimethyl-2-cyclohexenone to olefins that can compete with normal [2 + 2] cycloaddition.[9]

Once iminyl radical **11** is formed, at least three reaction paths are possible, as indicated in Schemes III and IV. Path c involves a 1,2-deuterium shift leading to the 1,4-biradical **13**, which may undergo β cleavage to give **6b**. However, this mechanism initially proposed[7a] cannot explain the observed complete loss of the deuterium in the presence of excess olefin and is inconsistent with the trapping experiments using mercaptan. Moreover, 1,2 hydrogen atom migration has no precedent in monoradicals in solution.[22] Path d involves hydrogen abstraction of iminyl radical **11** to give rise to monoradical **14**, which would be expected to undergo disproportionation leading to **8a** and **15**: this was not the case in acetonitrile, nor was a disproportionation product such as **15** detected in the reaction mixture. All of the experimental results are reasonably explained by the mechanism involving carbene **16** formed by α cleavage of the iminyl radical **11** (path e) as outlined in Scheme IV. Thus, hydrogen abstraction would compete with a 1,2-deuterium shift for carbene **16**. In the presence of a large excess of hydrogen donor, the former process becomes dominant, resulting in the formation of monoradical **17**, which subsequently loses D· to give undeuterated **6a**, whereas **6b** is formed by a 1,2-deuterium shift from **16** as was observed in the presence of 2 equiv of cyclopentene. In the presence of excess 1-propanethiol, carbene **16**, presumably in its triplet state, may abstract hydrogen from the mercaptan to result in the formation of monoradical **17** and thiyl radical **18**. Recombination of both radicals in the cage would furnish **9b**. In fact, the formation of di-*n*-butyl disulfide was observed as a result of the self-coupling of **18**. In this mechanism, the C-5 deuterium of **1b** is completely retained on the C-5 position of **9b**. The reactions of triplet carbenes with hydrogen donors are generally supposed to proceed through a hydrogen atom abstraction–recombination mechanism.[23,24] Alternatively, singlet carbene **16** may undero insertion into the S–H bond to lead directly to **9b** as a result of the facile singlet–triplet equilibration.[24] In none of these cases were observed cyclopropanation products with cyclopentene. This could also be explained by assuming that as the interaction of the nonbonded orbital of an adjacent nitrogen atom with the electron-deficient carbene p orbital as in **19** becomes significant, electrophilic attack of the carbene to the C–C double bond would be prevented, and hence hydrogen abstraction would become more favorable.[24]

Scheme IV





Solvent Effects. Another important feature of the photoreaction is the remarkable solvent effect on the product composition. In protic solvents, the formation of the rearranged product **6a** was

(18) (a) Kalvoda, J.; Botta, L. *Helv. Chim. Acta* **1972**, *55*, 356. (b) Kova, R. A.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6202. (c) Hawthorne, D. G.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1976**, *29*, 315. (d) Freeksen, R. W.; Pabat, W. E.; Raggio, M. C.; Sherman, S. A.; Wroble, R. R.; Watt, D. S. *J. Am. Chem. Soc.* **1977**, *99*, 1536.

(19) Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831.

(20) Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1978**, 43, 3627.

(21) For other examples of temperature-dependent anomalous photoreactions involving 1,4-biradicals, see: (a) Shimizu, N.; Ishikawa, M.; Ishikura, K.; Nishida, S. *J. Am. Chem. Soc.* **1974**, *96*, 6456. (b) Meyer, W.; Wendish, D.; Born, L.; Hartmann, W. *Chem. Ber.* **1981**, *114*, 1287.

(22) Beckwith, A. L. J.; Ingold, K. U. "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, p 253.

(23) For example: (a) Jones, M., Jr.; Baron, W. J.; Shen, Y. H. *J. Am. Chem. Soc.* **1970**, *92*, 4745. (b) Bethell, D.; Whittaker, D.; Callister, J. D. *J. Chem. Soc. B* **1969**, 749.

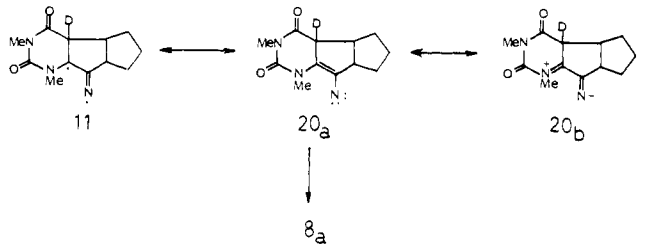
(24) For reviews, see: (a) Kirmse, W. "Carbene Chemistry", 2nd ed.; Academic Press: New York, 1971. (b) Moss, R. A., Jones, M., Eds. "Carbenes"; Wiley: New York, 1973, Vol. I; 1975, Vol. II.

Table III. Solvent Effect on the Photoreaction of **1a** with Cyclopentene[a]

solvent	product yield, % 6a[b]	7a[b]	8b[c]
CH_3CN	43	26	0
CH_3CN-CH_3COOH[d]	0	20	41
C_6H_6	35	20	0
$(C_2H_5)_2O$	30	25	0
CH_3OH	0	20	50
C_2H_5OH	0	23	51
CH_3OH-$(HOCH_2)_2$ (7:3)	0	10	25
CH_3CN-CH_3OH (19:1)	0	25	38

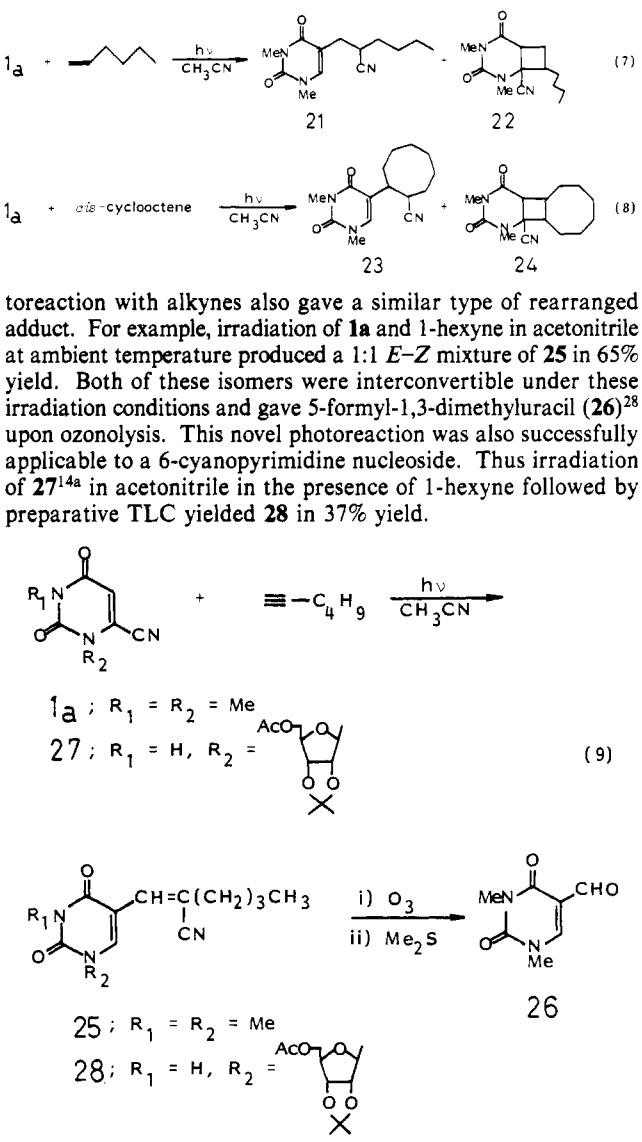
[a] [**1a**] = 10 mM, [cyclopentene] = 0.2 M. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] 10 equiv with respect to **1a**.

Scheme V



completely inhibited, and the [3 + 2]-cycloadduct **8b** was formed as the major product, with the yield of cyclobutane **7a** being unchanged. Hydrogen-donating ability of the solvents does not seem to play a major role in the formation of **8b** since addition of a large excess of 1-propanethiol, a good hydrogen donor, to the reaction system in acetonitrile never produced **8b** as mentioned earlier. In contrast, addition of a small amount of acetic acid dramatically changed the reaction mode; i.e., irradiation of **1a** and cyclopentene in acetonitrile containing acetic acid (10 equiv with respect to **1a**) gave **8b** as the major product (Table III). This strongly suggests that [3 + 2]-cycloadduct **8b** is formed by a proton-assisted reaction from the precursor of **6a**. A plausible mechanism that accounts for the formation of **8a** may involve nitrene intermediate **20a**, as indicated in Scheme V. Thus the 1,3-biradical **11**, when the unpaired spin becomes paired by spin inversion, would exist as resonance form **20a**, more favorable in protic solvents. Tautomerization of **20a** would immediately give **8a**. Since the vinyl nitrene **20a** should have a polar character owing to the contribution of the dipolar resonance form **20b**, a protic solvent such as methanol would probably accelerate this transformation. This might be the reason why carbene **16** is not formed in methanol. An alternative mechanism involving hydrogen abstraction of the iminyl radical **11** (Scheme III) cannot explain the observed solvent effect, although such a process probably exists in other systems.[9,19,25] Interestingly, this type of [3 + 2] photoannelation has been observed in the photoreaction of other cyano-substituted substrates such as 2-cyanopyridine,[8] 3-cyanocyclohexenone[9] and 2-cyanochromone[10] in the presence of olefins.

Synthetic Application. Considerable efforts have been made for the synthesis of 5-substituted pyrimidines owing to their potential biological activities.[26] In particular, the direct method for carbon–carbon bond formation at the C-5 position has attracted much attention as a route to C-5-substituted pyrimidine nucleosides.[27] From the synthetic standpoint, the present photoreactions provide a convenient, new method for appending a functionalized carbon chain of arbitrary length at the C-5 position of the uracil nucleus. Irradiation of **1a** with 1-hexene and *cis*-cyclooctene in acetonitrile gave **21** and **23** in 42% and 52% yields together with the corresponding cyclobutanes **22** and **24**, respectively. Photoreaction with alkynes also gave a similar type of rearranged adduct. For example, irradiation of **1a** and 1-hexyne in acetonitrile at ambient temperature produced a 1:1 *E*–*Z* mixture of **25** in 65% yield. Both of these isomers were interconvertible under these irradiation conditions and gave 5-formyl-1,3-dimethyluracil (**26**)[28] upon ozonolysis. This novel photoreaction was also successfully applicable to a 6-cyanopyrimidine nucleoside. Thus irradiation of **27**[14a] in acetonitrile in the presence of 1-hexyne followed by preparative TLC yielded **28** in 37% yield.



In summary, we have found a new photoaddition of 6-cyanouracils to alkenes and alkynes resulting in 1,4-transfer of a cyano group or the formation of [3 + 2] cycloadducts in competition with normal [2 + 2] cyclocyclization. The present photoreaction is unique in that the reaction course can be controlled by solvent and temperature. The carbene mechanism for the 1,4-transfer of a cyano group is proposed on the basis of labeling and trapping experiments. The present photoreaction also provides a useful synthetic route to C-5-functionalized uracil derivatives of potential biological interest. Finally, we would like to suggest that if congested triplet 1,4-biradicals are formed as intermediates and sufficient thermal activation is provided, interception of the biradicals by adjacent cyano groups would occur more generally in the photoaddition of α,β-unsaturated nitriles to olefins.

Experimental Section

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured on Varian HA-100 and FT-80A spectrometers, respectively, with Me_4Si as internal standard. Ultraviolet spectra were obtained on a Shimadzu UV-200 spectrophotometer. All irradiations were performed with a 100-W high-pressure mercury lamp surrounded by a Pyrex cooling jacket under a nitrogen atmosphere unless otherwise noted. For irradiation at high temperatures, a reaction vessel fitted with a reflux condenser

(25) Forrester, R. A.; Russell, M. G.; Napier, R. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 632.

(26) For reviews, see: (a) Bradshaw, T. K.; Hutchinson, D. W. *Chem. Soc. Rev.* **1977**, *6*, 43. (b) DeClerq, E.; Torrence, P. E. *J. Carbohydr., Nucleosides, Nucleotides* **1978**, *5*, 187.

(27) (a) Bigge, C. F.; Kalaritis, P.; Deck, J. R.; Mertes, M. P. *J. Am. Chem. Soc.* **1980**, *102*, 2033. (b) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, *22*, 421. (c) Bergstrom, D. E.; Ruth, M. J.; Warwick, P. *J. Org. Chem.* **1981**, *46*, 1432 and references therein.

(28) Alcântara, R.; Wang, S. Y. *Photochem. Photobiol.* **1965**, *4*, 465.

and a heating jacket was used. In the case of low-temperature irradiation, the reaction vessel was cooled in a dry ice–methanol bath (−78 °C) or ice–ethanol bath (−20 °C). Column chromatography and preparative TLC were carried out on Wako silica gel C-200 and Merck 60 PF_{254}, respectively. Elemental analyses were performed at the Analytical Center of Kyoto University and agreed with calculated values to within ±0.4%.

6-Cyanouracil derivatives were prepared according to literature procedure.[14] 6-Cyano-1,3-dimethyluracil (**1a**) (mp 138–140 °C (lit.[14b] mp 138–140 °C); UV (CH_3CN) 289 nm (log ε 3.89)); 6-cyano-1,3-dimethyluracil-5-d_1 (**1b**)[14b] (mp 137–139 °C; ^1H NMR ($CDCl_3$) δ 3.38 (s, 3 H), 3.60 (s, 3 H); mass spectrum, *m/e* (rel intensity) 166 (M^+, 100), 165 (9), 109 (70), 81 (67), deuterium content 90%); 5′-*O*-acetyl-6-cyano-2′,3′-*O*-isopropylideneuridine (**27**)[14a] white powder, mp 59–65 °C; UV (EtOH) 281 nm (log ε 3.93).

Photoaddition of 6-Cyano-1,3-dimethyluracil (1a) to 2-Methyl-2-butene in Acetonitrile. A solution of **1a** (165 mg, 1 mmol) and 2-methyl-2-butene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions described above for 10 h at room temperature. TLC analysis showed complete disappearance of **1a** and the formation of a single product. After evaporation of the solvent, the oily residue (270 mg) was subjected to preparative TLC (chloroform–ethyl acetate (3:1)) to yield a white powder (163 mg, 65%). Recrystallization from ether–hexane gave an analytically pure sample.

1,2,3,4-Tetrahydro-α,α,β,1,3-pentamethyl-2,4-dioxo-5-pyrimidinepropanenitrile (2): mp 119–120 °C; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.32 (d, 3 H, *J* = 7.2 Hz), 1.46 (s, 3 H), 3.16 (dd, 1 H, *J* = 7.2, 0.5 Hz), 3.36 (s, 3 H), 3.44 (s, 3 H), 7.32 (d, 1 H, *J* = 0.5 Hz); UV (CH_3CN) 271 nm (log ε 3.90); mass spectrum, *m/e* (rel intensity) 235 (M^+, 4), 167 (100), 110 (76), 69 (24); IR (KBr) 2220, 1695, 1655, 1640 cm^{-1}. Anal. ($C_{12}H_{17}N_3O_2$): C, H, N.

Conversion of 2 to 3. A solution of **2** (350 mg, 1.48 mmol) in 10 mL of acetic acid was treated with 17 mL of 40% sulfuric acid, and the solution was warmed on a water bath at 70 °C for 4 h. After neutralization with aqueous NaOH, the reaction mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and then filtered off. Evaporation of the solvent followed by preparative TLC (chloroform–ethyl acetate (3:1)) gave amide **3** (210 mg, 60%) as white powder.

1,2,3,4-Tetrahydro-α,α,β,1,3-pentamethyl-2,4-dioxo-5-pyrimidinepropanamide (3): mp 172–175 °C (from ether–hexane); ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.19 (s, 3 H), 1.20 (d, 3 H, *J* = 7.5 Hz), 3.31 (q, 1 H, *J* = 7.5 Hz, partially obscured), 3.34 (s, 3 H), 3.40 (s, 3 H), 6.00 (br, 2 H, NH_2), 7.11 (s, 1 H); UV (CH_3CN) 272 nm (log ε 3.94); mass spectrum, *m/e* (rel intensity) 253 (M^+, 3), 236 (3), 181 (17), 167 (100), 110 (70); IR (Nujol) 3420, 1700, 1650, 1620 cm^{-1}. Anal. ($C_{12}H_{19}N_3O_3$): C, H, N.

Photoaddition of 1a to 2-Methyl-2-butene in Ethanol. A solution of **1a** (165 mg, 1 mmol) and 2-methyl-2-butene (1.40 g, 20 mmol) in ethanol (100 mL) was irradiated under the standard conditions for 10 h at ambient temperature. TLC analysis showed complete disappearance of **1a** and the formation of a single product. After removal of the solvent, the oily residue was purified by preparative TLC (hexane–ethyl acetate (3:1)) to give a colorless oil (190 mg, 80%), which solidified on standing at room temperature. Recrystallization from acetone–hexane gave an analytically pure **4**.

6,7-Dihydro-7-imino-1,3,5,6,6-pentamethyl-1*H*-cyclopentapyrimidine-2,4(3*H*,5*H*)-dione (4): mp 119–120 °C; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.15 (s, 3 H), 1.21 (d, 3 H, *J* = 7 Hz), 2.82 (q, 1 H, *J* = 7 Hz), 3.36 (s, 3 H), 3.82 (s, 3 H), 9.90 (br, 1 H, NH); UV (CH_3CN) 306 nm (log ε 3.88); mass spectrum, *m/e* (rel intensity) 235 (M^+, 50), 220 (70), 178 (80), 163 (88), 149 (48), 135 (90), 28 (100); IR (KBr) 3250, 1710, 1696, 1660, 1640 cm^{-1}. Anal. ($C_{12}H_{17}N_3O_2$): C, H, N.

Hydrolysis of 4 to 5. To a solution of **4** (235 mg) in methanol (5 mL) was added 1 N HCl (2 mL) in one portion, and the mixture was allowed to stand at room temperature for 10 min. Evaporation of the solvent left a white mass (240 mg). Recrystallization from ether–hexane afforded colorless plates (210 mg, 90%).

6,7-Dihydro-1,3,5,6,6-pentamethyl-1*H*-cyclopentapyrimidine-2,4,7-(3*H*,5*H*)-trione (5): mp 71.5–74 °C; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3 H), 1.21 (s, 3 H), 1.29 (d, 3 H, *J* = 7.6 Hz), 2.94 (q, 1 H, *J* = 7.6 Hz), 3.40 (s, 3 H), 3.70 (s, 3 H); UV (CH_3CN) 311 (log ε 3.83), 247 nm (3.12); mass spectrum, *m/e* (rel intensity) 236 (M^+, 50), 221 (70), 193 (50), 163 (25), 136 (40), 28 (100); IR (Nujol) 1710, 1655 cm^{-1}. Anal. ($C_{12}H_{16}N_2O_3$): C, H, N.

Photoaddition of 1a to Cyclopentene in Acetonitrile. A. At 18 °C. A solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions described above at ambient temperature (18 °C) for 10 h. TLC analysis showed complete disappearance of **1a** and the formation of two products. After removal of the solvent in vacuo, the oily residue was purified by preparative TLC (chloroform–ethyl acetate (5:1)) to afford **6a** (100 mg, 43%) and **7a** (60 mg, 25%).

2-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)cyclopentanecarbonitrile (6a): mp 137–138 °C (from acetone–hexane); ^1H NMR ($CDCl_3$) δ 1.80–2.18 (m, 6 H), 3.08–3.22 (m, 1 H), 3.36 (s, 3 H), 3.42 (s, 3 H), 3.40–3.60 (m, 1 H), 7.15 (d, 1 H, *J* = 1 Hz); UV (CH_3CN) 269 nm (log ε 3.91); mass spectrum, *m/e* (rel intensity) 233 (M^+, 27), 206 (28), 180 (50), 165 (28), 28 (100); IR (Nujol) 2230, 1700, 1660, 1635 cm^{-1}. Anal. ($C_{12}H_{15}N_3O_2$): C, H, N.

Cyclobutane **7a** contains a small amount of a stereoisomer as impurity. Fractional recrystallization from hexane–ethyl acetate gave analytically pure **7a**.

Decahydro-1,3-dimethyl-2,4-dioxo-7b*H*-cyclopenta[3,4]cyclobuta[1,2-*d*]pyrimidine-7b-carbonitrile (7a): mp 89–90 °C; ^1H NMR ($CDCl_3$) δ 1.60–2.20 (m, 6 H), 2.80–2.94 (m, 1 H), 3.02 (s, 3 H), 3.08 (br d, 1 H, *J* = 6 Hz), 3.20 (br s, 1 H), 3.22 (s, 3 H); mass spectrum, *m/e* (rel intensity) 166 (M^+ − 67, 100), 68 (22), 67 (23), IR (Nujol) 2220, 1710, 1660 cm^{-1}. Anal. ($C_{12}H_{15}N_3O_2$): C, H, N.

B. At −78 °C. A Pyrex reaction vessel containing a solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetone (100 mL) was cooled to −78 °C in a dry ice–methanol bath. The sample was irradiated with a 400-W high-pressure mercury lamp placed at the center of the reaction vessel for 3 h. Care was taken to maintain the temperature at −78 °C during irradiation. After similar workup as described above, the oily residue was purified by preparative TLC to yield **7a** (175 mg, 75%).

C. At −20 °C. A Pyrex reaction vessel containing a solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was cooled to −20 °C in an ice–ethanol bath. A 400-W high-pressure mercury lamp, as described above was used to irradiate the sample for 3 h. After similar workup, the oily residue was purified by preparative TLC to give **6a** (35 mg, 15%) and **7a** (130 mg, 45%).

D. At 0 °C. A Pyrex reaction vessel containing a solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was cooled to 0 °C in an ice bath. Irradiation with a 100-W high-pressure mercury lamp was carried out for 10 h. During irradiation, the temperature was maintained at 0–2 °C. After similar workup, the oily residue was purified by preparative TLC to yield **6a** (90 mg, 39%) and **7a** (91 mg, 39%).

E. At 81 °C. A solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was heated at reflux. Irradiation as described above with a 400-W high-pressure mercury lamp was carried out for 3 h. After similar workup, the oily residue was purified by preparative TLC to yield **6a** (189 mg, 81%) together with considerable amounts of polymeric materials derived from cyclopentene.

Photoaddition of 1a to Cyclopentene in Methanol. A. At 18 °C. A solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry methanol (100 mL) was irradiated under the standard condition for 10 h at ambient temperature (18 ± 1 °C). Evaporation of the solvent in vacuo left a colorless viscous oil that solidified on standing at room temperature. TLC and ^1H NMR analyses of the crude reaction mixture revealed that it contained **7a** and a new adduct (**8b**) in a ratio of 2:5. However, it was impossible to separate these two compounds by column chromatography or preparative TLC. Fractional recrystallization was repeated to afford **8b** in more than 95% purity, whose spectral properties allowed us to assign the structure. The yields were determined by ^1H NMR.

1,4b,5,6,7,7a-Hexahydro-1,3-dimethylpentaleno[2,1-*d*]pyrimidine-2,4,8(3*H*)-trione (8b): mp 105–108 °C; ^1H NMR ($CDCl_3$) δ 1.40–2.10 (m, 6 H), 2.80–3.20 (m, 1 H), 3.38 (s, 3 H), 3.66 (s, 3 H), 3.40–3.60 (m, 1 H); UV (CH_3CN) 313 (log ε 3.82), 249 nm (3.27); mass spectrum, *m/e* (rel intensity) 234 (M^+, 90), 206 (67), 191 (25), 178 (77); IR (Nujol) 1700, 1660 cm^{-1}.

B. At −78 °C. A Pyrex reaction vessel containing a solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry methanol (100 mL) was cooled to −78 °C in a dry ice–methanol bath. Irradiation was made with a 400-W high-pressure mercury lamp placed at the center of the reaction vessel for 3 h. Care was taken to maintain the temperature at −78 °C during irradiation. After similar workup as described above, the oily residue was subjected to column chromatography to give a mixture (185 mg) of **7a** and **8b** in a ratio of 9:1 as determined by ^1H NMR.

C. At 0 °C. A Pyrex reaction vessel containing a solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry methanol (100 mL) was cooled to 0 °C in an ice bath. Irradiation was made with a 100-W high-pressure mercury lamp for 10 h. During irradiation, the temperature was maintained at 0–2 °C. After similar workup, the oily residue was purified by preparative TLC to afford a mixture (160 mg) of **7a** and **8b** in a ratio of 3:2 as determined by ^1H NMR.

D. At 65 °C. A solution of **1a** (165 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry methanol (100 mL) was heated at reflux. Irradiation was made with a 400-W high-pressure mercury lamp as described above for 3 h. After similar workup, the oily residue was purified by preparative TLC to give a mixture (191 mg) of **7a** and **8b** in a ratio of 1:15 as determined by ^{1}H NMR.

Photoaddition of 6-Cyano-1,3-dimethyluracil-5-d_1 (1b) to Cyclopentene. A. A solution of **1b** (166 mg, 1 mmol) and cyclopentene (1.40 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions for 10 h at ambient temperature. Products were isolated by preparative TLC in a similar manner to give **6a** and **7b**. ^{1}H NMR and mass spectra of the rearranged adduct were identical with those of **6a**. **7b**: mp 87–89 °C (from acetone); ^{1}H NMR ($CDCl_3$) δ 1.60–2.20 (m, 6 H), 2.80–2.94 (m, 1 H), 3.02 (s, 3 H), 3.08 (br s, 1 H), 3.22 (s, 3 H); mass spectrum, *m/e* (rel intensity) 167 ($M^+ - 67$), 68 (50).

B. A solution of **1b** (34 mg, 0.2 mmol) and cyclopentene (27 mg, 0.4 mmol) in dry acetonitrile (1 mL) in a sealed tube was irradiated externally at ambient temperature for 1 h. Products were isolated by preparative TLC as described before to give **6b** and **7b**. **6b**: ^{1}H NMR ($CDCl_3$) δ 1.80–2.18 (m, 6 H), 3.08–3.22 (m, 1 H), 3.36 (s, 3 H), 3.42 (s, 3 H), 3.50–3.60 (m, 1 H), 7.15 (s, ca. 0.5 H); mass spectrum, *m/e* (rel intensity) 234 (M^+, 11), 233 (9), 181 (25), 180 (22), 28 (100), deuterium content 55%.

C. A solution of **1a** (50 mg, 0.3 mmol) and cyclopentene (41 mg, 0.6 mmol) in toluene-d_8 (1 mL) in a sealed tube was irradiated externally at ambient temperature for 2 h. GLC analysis showed the existence of a trace amount of bibenzyl. Products were isolated by preparative TLC as described before to give **6b** and **7a**. **6b**: ^{1}H NMR ($CDCl_3$) δ 1.80–2.18 (m, 6 H), 3.08–3.22 (m, 1 H), 3.36 (s, 3 H), 3.42 (s, 3 H), 3.50–3.60 (m, 1 H), 7.15 (s, ca. 0.9 H); mass spectrum, *m/e* (rel intensity) 234 (M^+, 12), 233 (43), deuterium content 10%.

Solvent Effect on the Formation of 6a, 7a, and 8b. Solutions of **1a** (10 mM) and cyclopentene (0.02 M) in various solvents were irradiated with a 100-W high-pressure mercury lamp through a Pyrex filter for 10 h. In each run the photoproducts (**6a**, **7a**, and **8b**) were isolated by preparative TLC as described before. The results are shown in Table III.

Xanthone-Sensitized Photoaddition of 1a to Cyclopentene. A solution of **1a** (165 mg, 1 mmol), cyclopentene (1.4 g, 20 mmol), and xanthone (3.7 g, 18.8 mmol) in dry acetonitrile (100 mL) was irradiated with a 100-W high-pressure mercury lamp through a Pyrex filter at room temperature for 20 h. Under these conditions, more than 90% of the incident light was absorbed by the sensitizer. After removal of the solvent, the residue was subjected to column chromatography to remove xanthone. Successive preparative TLC (chloroform–ethyl acetate (3:1)) of the residue yielded **6a** (90 mg, 38%) and **7a** (38 mg, 16%) together with considerable amounts of polymeric materials. Essentially the same result was obtained when methanol was used as solvent.

Inhibitory Effect of Piperylene. A solution of **1a** (165 mg, 1 mmol), cyclopentene (1.40 g, 20 mmol), and piperylene (10 g, 0.147 mol) in dry acetonitrile (100 mL) was irradiated under the identical conditions as described before for 10 h at ambient temperature (18 °C). After removal of the solvent, the viscous oily residue was purified by preparative TLC to give unreacted **1a** (57 mg), **6a** (20 mg, 13%), and **7a** (10 mg, 6%) together with considerable amounts of polymeric materials.

Effect of Acetic Acid. A solution of **1a** (165 mg, 1 mmol), cyclopentene (1.40 g, 20 mmol), and acetic acid (0.7 g, 10 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions for 10 h. After removal of the solvent, the oily residue was purified by preparative TLC to yield a 1:2 mixture (145 mg) of **7a** and **8b** as determined by ^{1}H NMR.

Irradiation of 1a with Cyclopentene in the Presence of 1-Propanethiol. A solution of **1a** (165 mg, 1 mmol), cyclopentene (350 mg, 5 mmol), and 1-propanethiol (760 mg, 10 mmol) in dry acetonitrile (100 mL) was irradiated for 10 h at room temperature. TLC analysis showed complete disappearance of **1a**. Removal of the solvent in vacuo gave a yellow oil (960 mg). Column chromatography (silica gel, benzene) and successive preparative TLC (hexane–ethyl acetate (3:1)) yielded **7a** (59 mg, 25%), di-*n*-propyl disulfide (360 mg), and adduct **9a** (109 mg, 35%). Trituration of the adduct (**9a**) with water gave a white powder, which was recrystallized from ether–hexane.

5-(2-Cyanocyclopentyl)-6-(propylthio)-5,6-dihydro-1,3-dimethyluracil (9a): mp 103–104.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.5 Hz), 1.46–2.30 (m, 9 H), 2.58 (t, 2 H, J = 7.5 Hz), 2.90 (m, 1 H), 3.09 (dd, 1 H, J = 1.6, 10.5 Hz, partially obscured), 3.12 (s, 3 H), 3.19 (s, 3 H), 4.37 (d, 1 H, J = 1.6 Hz); mass spectrum, *m/e* (rel intensity) 233 ($M^+ - C_3H_7SH$, 66), 206 (69), 193 (37), 180 (100), 165 (94), 76 (80); IR (KBr) 2240, 1725, 1680 cm^{-1}. Anal. ($C_{15}H_{23}N_3O_2S$): C, H, N, S.

Conversion of 9a to 6a. To a solution of **9a** (10 mg, 0.032 mmol) in methanol (2 mL) was added $NaIO_4$ (35 mg, 0.16 mmol) in water (2 mL), and the mixture was stirred on a water bath (50 °C) for 1 h. White precipitate was filtered off, and the mixture was diluted with water and then extracted with ethyl acetate (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated to leave a colorless oil (5 mg), which solidified on standing at room temperature. The ^{1}H NMR and IR spectra were identical with those of **6a**.

Effect of *n*-Propyl Mercaptan on the Formation of 9a. Solutions of **1a** (10 mM) and cyclopentene (50 mM) in acetonitrile containing varying amounts of *n*-propyl mercaptan were irradiated with a 100-W high-pressure mercury lamp through a Pyrex filter for 10 h under identical conditions. In each run, the photoproducts (**6a**, **7a**, and **9a**) were isolated by preparative TLC. The results are shown in Figure 1.

Irradiation of 6-Cyano-1,3-dimethyluracil-5-d_1 (1b) with Cyclopentene in the Presence of 1-Propanethiol. A solution of **1b** (166 mg, 1 mmol), cyclopentene (350 mg, 5 mmol), and 1-propanethiol (760 mg, 10 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions as described before for 10 h at room temperature. After removal of the solvent, the oily residue was purified by a similar procedure to yield **7b** (55 mg, 23%), **9b** (85 mg, 27%), and a considerable amount of di-*n*-propyl disulfide. **9b**: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.5 Hz), 1.46–2.30 (m, 9 H), 2.58 (t, 2 H, J = 7.5 Hz), 2.90 (m, 1 H), 3.12 (s, 3 H), 3.19 (s, 3 H), 4.37 (s, 1 H).

Photoaddition of 1a to 1-Hexene. A solution of **1a** (165 mg, 1 mmol) and 1-hexene (1.70 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions for 10 h at room temperature. After removal of the solvent, the oily residue was purified by preparative TLC (ethyl acetate–hexane (3:1)) to yield **21** (105 mg, 42%) and **22** (99 mg, 40%).

α-Butyl-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinepropanenitrile (21): viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 6 Hz), 1.20–1.80 (m, 6 H), 2.12–3.00 (m, 3 H), 3.24 (s, 3 H), 3.36 (s, 3 H), 7.24 (s, 1 H); UV (CH_3CN) 270 nm (log ϵ 3.93); mass spectrum, *m/e* (rel intensity) 249 (M^+, 7), 207 (4), 154 (100), 119 (14), 97 (62); IR (neat) 2230, 1705, 1665, 1640 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_2$): C, H, N.

8-Butyl-2,4-dimethyl-3,5-dioxo-2,4-diazabicyclo[4.2.0]octane-1-carbonitrile (22): viscous oil; ^{1}H NMR (CCl_4) δ 0.97 (t, 3 H, 7 Hz), 1.20–2.85 (m, 7 H), 3.01 (s, 3 H), 3.14 (s, 3 H), 3.66 (dd, 1 H, M = 9.5, 10.5 Hz); IR (neat) 2225, 1700, 1665 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_2$): C, H, N.

Photoaddition of 1a to *cis*-Cyclooctene. A solution of **1a** (165 mg, 1 mmol) and *cis*-cyclooctene (2.20 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions as described before for 10 h at room temperature. After removal of the solvent, the oily residue was purified by preparative TLC (ethyl acetate–hexane (3:1)) to yield **23** (143 mg, 52%) and **24** (97 mg, 35%).

2-(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)cyclooctanecarbonitrile (23): mp 105–112 °C (ether–hexane): ^{1}H NMR ($CDCl_3$) δ 1.30–2.20 (m, 12 H), 2.90–3.30 (m, 2 H), 3.30 (s, 3 H), 3.36 (s, 3 H), 7.06 (s, 1 H); UV (CH_3CN) 260 nm (log ϵ 3.91); IR (Nujol) 2230, 1700, 1665 cm^{-1}. Anal. ($C_{15}H_{21}N_3O_2$): C, H, N.

Dodecahydro-1,3-dimethyl-2,4-dioxocyclooct[3,4]cyclobuta[1,2-*d*]pyrimidine-10b(1*H*)-carbonitrile (24): viscous oil; ^{1}H NMR ($CDCl_3$) δ 1.10–2.90 (m, 14 H), 3.03 (s, 3 H), 3.21 (s, 3 H), 3.26 (partially obscured m, 1 H); IR (neat) 2225, 1695 cm^{-1}. Anal. ($C_{15}H_{21}N_3O_2$): C, H, N.

Photoaddition of 1 to 1-Hexyne. A solution of **1a** (165 mg, 1 mmol) and 1-hexyne (1.70 g, 20 mmol) in dry acetonitrile (100 mL) was irradiated under the standard condition for 10 h at room temperature. TLC analysis showed complete disappearance of **1a** and the formation of two products. After removal of the solvent, the oily residue (230 mg) was purified by preparative TLC (ethyl acetate–hexane (3:1)) to yield *E*-**25** (90 mg, 36%) and *Z*-**25** (83 mg, 35%) together with a considerable amount of polymeric materials derived from 1-hexyne.

(*E*)-2-[(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)-methylene]hexanenitrile (25): viscous oil; ^{1}H NMR (CCl_4) δ 0.95 (t, 3 H, J = 6.6 Hz), 1.22 –1.76 (m, 4 H), 2.32 (t, 2 H, J = 7 Hz), 3.25 (s, 3 H), 3.42 (s, 3 H), 6.86 (br s, 1 H), 7.44 (s, 1 H); UV (CH_3CN) 303 (log ϵ 4.02), 258 nm (3.79); mass spectrum, *m/e* (rel intensity) 247 (M^+, 17), 218 (15), 153 (14), 106 (10), 28 (100).

(*Z*)-2-[(1,2,3,4-Tetrahydro-1,3-dimethyl-2,4-dioxo-5-pyrimidinyl)-methylene]hexanenitrile (25): viscous oil; ^{1}H NMR (CCl_4) δ 0.94 (t, 3 H, J = 6.4 Hz), 1.16–1.74 (m, 4 H), 2.36 (t, 2 H, J = 7 Hz), 3.25 (s, 3 H), 3.46 (s, 3 H), 6.95 (br s, 1 H), 8.23 (s, 1 H); UV (CH_3CN) 313 (log ϵ 4.05), 259 nm (3.92); mass spectrum, *m/e* (rel intensity) 247 (M^+, 12), 218 (15), 153 (12), 106 (10), 28 (100); IR (neat) 2205, 1710, 1655 cm^{-1}. Further support for the structure of **25** was obtained by ozonolysis. A solution of *E*-**25** (105 mg, 0.42 mmol) in dry methylene chloride (10 mL) in a two-necked flask equipped with a drying tube and gas inlet was cooled to −78 °C in a dry ice–methanol bath. Ozone was slowly passed into the solution for 10 min. To this solution was added a solution of dimethyl sulfide (1 g) in methylene chloride (3 mL), and then it was allowed to stand at room temperature for 1 h. Evaporation of the solvent

gave a colorless oil (120 mg), which was purified by preparative TLC (chloroform–ethyl acetate (5:2)) to afford 26 (41 mg, 58%). Essentially the same result was obtained with *Z*-**25**.

Photoaddition of 5′-*O*-Acetyl-6-cyano-2′,3′-*O*-isopropylideneuridine (27) to 1-Hexyne. A solution of **27**[14a] (188 mg, 0.55 mmol) and 1-hexyne (1.03 g, 12.5 mmol) in dry acetonitrile (100 mL) was irradiated under the standard conditions for 10 h at room temperature. After removal of the solvent, the oily residue was purified by preparative TLC (chloroform–ethyl acetate (5:1)) to yield **28** (86 mg, 37%).

5′-*O*-Acetyl-2′,3′-*O*-isopropylidene-5-(2-cyano-1-hexen-1-yl)uridine (28): viscous oil; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3 H, J = 7 Hz), 1.76 (s, 3 H), 1.98 (s, 3 H), 1.60–2.10 (m, 4 H), 2.46 (s, 3 H), 2.75 (t, 2 H, J = 7 Hz), 3.65–3.80 (m, 1 H), 3.76 (d, 2 H, J = 1 Hz), 4.18–4.26 (m, 1 H), 4.38 (dd, 1 H, J = 6, 2 Hz), 5.30 (d, 1 H, J = 2 Hz), 6.42 (s, 1 H), 7.76 (s, 1 H), 9.50 (br, 1 H); mass spectrum, *m/e* (rel intensity) 433 (M^+, 18), 418 (30), 375 (17), 298 (5), 215 (100), 157 (60); high-resolution mass spectrum, calcd for $C_{21}H_{27}O_7N_3$: 433.1848, found 433.1816.

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A Method for the Analysis of Puckering Disorder in Five-Membered Rings: The Relative Mobilities of Furanose and Proline Rings and Their Effects on Polynucleotide and Polypeptide Backbone Flexibility

E. Westhof† and M. Sundaralingam*

Contribution from the Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin—Madison, Madison, Wisconsin 53706. *Received August 14, 1981*

Abstract: In crystals, furanose or pyrrolidine rings are sometimes found disordered between different puckers. This puckering or pseudorotational disorder is classified into case I, three atoms anchored in the crystal (or one endocyclic bond angle constant), and case II, four atoms fixed in the crystal (or one endocyclic torsion angle constant). For each case, the geometrically possible disordered puckered states are investigated and analyzed in the framework of the pseudorotation concept. For case I, the pseudorotational domain available is generally restricted to one quadrant of the pseudorotational wheel. For case II, the pseudorotational domains available consist of narrow bands centered on the axis defined by the envelope states of the atom opposite the constant torsion angle. The method provides a knowledge of the possible disordered puckered states and their geometries that will be useful in crystallographic refinement of the nucleic acid monomers and oligomers as well as the polymers. The mobilities of the five-membered pyrrolidine and furanose ring in proline derivatives and nucleic acids, respectively, are compared from solid-state and solution data in the pseudorotation framework. In both systems, hydroxylation decreases flexibility (dR (DNA) vs. R (RNA); Pro vs. Hyp). In general, the proline ring is more flexible, and therefore more liable to disorder, than the furanose ring. However, the effects of the ring mobility or pseudorotational disorder on the polymer backbone are less pronounced in proline-containing polypeptides than in polynucleotides.

It is well-known that, in the solid state, the furanose ring of nucleic acid constituents is not planar but commonly puckered at either the C(2′) or C(3′) atom or at both atoms.[1,2] Usually, in nucleosides and nucleotides only one puckered state of the five-membered sugar ring is observed. In crystals of dinucleotides, the puckers of the two sugars are sometimes different but each nucleotide fragment has a precise pucker. When there is more than one molecule in the asymmetric unit, different conformations of the sugar,[3] the glycosyl bond torsion,[4] and the C(4′)–C(5′) exocyclic group,[5] are often observed. In these cases, each molecule has the same conformation in all of the unit cells of the crystal. Puckering disorder or pseudorotational disorder of a furanose ring with two different sugar conformations at the same position (crystallographic disorder) has been observed only recently.[6-8]

In contrast to furanose rings, the five-membered pyrrolidine ring of the imino acid proline is often found disordered in the solid state (e.g., see ref 9 and 10). The pyrrolidine ring is usually puckered at the C(γ) and/or C(β) carbon atoms,[11-15] and the disorder in the ring involves either C(γ) alone or both C(γ) and C(β) atoms.

The various puckered states of five-membered rings are best understood in the framework of the pseudorotation concept[16]

† Present address: Centre National de La Recherche Scientifique, Institut de Biologie Moléculaire et Cellulaire, 67084 Strasbourg, France.

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