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Novel Furocoumarin Derivatives as a Model Related to DNA-Intercalating Molecules. Synthesis and Photochemical Reactivity[1)]

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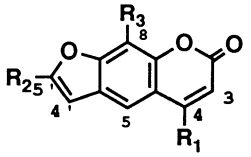
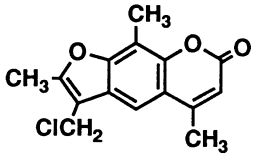
The synthesis and the photochemical reactivity of novel furocoumarins are studied. The formation of intramolecular photoaddition product suggests the importance of proximity effect in promoting the reactivity of the furocoumarin's 4',5'-double bond in the biological environment.

Photochemical reactivity of furocoumarin 1 has long been applied in the treatment of skin disorders such as psoriasis and vitiligo. Their biological activity is ascribed to the cross-linking of two strands of DNA resulting from photoaddition of a furocoumarin with thymine residue of one strand, followed by a second photoaddition with thymine residue of the other strand.[2)] Interestingly, the reactivity of two double bonds of furocoumarins intercalating in DNA is different from that in solution. In DNA the 4',5'-double bond of photo-excited furocoumarins first reacts with a thymine residue as an unsaturated component, as opposed to the 3,4-double bond reacting first in solution.[3)] Such a remarkable contrast suggests the non-bonded interaction (intercalation) of furocoumarins in DNA plays a large role in altering the reactivity order of the two reactive sites. In order to disclose the nature of the intercalation that promotes the reaction at the 4',5'-double bond in DNA, novel furocoumarins are synthesized and their photochemical reactivity is studied as a model related to DNA-intercalating molecules. These furocoumarin derivatives are characterized by having an unsaturated component in the 4'-substituent. Thus, one of the reactive sites, the 4',5'-double bond, is designed to stay close to the unsaturated moiety attached to the 4'-position.



1a: $R_1=R_2=R_3=H$
b: $R_1=R_2=R_3=CH_3$
c: $R_1=R_2=H$, $R_3=OCH_3$



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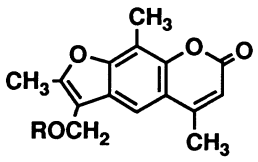
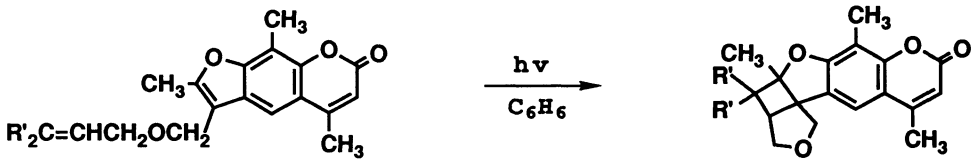


3a: $R=CH_3$
b: $=CH_2CH_2CH_3$
c: $=CH_2CH=CH_2$
d: $=CH_2CH=C(CH_3)_2$

Novel furocoumarin derivatives 3 were synthesized by refluxing 4'-chloromethyl-4,5',8-trimethylfurocoumarin 2 [4] (2×10^{-4} mol) in an appropriate alcohol (30 mL) for two hours and purified by column chromatography on silica gel.[5] A new shoulder in the UV absorption of 4'-allyloxymethyl-4,5',8-trimethylfurocoumarin 3c was detected at *ca.* 359 nm (log ε = 3.8), which is not observed in a simple mixture of an equal amount of 4'-chloromethyl-4,5',8-trimethylfurocoumarin 2 and allyl alcohol. This indicates the presence of intramolecular interaction between furocoumarin moiety and unsaturated side chain in the ground state of 3c.[6]

When the benzene solution of 3c (1×10^{-4} M) was irradiated, the intramolecular cycloaddition at the 4',5'-double bond yielded a cyclobutane 4c in 41%(Scheme 1).[7] Similar intramolecular photoaddition product 4d was identified in the reaction of 3d (Scheme 1). On the other hand, the intermolecular photoaddition product 5a or 5b [8] at the 3,4-double bond was formed in the photochemical reaction of 4'-alkoxymethyl-4,5',8-trimethylfurocoumarin such as 3a [4] or 3b in the reaction with 2,3-dimethyl-2-butene, respectively (Scheme 2). These furocoumarin derivatives do not carry unsaturated components in their 4'-substituents. Therefore, it is suggested that the proximity effect, not the electronic effect, in 3c or 3d enhances the reactivity of the 4',5'-double bond in the excited state. The observed higher reactivity of the 4',5'-double bond in these model compounds is similar to that reported for the reactivity of furocoumarin intercalating in DNA.

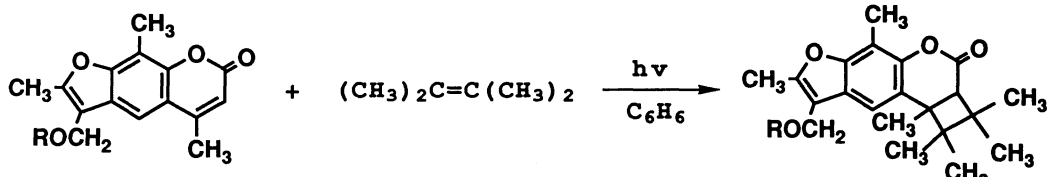
The intermolecular photoaddition product 5c of the reaction between 3c and 2,3-dimethyl-2-butene was also isolated along with the intramolecular photoadduct 4c, when a large excess of 2,3-dimethyl-2-butene as an external alkene was added to the reacting system (Scheme 2).[9, 10]



3c: R'=H
3d: =CH3

4c: R'=H
4d: =CH3

Scheme 1.



3a: R=CH3
3b: =CH2CH2CH3
3c: =CH2CH=CH2
3d: =CH2CH=C(CH3)2

5a: R=CH3
5b: =CH2CH2CH3
5c: =CH2CH=CH2
5d: =CH2CH=C(CH3)2

Scheme 2.

The intramolecular photochemical reactivity of other furocoumarins having unsaturated moiety as the substituent was recently reported.[11] In these studies, however, the unsaturated substituent is located either at the 5- or the 8-position of furocoumarin ring. Therefore, both reactive sites, the 3,4- and the 4',5'-double bond, are in the similar spatial distance from the introduced unsaturated moiety. Thus, upon irradiation, the intramolecular photoaddition reaction was found to take place at the 3,4-double bond, which has the intrinsically higher reactivity toward alkene.[3]

The effect of bond length separating the unsaturated component in the 4'-substituent from the furocoumarin ring is currently being investigated. However, the present study indicates the proximity effect promotes the reaction at the 4',5'-double bond of furocoumarins, otherwise less reactive than the 3,4-double bond. The present result also suggests the proximity effect caused by intercalation would be responsible for altering the reactivity order of two double bonds of furocoumarin in DNA from that in solution.

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References

1) Presented in part by A. J. H. at the Southern California Undergraduate Research Conference, University of California at Los Angeles, CA, April 22, 1989, by T. O. and A. J. H. at the 31st National Organic Symposium (B-28), Cornell Univ., Ithaca, NY, June 18 - 22, 1989, and by A. J. H. at the 1989 International Chemical Congress of Pacific Basin Societies (ORGN 574), Honolulu, HI, December 17 - 22, 1989.

2) G. C. Cimino, H. G. Gamper, S. T. Isaacs, and J. E. Hearst, Ann. Rev. Biochem., 54, 1151 (1985) and the references cited therein.

3) T. Otsuki, Chem. Lett., 1987, 453; B. D. Ratiner and T. Otsuki, ibid., 1989, 1035.

4) S. T. Isaacs, C-K. J. Shen, J. E. Hearst, and H. Rapoport, Biochemistry, 16, 1058 (1977).

5) 3b: Yield; 90%. MS: m/z Found 300.1365; Calcd for $C_{18}H_{20}O_4$ 300.1362. ^{1}H-NMR ($CDCl_3$): δ 7.58(1H, s), 6.21(1H, s), 4.60(2H, s), 3.44(2H, t, J=6.6 Hz), 2.54(3H, s), 2.47(6H, s), 1.63(2H, m), 0.93(3H, t, J=7.3 Hz) ppm. ^{13}C-NMR($CDCl_3$): δ 161.5, 154.6, 154.5, 153.3, 149.0, 125.1, 115.9, 112.5, 112.1, 111.6, 108.8, 71.8, 62.9, 22.8, 19.2, 12.2, 10.6, 8.3 ppm. IR(KBr): 1709.5 cm^{-1}. 3c: Yield; 88%. MS: m/z Found 298.1196; Calcd for $C_{18}H_{18}O_4$ 298.1205. ^{1}H-NMR($CDCl_3$): δ 7.62(1H, s), 6.25(1H, s), 5.92(1H, m), 5.31(1H, dm, J=18.0 Hz), 5.24(1H, dm, J=11.2 Hz), 4.64(2H, s), 4.03(2H, dm, J=4.3 Hz), 2.58(3H, s), 2.50(3H, s), 2.49(3H, s) ppm. ^{13}C-NMR($CDCl_3$): δ 161.5, 154.8, 153.3, 134.6, 125.2, 117.4, 116.2, 112.8, 112.0, 111.7, 109.1, 70.7, 62.2, 19.3, 12.3, 8.5 ppm. IR(KBr): 1708.7 cm^{-1}.

6) Although the quantitative comparison of the intensities of UV absorptions remains to be studied in order to analyze the details of such non-bonded interactions, the hypochromism in the UV absorptions of intramolecular furocoumarin-

adenine/thymine complexes was once applied to detect the intramolecular interaction between two chromophores. Cf. J. L. Decout and J. Lhomme, Tetrahedron Lett., 22, 1247 (1981); J. L. Decout and J. Lhomme, Photochem. Photobiol., 37, 155 (1988).

7) 4c: Yield; 41%. MS: m/z Found 298.1200; Calcd for $C_{18}H_{18}O_4$ 298.1205. ^{1}H-NMR ($CDCl_3$): δ 7.07(1H, s), 6.12(1H, s), 4.22(1H, d, J=10.3 Hz), 3.89(2H, m), 3.76 (1H, d, J=10.3 Hz), 2.94(1H, m), 2.73(1H, dd, J=13.7, 9.4 Hz), 2.39(3H, s), 2.30 (3H, s), 2.04(1H, dd, J=13.7, 5.1 Hz), 1.50(3H, s) ppm. ^{13}C-NMR($CDCl_3$): δ 161.5, 153.8, 152.7, 124.3, 115.3, 113.6, 110.9, 108.3, 92.6, 77.2, 74.2, 69.5, 60.4, 45.5, 39.2, 19.2, 19.0, 8.5 ppm. IR(KBr): 1708.5 cm^{-1}.

8) 5a: Yield; 21%. MS: m/z Found 356.1974; Calcd for $C_{22}H_{28}O_4$ 356.1988. ^{1}H-NMR ($CDCl_3$): δ 7.01(1H, s), 4.51(2H, s), 3.33(3H, s), 3.00(1H, s), 2.43(6H, s), 1.37 (3H, s), 1.24(3H, s), 1.15(3H, s), 0.88(3H, s), 0.79(3H, s) ppm. ^{13}C-NMR($CDCl_3$): δ 167.1, 153.9, 152.0, 145.8, 124.2, 122.1, 115.5, 111.4, 109.1, 64.6, 57.5, 51.1, 45.4, 43.1, 41.8, 27.5, 25.5, 22.9, 22.7, 21.5, 12.1, 8.9 ppm. IR(KBr): 1748.4 cm^{-1}. 5b: Yield; 21%. MS: m/z Found 384.2322; Calcd for $C_{24}H_{32}O_4$ 384.2301. ^{1}H-NMR($CDCl_3$): δ 7.04(1H, s), 4.56(2H, s), 3.40(2H, t, J=6.6 Hz), 3.01(1H, s), 2.43(6H, s), 1.56(2H, m), 1.37(3H, s), 1.24(3H, s), 1.16(3H, s), 0.91(3H, t, J= 7.3 Hz), 0.89(3H, s), 0.79(3H, s) ppm. ^{13}C-NMR($CDCl_3$): δ 167.0, 153.4, 152.1, 145.9, 124.4, 122.0, 115.7, 111.9, 109.0, 71.6, 63.1, 51.2, 45.5, 43.1, 41.8, 27.4, 25.6, 23.0, 22.9, 22.8, 21.5, 12.1, 10.8, 8.8 ppm. IR(KBr): 1751.7 cm^{-1}.

9) 5c: Yield; 31%. MS: m/z Found 382.2152; Calcd for $C_{24}H_{30}O_4$ 382.2144. ^{1}H-NMR ($CDCl_3$): δ 7.27(1H, s), 5.93(1H, m), 5.23(2H, m), 4.59(2H, s), 3.99(2H, m), 3.01 (1H, s), 2.44(6H, s), 1.38(3H, s), 1.25(3H, s), 1.16(3H, s), 0.89(3H, s), 0.80 (3H, s) ppm. ^{13}C-NMR($CDCl_3$): δ 167.0, 153.6, 152.2, 145.9, 134.7, 124.3, 122.1, 117.1, 115.7, 111.6, 109.1, 70.4, 62.3, 51.2, 45.5, 43.2, 41.8, 27.4, 25.6, 22.9, 22.8, 21.6, 12.2, 8.9 ppm. IR(KBr): 1752.1 cm^{-1}.

10) Further quantitative study on the competitive intramolecular vs intermolecular photoaddition reactions of 3c is in progress. The intermolecular photoaddition product 5c was found to be formed as a minor product (16%) along with the intramolecular photoaddition product 4c (45%) when a hundred fold excess of 2,3-dimethyl-2-butene was added to the reaction mixture.

11) J. L. Decout, G. Huart, and J. Lhomme, Nouv. J. Chim., 8, 433 (1984); J. L. Decout, G. Huart, and J. Lhomme, Photochem. Photobiol., 48, 583 (1988); J. L. Decout and J. Lhomme, ibid., 48, 597 (1988).

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