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Photocyclization of 2′-Hydroxychalcones to 4-Flavanones

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On irradiation with light of $\lambda \geqq 365$ nm, parent and methoxy-substituted 2′-hydroxychalcones undergo facile photocyclization to give corresponding 4-flavanones in high efficiencies in ethyl acetate or dioxane, whereas in low or nil efficiencies in benzene, chloroform, carbon tetrachloride, ether, acetonitrile, ethanol, or *t*-butyl alcohol. The low reactivity in benzene is, however, significantly increased by the addition of liquid paraffin to increase the solvent viscosity. 3′,4′-Benzo-2′-hydroxychalcone showed low reactivities in any solvents. The formation of 4-flavanones is neither quenched by triplet quenchers nor depressed by the addition of free radical scavengers. The reaction mechanism is discussed in terms of enolization.

It has previously been reported that the photolysis of substituted 4-flavanones undergo ring opening to give 2′-hydroxychalcones[1-3] or hydrogen atom abstraction to give dimeric products,[2,3] depending on the substituent and solvent.

The photocyclization of 2′-hydroxychalcone in benzene has been reported as a new method for flavanone synthesis (53% yield),[4] though the mechanism has little been studied. The photocyclization of 2′-hydroxychalcones is apparently the reverse process of the photochemical ring opening of 4-flavanones, and it appeared of interest to investigate further the scope of these reactions. The present investigation has emphasized on the solvent effects on the relative reactivity or yield for the photocyclization of parent and substituted 2′-hydroxychalcones.

Experimental

2′-Hydroxychalcones[5] and 4-flavanones[6] were prepared according to the literatures methods. Other reagents and solvents were of guaranteed grade (Wako Chemicals).

Each sample solution was degassed by bubbling with purified nitrogen and sealed in a 5 ml or 10 ml pyrex ampul prior to irradiation. The light source was a 400 W high pressure mercury lamp. A cut-off glass filter (Toshiba UV-35) or an aqueous copper(II) solution filter[7] was employed to eliminate short wavelength regions. The transmittance characteristics of the filters and the main emission from the light source, as well as the absorption spectra of **1a** and **1b**, are illustrated in Fig. 1. Irradiation was carried out by means of a merry-go-round apparatus in a thermostat controlled at 20±1 °C.

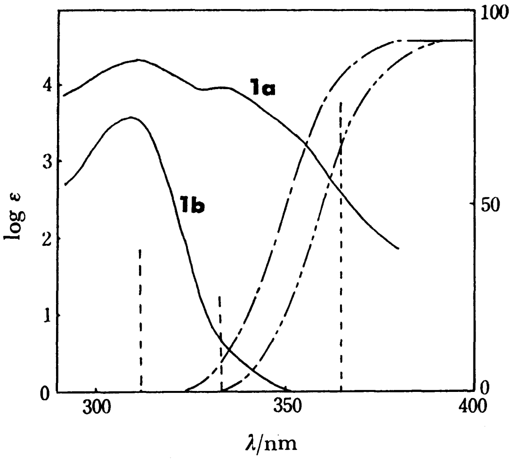


Fig. 1. Absorption spectra of **1a** and **1b** in benzene, and the transmittance characteristics of cut-off filters for selective excitation of **1a**. (— — —): Transmittance of a UV-35 glass filter, (—·—·—): transmittance of aqueous copper(II) solution filter, (----): emission from a high pressure mercury lamp.

Photolyzed mixture solutions were condensed below 40 °C and separated by PLC on silica gel-benzene. The photoproducts from **1a** and **2a** were confirmed to be **1b** and **2b** respectively by comparing their NMR and IR spectra, while the photoproducts from **3a**—**5a** were assigned to be **3b**—**5b** respectively by comparing their UV spectra and TLC, with those of the authentic samples prepared independently. The amounts of the products and the reactants in the photolyzed mixtures were determined by colorimetric or gravimetric analysis after separation by PLC on silica gel-benzene. Quantum yields were measured with monochromatic 360—366 nm light from the light source by using a combination of filters (Toshiba UV-35 and UV-D2). For the estimation of the light quanta absorbed by the sample solutions, a mixture of 0.1 M benzophenone and 0.1 M benzhydrol in benzene[8] was used.

UV absorption spectra were measured by the use of a Hitachi 124 spectrophotometer. NMR and IR spectra were measured by means of a Hitachi R-24 NMR spectrometer and a Nihonbunko IRA-1 IR spectrometer, respectively.

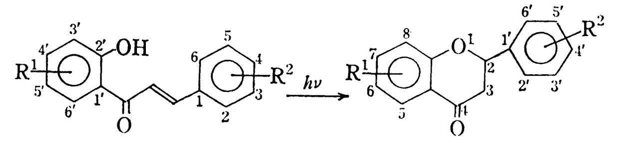
Results

Photocyclization of 2′-Hydroxychalcones in Various Solvents. By selective excitation with light of $\lambda \geqq 365$ nm, a series of 2′-hydroxychalcones **1a**—**5a** in deoxygenated solutions underwent photocyclization to give corresponding 4-flavanones **1b**—**5b**, respectively (Scheme 1).

Photolyses of **1a**—**5a** were carried out in a variety of solvents, and the qualitative results are shown in Table 1. Both **1a** and **2a** undergo photocyclization in benzene, ether, ethyl acetate, 1,4-dioxane, acetonitrile, and ethanol, but not in chloroform and *t*-butyl alcohol. Both **3a** and **4a** photocyclize in benzene, ether, ethyl acetate, and 1,4-dioxane, but not in chloroform, carbon tetrachloride, acetonitrile, ethanol, and *t*-butyl alcohol. **5a** shows low reactivity in most solvents.

Effects of the Wavelength of Light. Irradiation of light involving shorter wavelength regions led to the complication of the reaction and the decrease in the rates. Figure 2 illustrates wavelength effects on the relative rates of **2a** and **4a** in benzene.

On irradiation with light of $\lambda \geqq 313$ nm, the consumption rate of **4a** is decreased to 2/5 of that with $\lambda \geqq 334$



1a—5a

2'-Hydroxychalcone	R^1	R^2
1a	H	H
2a	H	2-OMe
3a	4'-OMe	H
4a	6'-OMe	H
5a	3',4'-Benzo	H

1b—5b

4-Flavanone	R^1	R^2
1b	H	H
2b	H	2'-OMe
3b	7-OMe	H
4b	5-OMe	H
5b	7,8-Benzo	H

Scheme 1.

TABLE 1. FORMATION OF 4-FLAVANONES **1b—5b** BY THE PHOTOLYSES OF 2'-HYDROXYCHALCONES **1a—5a**

2'-Hydroxy-chalcone	Benzene	Carbon tetrachloride	Chloro-form	Ethyl ether	Ethyl acetate	1,4-Dioxane	Aceto-nitrile	Ethanol	*t*-Butyl alcohol
1a	**1b**	**1b**	—	**1b**	**1b**	**1b**	**1b**	**1b**	—
2a	**2b**	—	—	**2b**	**2b**	**2b**	**2b**	**2b**	—
3a	**3b**	—	—	**3b**	**3b**	**3b**	—	—	—
4a	**4b**	—	—	**4b**	**4b**	**4b**	—	—	—
5a	**5b**	—	—	—	**5b**	**5b**	—	—	—

a) Irradiated with a 400 W high pressure mercury lamp through a UV-35 glass filter for 10 h at 20 °C. Initial concentrations of 2'-hydroxychalcones were 1 mM. 4-Flavanones formed were detected by TLC on silica gel–benzene.

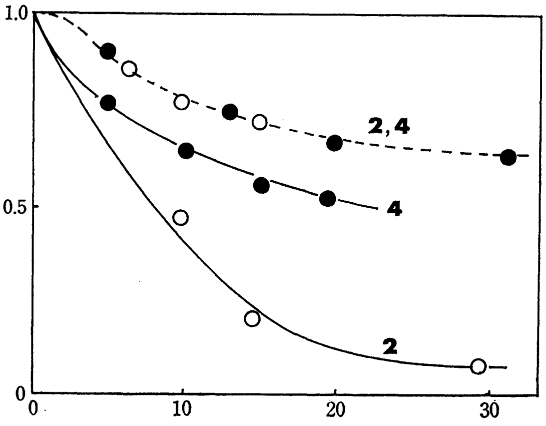


Fig. 2. Wavelength effects on the photoreaction rates of **2a** (○) and **4a** (●) in benzene. (—○—): Irradiation of **2a** with $\lambda \geqq 334$ nm, (--○--): Irradiation of **2a** with $\lambda \geqq 313$ nm, (—●—): irradiation of **4a** with $\lambda \geqq 365$ nm, (--●--): irradiation of **4a** with $\lambda \geqq 334$ nm.

TABLE 2. VARIATION IN THE RELATIVE RATES WITH SOLVENT AND SUBSTITUENT[a)]

2'-Hydroxy-chalcone	Consumption of 2'-hydroxychalcone (%) in		
	Benzene	1,4-Dioxane	Ethyl acetate
1a	8.2	94	95
2a	10	97	91
3a	14	35	63
4a	30	30	84
5a	7.4	1.4	1.3

a) Initial concentration of each 2'-hydroxychalcone was 1 mM, irradiation time was 5 h.

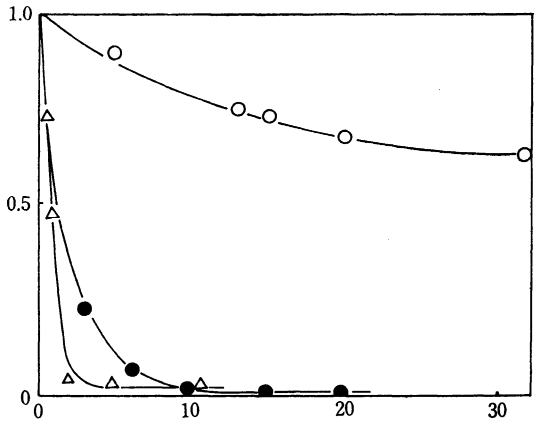


Fig. 3. Consumption of **2a** with irradiation time in benzene (○), 1,4-dioxane (△), and ethyl acetate (●). Similar plots were obtained for **1a**.

nm. Similarily, the rate of **2a** on irradiation with $\lambda \geqq 334$ nm is 3/5 of that with $\lambda \geqq 365$ nm. A UV-35 (Toshiba) glass filter or an aqueous copper(II) solution filter appears to be suitable to cut shorter wavelength regions (see also Fig. 1).

Variation in the Photoreaction Rates. Relative rates of the reaction were measured in benzene, ethyl acetate, and 1,4-dioxane, since in these solvents all of the 2'-hydroxychalcones **1a—5a** undergo photocyclization (Table 1). Table 2 compares the consumption rates at a constant (5 h) irradiation time, while Figs. 3 and 4

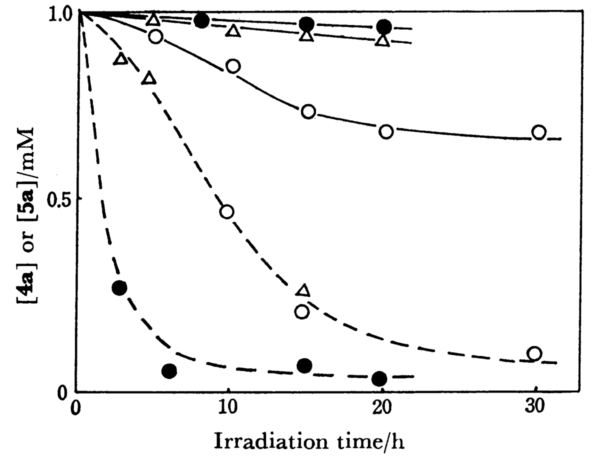


Fig. 4. Consumption of **4a** (broken line) and **5a** (solid line) with irradiation time in benzene (○), 1,4-dioxane (△), and ethyl acetate (●).

illustrate the concentration changes with irradiation time.

The results show that the rates are high in ethyl acetate or 1,4-dioxane, and low in benzene, though **5a** has the lowest reactivities in each solvent. It is notable that the rates of **1a** and **2a** are higher in ethyl acetate than in benzene by a factor of 20—40 (Fig. 3).

The quantum yields for the consumption of **1a** and **2a** (1 mM) excited at 365—366 nm were 0.3—0.4 in ethyl acetate and 0.01 in benzene, though they varied depending on the concentration of the reactants and on the extent of the reaction. The low reactivity of **2a** in benzene is significantly increased with the increase in the solvent viscosity (Table 3).

Table 3. Effects of solvent viscosity on the quantum yield for the consumption of **2a** in benzene–liquid paraffin

Liquid paraffin/vol%	Relative viscosity[a]	Quantum yield × 100
0	1.0	1.0
20	1.4	1.1
40	2.3	1.7
60	4.8	2.7
80	18	3.8
100	150	11

a) Measured at 20 ± 0.5 °C by means of an Ostwald viscositometer.

Variation in the Yields of ***2b***. The amounts of **2b** formed and **2a** recovered were determined at various irradiation time for the photoreaction of **2a**. Figure 5 illustrates the increasing curve of **2b** and the decreasing curve of **2a** in benzene and ethyl acetate.

The curves of **2a** and **2b** are symmetrical to each other, indicating that the reaction is *clean*. The yields of **2b** based on the consumed amounts of **2a** are listed in Table 4.

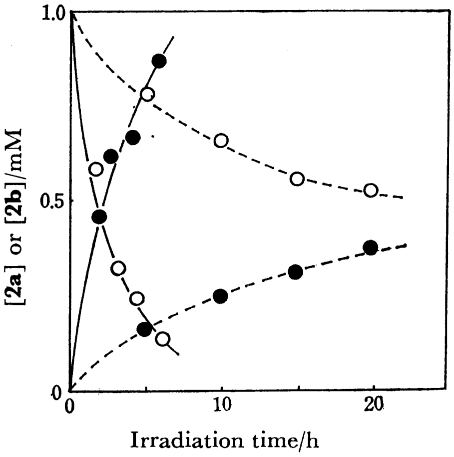


Fig. 5. Concentration changes in **2b** (●) and **2a** (○) with irradiation time in benzene (broken line) and ethyl acetate (solid line).

Table 4. Yields of **2b** at various irradiation time in benzene, 1,4-dioxane, and ethyl acetate[a]

Solvent	Irradiation time/h	[**2a**]/mM Recovered	[**2b**]/mM Formed	Yield of **2b**/%[b]
Benzene	5	0.77	0.17	74
	10	0.66	0.24	71
	15	0.55	0.34	69
	20	0.52	0.40	83
Dioxane	1	0.79	0.17	82
	2	0.57	0.48	100
	3	0.31	0.55	79
	4	0.06	0.35	58
Ethyl acetate	2	0.57	0.45	100
	3	0.32	0.62	91
	4.5	0.23	0.65	84
	6	0.14	0.86	100

a) Initial concentration of **2a** was 1 mM. Cut-off filter was a 1.5 cm-depth solution of copper(II) sulfate (80 g) and copper(II) nitrate (80 g) in 400 ml water, which had been pre-irradiated for 10 h. The amounts of **2a** and **2b** in the photolyzed mixtures were determined colorimetrically after separation by PLC. b) The yield of **2b** based on the consumed amount of **2a**.

Though the values are somewhat scattered, the yields of **2b** are equal or close to unity in ethyl acetate. This implies that the quantum yield for the formation of **2b** is equal or close to the quantum yield value for the consumption of **2a**, or 0.3—0.4 in ethyl acetate. It should be noted that longer irradiation may lower the yield, thus the practical conversion yield of **2b** is 55% at best in 1,4-dioxane. In ethyl acetate the conversion yield of **2a** into **2b** is fairly high, *e.g.*, 86% at 6 h irradiation. The high conversion yield and the cleanness of the reaction (the high yield of **2b** based on the consumed amount of **2a**) in ethyl acetate may be of preparative use, if the wavelength and the time of irradiation *etc.* are suitablly controlled. Since the reaction can be achieved in neutral (mild) media, it may be useful for cyclization of 2′-hydroxychalcones having labile groups to acid or base.

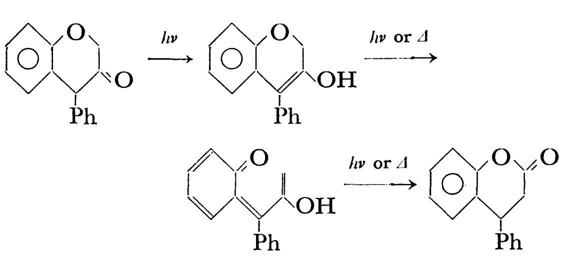
Effects of Triplet Quenchers and Radical Scavengers. The formation of **2b** by the photolysis of **2a** in aerated benzene was not significantly quenched, though unknown side products were also formed. The formation of **2b** was not quenched in the photolysis of **2a** (1 mM) in benzene in the presence of ferrocene (1 mM), *trans*-stilbene (1 mM), or acenaphthylene (2 mM). Selective excitation of **2a** in the presence of acenaphthylene gave isomeric dimers of acenaphthylene, though the formation of **2b** was not quenched. Further, the *anti*/*syn* ratio of dimers was higher than that by direct excitation of acenaphthylene. Thus, the formation of **2b** is not quenched, even when triplet energy is transferred from **2a** to the quenchers.

The addition of 2,6-di-*t*-butylphenol (1 mM) altered neither the rate nor the yield of the formation of **1b** in the photolysis of **1a** (1 mM) in ethyl acetate.

Discussion

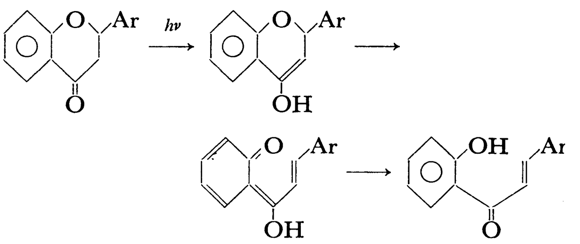
The lack of quenching by triplet quenchers and the lack of inhibition by free radical scavengers (2,6-di-*t*-butylphenol and dissolved oxygen) may imply that a mechanism involving triplet states or free radicals is unlikely. The higher reactivities in polar solvents than in nonpolar solvent (Fig. 3 and Table 2) may support that the reaction takes place through ionic or polar processes.

Though the effects of solvent and substituent on the reactivities (Table 1) are far from explainable as yet, it seems that polar solvents, particularly aprotic polar solvents (basic solvents), are effective for the reaction, while nonpolar solvents are less effective. This may suggest some role of the interactions of solvent with the hydroxyl group of 2′-hydroxychalcones. One may assume, for example, that the intramolecular hydrogen bonding of the 2′-hydroxychalcones would be broken or loosened by solvation or proton transfer from the hydroxyl group to a basic or polar solvent, affecting the structures and reactivities in their ground state or excited states. The NMR signal of the phenolic proton of **1a** at $\delta \approx 12.5$ ppm was not changed at all with the change in the solvent from benzene to ethyl acetate, 1,4-dioxane, and 1,4-dioxane–water (3: 1), implying that the intramolecular hydrogen bonding in the ground state remains unchanged even in basic or polar solvents. Thus, the ground state structures of the 2′-hydroxychalcones may be represented by **10** regardless of solvent.



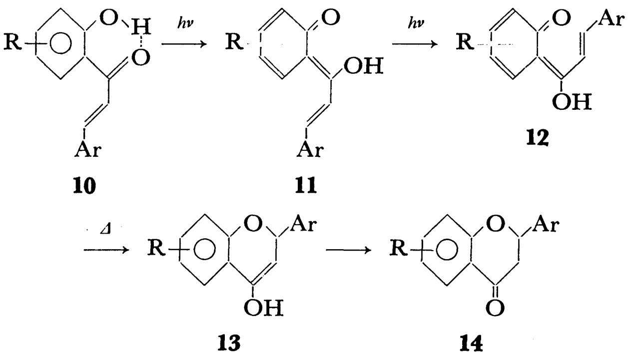
Scheme 2.

A. Padwa *et al.* have shown that the photochemical rearrangements of 3-chromanone derivatives take place *via* enolization (Scheme 2).[9] Similar mechanism has also been proposed for the photochemical ring opening reaction of the substituted 4-flavanones in benzene (Scheme 3).[3] It is noted that the photocyclization of the 2′-hydroxychalcones to the 4-flavanones is apparently the reverse reaction of the photochemical ring opening of the 4-flavanones and that the both reactions can indeed be reversible under suitable conditions.



Scheme 3.

It seems, therefore, reasonable to assume a similar mechanism (involving enolization) for the photocyclization (Scheme 4). Photochemical excitation of **10** would lead to enolization to give **11**, which needs, however, to undergo *cis-trans* isomerization to **12** for the subsequent cyclization to occur. The cyclization of **12** to **13** may be exothermic or less endothermic due to the recovery of aromatic stability, and proceed effectively *via* a thermal 6-π electrocyclic process.



Scheme 4.

The two-photon mechanism in Scheme 4 requires that the upper limit of the quantum yield for the formation of 4-flavanone should be 0.5. The quantum yield estimated for the formation of **2b** in ethyl acetate ranges in 0.3—0.4, which is close to the upper limit. The estimated quantum yield is strikingly high despite the short lifetimes of the excited singlet states of aromatic ketones in solution. The reaction would proceed so rapidly and effectively that it dominates over rapid deactivation processes of excited singlet states, such as intersystem crossing and internal conversion *etc.* It is known that the acidities of phenols are greatly increased in the excited singlet states.[10] The increased acidity of **10** in the excited singlet state would allow facile acid-catalyzed enolization, and polar solvents may accelerate the reaction by stabilization of the enols.

In non polar solvents, such as benzene, the enols would be less stabilized and the reaction is less efficient so that deactivation processes may compete with or dominate over. The increase in the reaction efficiency with the solvent viscosity (Table 3) may imply that bimolecular deactivation processes, as well as unimolecular ones, compete well with the forward reaction in benzene.

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