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Thermal Isomerization Equilibrium between 2′-Hydroxychalcones and Flavanones

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Synopsis. Nine substituted 2′-hydroxychalcones and the corresponding flavanones were heated separately at 230±0.2 °C in nitrogen atmosphere. Both materials were mutually isomerized under these reaction conditions and the equilibrium constants of this isomerization were measured by means of HPLC analyses. The substituent effect on the equilibrium is discussed and thermodynamic functions (ΔG, ΔH, and ΔS) are calculated.

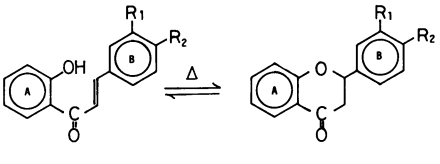
2′-Hydroxychalcones (**1**) and flavanones (**2**) constitute an important class of naturally occuring pharmacological compounds[1] and are intermediates in the biosynthesis of flavonoids.[2] Both materials are the structual isomers of each other; the isomerization of 2′-hydroxychalcones results in the corresponding flavanones and is usually effected under the influence of mineral acids and enzymes.[3] Kinetic studies on the isomerization equilibrium between **1** and **2** in an aqueous alkali and in an alkaline methanolic medium have also been reported.[4]

In the related work on flavonoids, we discovered the fact that **1** and **2** are mutually isomerized (partially) in a column (TENAX-GC) of gas chromatography at 285 °C. We now report on experimental results concerning the thermal isomerization equilibrium between **1** and **2** in a none-solvent environment at temperatures above those melting points.

Table 1. Equilibrium Constants of the Thermal Isomerization between 2′-Hydroxychalcones and Flavanones

Compd **1**, **2**	K[a)]	Temp/°C
a	1.41	200
	1.38	210
	1.33	220
	1.29	230
	1.18	240
	1.16	250
b	0.626	230
c	0.886	
d	0.943	
e	1.05	
f	1.47	
g	1.40	
h	1.55	
i	1.69	

a) $K = C_f/C_c$, where C_c and C_f are the concentrations of 2′-hydroxychalcones and flavanones, respectively.



a $R_1 = R_2 = H$
b $R_1 = H$, $R_2 = OCH_3$
c $R_1 = H$, $R_2 = CH_3$
d $R_1 = H$, $R_2 = CH(CH_3)_2$
e $R_1 = CH_3$, $R_2 = H$
f $R_1 = H$, $R_2 = Cl$
g $R_1 = H$, $R_2 = Br$
h $R_1 = Cl$, $R_2 = H$
i $R_1 = Br$, $R_2 = H$

When 2′-hydroxychalcone (**1a**) and flavanone (**2a**) were heated separately at 230±0.2 °C, both materials mutually isomerized. These equilibria were attained in about 5 h. The equilibrium constants were measured as the concentration ratio of **2a** to **1a** by means of an HPLC analysis using the calibration method of the peak area ratio vs. the concentration ratio. The attainment of equilibrium was confirmed by an agreement of both equilibrium constants within the experimental error.

Under the same reaction conditions and using the same analytical procedures, 3 or 4-substituted chalcones (**1b—i**) and the corresponding flavanones (**2b—i**) were examined. The results are summarized in Table 1. In all cases, no material was detected outside of the chalcones and the flavanones. Nitro derivatives of **1** and **2** could not be correctly examined because of considerable resinification or the carbonization.

Although extreme equilibrium shifts due to the introduction of substituents were not observed, Table 1 shows that the equilibrium constant decreased due to the electron-donating group on the B-ring; this increased as a result of the electron-withdrawing group. These results gave an excellent Hammett-type linear free energy relationship using Brawn–

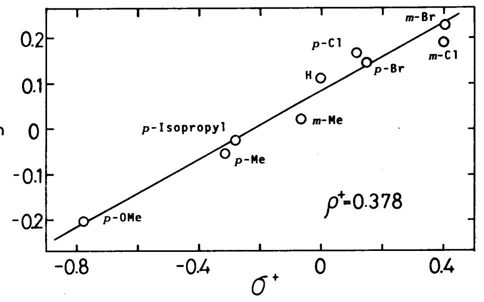
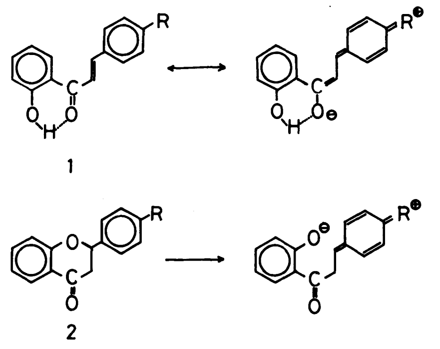


Fig. 1. Hammett plots for the thermal isomerization equilibrium between 2′-hydroxychalcones and flavanones.



Scheme 1.

Okamoto's σ^+ constant (r=0.996, Fig. 1). In the liquid state, **1** seem to have a strong intramolecular hydrogen bond and the electron-donating groups on the para-position in the B-ring tend to strengthen it further by resonance (Scheme 1). Thus those groups can prevent the cyclization of **1** into **2**; this can result in a decrease in the equilibrium constant, i.e., the advantage of **1**. On the other hand, the above-mentioned substituents can facilitate a bond cleavage between the oxygen atom of heterocycle and C_2-carbon atom in the case of the conversion of **2** into **1** as shown in Scheme 1, and also bring about a similar effect regarding equilibrium.

In order to obtain the thermodynamic parameters, the equilibrium constants at several temperatures were measured regarding the interconversion of **1a** and **2a**. The obtained results are also shown in Table 1. These results show that the equilibrium shifts to **1a** as the temperature rises. **1a** might be more stable than **2a** at high temperatures. According to Eq. 1, the thermodynamic parameters (ΔG, ΔH, and ΔS) for this equilibrium condition were calculated on the basis of a plot

$$RT\ln K = -\Delta G = -\Delta H + T\Delta S \qquad (1)$$

of $\ln K$ vs. $1/T$ (Fig. 2). The following values were obtained: $\Delta G^{503}=-1.07$ (kJ mol^{-1}), $\Delta H=-8.78$ (kJ mol^{-1}) and $\Delta S=-15.5\pm0.2$ (J mol^{-1} K^{-1}). The negative value of ΔS might be due to a decrease in the degree of freedom owing to cyclization. From the value of ΔH, it is clear that the conversion of **1a** into **2a** is an exothermic reaction.

Experimental

Materials. Chalcones and flavanones were prepared according to the known procedures;[5] related physical data have already been reported,[6] except for the following derivatives. Melting points are uncorrected.

4-Methyl-2′-hydroxychalcone (1c): Mp 120.0—121.5 °C; ^{1}H NMR (CCl_4) δ=2.36 (3H, s, 4-CH_3), 6.70—7.88 (10H, m, Olefin and Aromatic), 12.66 (1H, s, 2′-OH). Found: C, 80.73; H, 5.75%. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92%.

4-Isopropyl-2′-hydroxychalcone (1d): Mp 74—75 °C; ^{1}H NMR (CCl_4) δ=1.26 (6H, d, $CH(\underline{CH_3})_2$, J=6.5 Hz), 2.91 (1H, septet, $\underline{CH}(CH_3)_2$, J=6.5 Hz), 6.72—7.92 (10H, m, Olefin and Aromatic), 12.65 (1H, s, 2′-OH). Found: C, 81.11; H, 6.71%. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81%.

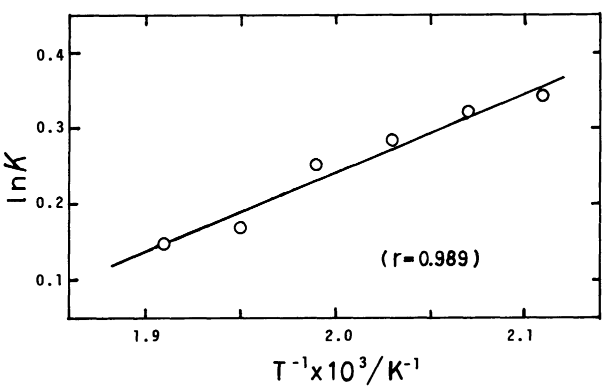


Fig. 2. Temperature dependence of the equilibrium constants of the thermal isomerization.

4-Bromo-2′-hydroxychalcone (1g): Mp 146—147 °C; ^{1}H NMR ($CDCl_3$) δ=6.82—7.92 (10H, m, Olefin and Aromatic), 12.68, (1H, s, 2′-OH). Found: C, 59.42, H, 3.64, Br, 26.30%. Calcd for $C_{15}H_{11}O_2Br$: C, 59.43, H, 3.66, Br, 26.36%.

3-Chloro-2′-hydroxychalcone (1h): Mp 104—105 °C; ^{1}H NMR (CCl_4) δ=6.75—7.86 (10H, m, Olefin and Aromatic), 12.49 (1H, s, 2′-OH). Found: C, 69.46, H, 4.15, Cl, 13.65%. Calcd for $C_{15}H_{11}O_2Cl$: C, 69.64, H, 4.29, Cl, 13.70%.

3-Bromo-2′-hydroxychalcone (1i): Mp 104—106 °C; ^{1}H NMR (CCl_4) δ=6.73—7.86 (10H, m, Olefin and Aromatic), 12.46 (1H, s, 2′-OH). Found: C, 59.20, H, 3.59, Br, 26.25%. Calcd for $C_{15}H_{11}O_2Br$: C, 59.43, H, 3.66, Br, 26.36%.

4′-Isopropylflavanone (2d): Mp 76—77 °C; ^{1}H NMR (CCl_4) δ=1.27 (6H, d, $CH(\underline{CH_3})_2$, J=9.0 Hz), 2.64—3.14 (3H, m, $\underline{CH}(CH_3)_2$ and $\underline{C_3\text{-}H_{ax},\ H_{eq}}$), 5.37 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=12.5 Hz, $J_{ax\cdot eq}$=5.0 Hz), 6.88—7.49 (7H, m, Aromatic), 7.85 (1H, d·d, C_5-H, J_{ortho}=8.5 Hz, J_{meta}=2.0 Hz). Found: C, 81.10, H, 6.70%. Calcd for $C_{18}H_{18}O_2$: C, 81.17, H, 6.81%.

General Procedure. In two test tubes (15 mmϕ×105 mm), ca. 0.1 g of **1a** and **2a** were placed separately, and the air in the tubes was displaced with nitrogen to avoid any resinification or carbonization. Then, these tubes were tightly sealded with Uni-stoppers and were dipped in a silicone oil bath adjusted to 230±0.2 °C. After about 5 h, the reaction mixtures were rapidly cooled at room temperature and solved in chloroform (50 ml). Then, the equilibrium constants were determined by an HPLC analysis using instruments by Yanagimoto High Speed Liquid Chromatograph L-2000.

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