Ortho Substituent Effect of the Side-Chain Phenyl Group on the Dehydrogenation of Flavanones with 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone

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Synopsis. Rates of the dehydrogenation of 2′-substituted flavanones with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone were measured by means of HPLC analyses. All substituents at the ortho position of the side-chain phenyl group of flavanones showed a retarding effect on the reaction. A correlation analysis for the ortho effect using the linear combination model has led to a conclusion that the inductive effect is much more important than the steric and the resonance effect, and that the steric effect is slightly greater than the resonance effect.

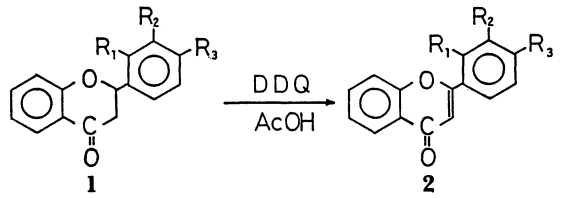
We previously examined the rate of dehydrogenation of flavanones (**1**) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in dry benzene in the presence of acetic acid.[1] The following conclusions were drawn: (1) the reaction is first-order in both concentrations of substrate and DDQ; (2) the reaction proceeds along a path of the two-step ionic mechanism and its rate-determining step is a hydride abstraction by quinol cation of DDQ (Scheme 2); (3) the rate is increased by introduction of an electron-donating group at the meta or para position of the side-chain phenyl group, and decreased by introduction an electron-withdrawing one; (4) the apparent second order rate constant, $k_{2,a}$, is proportional directly to the square root of the initial concentration of acetic acid.

On the other hand, it is generally considered that the ortho substituent effect on the reactivity results in various kinds of influences depending upon the sort and condition of reaction. Namely, the steric and proximity effects may participate complicatedly in addition to the normal inductive and resonance ones. Thus, it is general to analyse the ortho substituent effect independently of the meta and/or para substituent ones.

Now, for the purpose of examination of the ortho substituent effect on the dehydrogenation of flavanones, reactions of 2′-substituted flavanones (**1b—f**) with DDQ were conducted under the same reaction conditions as those in the previous work.[1] All analyses of rates of reaction were continued for ten hours after the beginning of reaction (percentages of reaction were ca. 15—33%) by means of HPLC analyses. In this series also, all reactions for five flavanone derivatives followed the second rate law (Eq. 1):

$$dx/dt = k_{2,a}(a-x)(b-x) \quad (1)$$

where a and b are the initial concentrations of substrate and DDQ, respectively, and x is the concentration of product. Rates were determined by the calibration method from the peak area ratio vs. the concentration ratio. Values of $k_{2,a}$, which are the mean of three runs for each sample, are summarized in Table



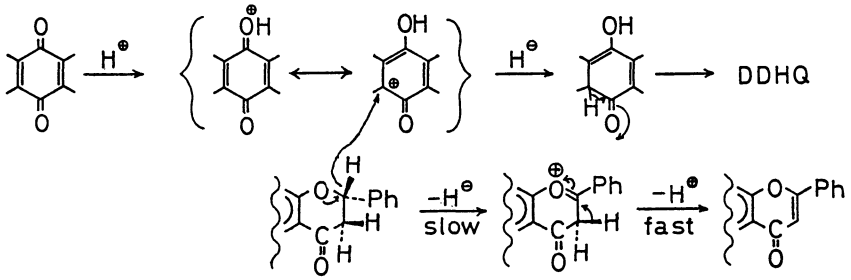
a $R_1=R_2=R_3=H$ **d** $R_1=OCH_3$, $R_2=R_3=H$
b $R_1=Cl$, $R_2=R_3=H$ **e** $R_1=R_3=CH_3$, $R_2=H$
c $R_1=CH_3$, $R_2=R_3=H$ **f** $R_1=R_2=OCH_3$, $R_3=H$

Scheme 1.

Table 1. Apparent Second Order Rate Constants and Relative Rates of Dehydrogenation of 2′-Substituted Flavanones with DDQ[a] at 80.0±0.2 °C

Substrate	Product	$k_{2,a}\times10^3$ / 1 mol^{-1} s^{-1}	k_{rel}[b]
1a	**2a**	1.43[c]	1.00
1b	**2b**	0.472	0.330
1c	**2c**	1.18	0.825
1d	**2d**	0.706	0.494
1e	**2e**	1.49	1.04
1f	**2f**	0.881	0.616

a) Initial concentrations: $[Substrate]_0=[DDQ]_0=1.0\times10^{-2}$ mol l^{-1}; $[CH_3COOH]_0=0.920$ mol l^{-1}. b) k_{rel} relative to $k_{2,a}$ for **1a**. c) From Ref. 1.

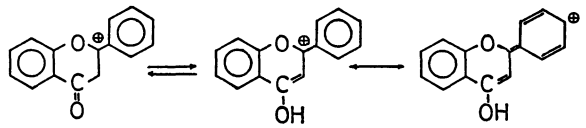


Scheme 2.

1. In the table, k_{rel} is the value relative to $k_{2,a}$ of **1a**. When the reaction proceeded above ca. 50%, correct analysis of the rate was no longer possible because of the precipitation of 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ).

From the results in Table 1, it is clear that all the reaction rates decrease as compared with **1a**, except for **1e**. In contrast with the previous results (conclusion (3)), it is suggested that all the ortho substituents function with a retarding effect on this reaction regardless of their electronic properties. Although the reaction rate of **1e** is slightly greater than that of **1a**, it should be considered that an acceleration effect of the para-methyl group on the rate is comparatively canceled by the ortho-methyl group, because the relative rate of dehydrogenation of 4′-methylflavanone is 1.10.[1)]

A transition state of this reaction is a carbonium cation having a positive charge on the C_2-atom (conclusion (2) and Scheme 3). This carbocation corresponds to a flavylium cation (Scheme 3). In our work



Scheme 3.

on the basicity of flavones,[2)] it has been revealed that the side-chain phenyl group would be planar with the benzopyrylium ring in the state where the proton is added at the carbonyl oxygen atom. When a substituent is present at the ortho position of the side-chain phenyl group, the above-mentioned coplanarity seems to be prohibited in the transition state of this reaction. Thus the resonance effect of the substituent on the phenyl group is inhibited for such a steric reason. Furthermore, the reaction center, the C_2-position, might be blocked by the ortho substituent for the approach of an attacking species, and the rate of reaction decreases consequently. The values of **1b** and **1d** suggest that the inductive effect appears more eminent than the resonance one, because the former effect of the chlorine atom and methoxyl group functions in a retarding way for this reaction; the relative rates of the corresponding para-isomers are 0.923 and 1.37, respectively.[1)]

Taft[3)] and Charton[4)] represented the ortho effect as a linear combination of the inductive, resonance, and steric effects as Eq. 2:

$$\log(k_{rel})_{ortho}=\rho_I\sigma_I+\rho_R\sigma_R+\delta E_s \quad (2)$$

where σ_I, σ_R, and E_s are the inductive, resonance, and steric substituent constants, and ρ_I, ρ_R, and δ are the inductive, resonance, and steric reaction constants, respectively. In the present work, **1e** and **1f** have a meta or para substituent in addition to the ortho one. Then the relation obtained in the previous work[1)] for the meta or para substituted derivatives is added to both sides of Eq. 2 to give Eq. 3:

$$\log(k_{rel})_{o,m,p}=\rho_I\sigma_I+\rho_R\sigma_R^+ +\delta E_s-0.190\sigma^+_{(m,p)} \quad (3)$$

where σ_R^+ is used instead of σ_R because of the introduction of Brown-Okamoto's electrophilic substituent constants, $\sigma^+_{(m,p)}$. According to Eq. 3, ρ_I, ρ_R, and δ were calculated by means of multiple least squares, where the values proposed by Ehrenson et al.[5)] were used for σ_I and σ_R^+ and those by Taft[3)] and Kutter and Hansch[6,7)] were used for E_s (Table 2). The reason for the adoption of these values is their popularity. Particularly, values of constant E_s were derived for heteroatom substituents and for symmetrical-top groups such as H and CX_3 (X=H, halogen, or CH_3). Consequently Eq. 4 was obtained as a linear free energy relationship for the substituent effect on the side-chain phenyl group in this reaction:

$$\log(k_{rel})_{o,m,p}=-0.893\sigma_I-0.042\sigma_R^+ +0.088E_s-0.190\sigma^+_{(m,p)} \quad (4)$$

The correlation coefficient of Eq. 4, 0.999, was obtained on the basis of a slope of the relation between the observed and the calculated values of the logarithmic relative rate (Fig. 1).

Table 2. Ortho Substituent Parameters for the Correlation Using the Linear Combination Model

Substituent	ρ_I[a)]	σ_R^+[b)]	E_S[c)]
H	0	0	0
Cl	0.46	−0.36	−0.97
CH_3	−0.04	−0.25	−1.24
OCH_3	0.27	−1.02	−0.55

a) Inductive substituent constant cited from Ref. 5.
b) Resonance substituent constant cited from Ref. 5.
c) Steric substituent constant cited from Refs. 3, 6, and 7.

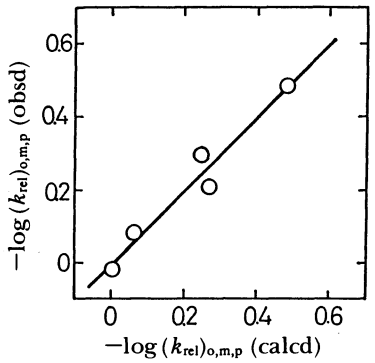


Fig. 1. Correlation between the calculated and the observed logarithmic relative rate.

From the results in Table 1 and Eq. 4, it can be concluded that, in the ortho substituent effect on the side-chain phenyl group for the dehydrogenation of flavanones with DDQ, the inductive effect (ρ_I= −0.893±0.05) is much more important than the steric and resonance effects, of which the steric one is somewhat influential, whereas the latter one is negligibly small. This conclusion is in accord with our recently proposed stepwise mechanism[1)] via the benzopyrylium type cationic intermediate for the DDQ dehydrogenation.

Experimental

All melting points were uncorrected. ^{1}H NMR spectra

were obtained with a Hitachi R-22 (90 MHz) spectrometer by using tetramethylsilane as an internal standard. HPLC analyses were conducted with a Yanagimoto High Speed Liquid Chromatograph L-2000 under the following conditions:

Stationary phase: Yanapak-SA-1

Mobile phase: Hexane-EtOH=10/1 (v/v) for **1d** and **1f**, and 40/1 (v/v) for **1b**, **1c**, and **1e**.

Detector: Yanagimoto U-212 Spectrometer (240 and 300 nm) Estimation: Yanagimoto Computing Integrator-SYSTEM 1000.

Materials. Benzene, acetic acid, and DDQ were of the same grade as those used in the previous work.[1] Flavanones were synthesized from the corresponding 2′-hydroxychalcones by the known procedures,[8] and identified by melting points, ^{1}H NMR, and elemental analyses.

2′-Chloroflavanone (1b): Mp 100—101 °C: ^{1}H NMR (CCl_4) δ=2.52—3.72 (2H, m, C_3-H_{ax}, H_{eq}), 5.75 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=12.0 Hz, $J_{ax\cdot eq}$=3.5Hz), 6.89—7.55 (7H, m, Aromatic), and 7.83 (1H, d·d, C_5-H, J_{ortho}=7.5Hz, J_{meta}=2.4 Hz). Found: C, 69.65; H, 4.13; Cl, 13.72%. Calcd for $C_{15}H_{11}O_2Cl$: C, 69.64; H, 4.29; Cl, 13.70%.

2′-Methylflavanone (1c): Mp 68.5—70.0 °C; ^{1}H NMR (CCl_4) δ=2.39 (3H, s, 2′-CH_3), 2.58—3.11 (2H, m, C_3-H_{ax}, H_{eq}), 5.58 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=12.2 Hz, $J_{ax\cdot eq}$=5.0 Hz), 6.89—7.56 (7H, m, Aromatic), and 7.85 (1H, d·d, C_5-H, J_{ortho}=8.4 Hz, J_{meta}=2.3 Hz). Found: C, 80.61; H, 6.03%. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 6.03%.

2′-Methoxyflavanone (1d): Mp 61.0—62.0 °C; ^{1}H NMR (CCl_4) δ=2.53—3.11 (2H, m, C_3-H_{ax}, H_{eq}), 3.83 (3H, s, 2′-OCH_3), 5.76 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=11.0 Hz, $J_{ax\cdot eq}$=6.4 Hz), 6.78—7.60 (7H, m, Aromatic), and 7.85 (1H, d·d, C_5-H, J_{ortho}=8.0 Hz, J_{meta}=1.6 Hz). Found: C, 75.50; H, 5.62%. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55%.

2′,4′-Dimethylflavanone (1e): Mp 88—89 °C; ^{1}H NMR (CCl_4) δ=2.33 and 2.36 (3H, 3H, s, s, 2′ and 4′-CH_3), 2.56—3.12 (2H, m, C_3-H_{ax}, H_{eq}), 5.56 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=12.5 Hz, $J_{ax\cdot eq}$=4.6 Hz), 6.92—7.53 (6H, m, Aromatic), and 7.88 (1H, d·d, C_5-H, J_{ortho}=7.8 Hz, J_{meta}=2.2 Hz). Found: C, 81.31; H, 6.55%. Calcd for $C_{17}H_{16}O_2$: C, 81.25; H, 6.42%.

2′,3′-Dimethoxyflavanone (1f): Mp 96.0—96.5 °C; ^{1}H NMR (CCl_4) δ=2.64—3.08 (2H, m, C_3-H_{ax}, H_{eq}), 3.87 (6H, s, 2′ and 3′-OCH_3), 5.74 (1H, d·d, C_2-H_{ax}, $J_{ax\cdot ax}$=10.5 Hz, $J_{ax\cdot eq}$=6.8 Hz), 6.79—7.52 (6H, m, Aromatic), and 7.88 (1H, d·d, C_5-H, J_{ortho}=8.5 Hz, J_{meta}=2.0 Hz). Found: C, 72.20; H, 5.74%. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%.

Flavones as authentic samples for HPLC analyses were prepared by the same reaction as carried out in the kinetic experiment, and were isolated and purified by the known procedures.[9] Their physical data are as follows, except for **2c** which was identified by the value in literature.[10]

2′-Chloroflavone (2b): Mp 117.0—117.5 °C; ^{1}H NMR (CCl_4) δ=6.48 (1H, s, C_3-H), 7.27—7.75 (7H, m, Aromatic), and 8.14 (1H, d·d, C_5-H, J_{ortho}=8.3 Hz, J_{meta}=2.3 Hz). Found: C, 70.40; H, 3.47; Cl, 13.71%. Calcd for $C_{15}H_9O_2Cl$: C, 70.19; H, 3.53; Cl, 13.76%.

2′-Methylflavone (2c): Mp 46.0—47.5 °C (lit, 47.5 °C[10]).

2′-Methoxyflavone (2d): Mp 98.5—100 °C; ^{1}H NMR (CCl_4) δ=3.93 (3H, s, 2′-OCH_3), 6.84 (1H, s, C_3-H), 6.92—7.83 (7H, m, Aromatic), and 8.11 (1H, d·d, C_5-H, J_{ortho}=8.2 Hz, J_{meta}=2.0 Hz). Found: C, 76.09; H, 4.80%. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79%.

2′,4′-Dimethylflavone (2e): Mp 64.5—66.0 °C; ^{1}H NMR (CCl_4) δ=2.34 (3H, s, 4′-CH_3), 2.43 (3H, s, 2′-CH_3), 6.24 (1H, s, C_3-H), 6.96—7.66 (6H, m, Aromatic), and 8.12 (1H, d·d, C_5-H, J_{ortho}=8.5 Hz, J_{meta}=2.0 Hz). Found: C, 81.50: H, 5.71%. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64%.

2′,3′-Dimethoxyflavone (2f): Mp 85.5—87.5 °C; ^{1}H NMR (CCl_4) δ=3.91 and 3.94 (3H, 3H, s, s, 2′ and 3′-OCH_3), 6.98 (1H, s, C_3-H), 7.05—7.80 (6H, m, Aromatic), and 8.25 (1H, d·d, C_5-H, J_{ortho}=7.6 Hz, J_{meta}=1.5 Hz). Found: C, 67.64; H, 4.77%. Calcd for $C_{17}H_{14}O_4$: C, 67.55; H, 4.67%.

Procedures. Reactions and kinetic analyses were carried out in almost the same conditions and procedures as in the previous work.[1] Some comments are given in the footnote of Table 1.

References

1) Y. Hoshino and N. Takeno, *Nippon Kagaku Kaishi*, **1986**, 157.

2) Y. Hoshino, S. Takeda, M. Hamada, and N. Takeno, *Nippon Kagaku Kaishi*, **1982**, 1564.

3) R. W. Taft, "Steric Effects in Organic Chemistry," ed by M. S. Newman, John Wiley & Sons, New York (1956), p. 556.

4) M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971).

5) S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).

6) E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 674 (1969).

7) R. W. Taft, T. Fujita, and T. Nishioka, "Progress in Physical Organic Chemistry," Vol. 12, John Wiley & Sons, New York (1976), p. 49.

8) T. Oyamada, *Nippon Kagaku Zasshi*, **55**, 1256 (1934); S. Fujise, Y. Fujii, H. Maeda, K. Takagi, and S. Nakamura, *Nippon Kagaku Zasshi*, **74**, 827 (1953); B. Sen, *J. Am. Chem. Soc.*, **74**, 3446 (1952).

9) P. T. Kropp, *J. Org. Chem.*, **29**, 3110 (1930).

10) F. Cramer and G. H. Elschnig, *Chem. Ber.*, **89**, 1 (1956).