Cyclization of Substituted 2'-Hydroxychalcones to Flavanones. Solvent and Isotope Effects

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The kinetic isotope effects on the cyclization of substituted 2'-hydroxychalcones (R = 3-hydroxy, 4'-hydroxy, 4,4'-dihydroxy, 4'-hydroxy-4-nitro, 4-nitro, or 5'-methyl) into the corresponding substituted flavanones have been measured in water and/or methanol. The pronounced isotope effects observed are consistent with the slow rupture of a bond to hydrogen. The effect of the medium permittivity on the rate of cyclization of 2'-hydroxy, 2',4-dihydroxy-, and 2',4'-dihydroxychalcones have been also studied in several mixed solvents and the observed dependence is consistent with a reaction between one ion and one dipole. These results confirm a mechanism that involves general acid attack of the ionized form of the 2'-hydroxychalcones, concerted rotation through the $CO-C_\alpha$ bond, and annellation to the flavanone.

The chalcone system is the subject of increasing interest because it has been found to be a useful intermediate for the synthesis of compounds containing the benzopyran ring system,[1] and for other related substances.[2] Several substituted chalcones have been isolated from plants[3,4] and have been found to exhibit pharmacological properties.[5] In particular, 2'-hydroxychalcones (1) [equation (1)] can be isolated as such or in the form of the cyclization product, the flavanone (2). Reaction (1) is catalysed in plants by chalcone–flavanone isomerase and it seems to be involved in the biosynthesis of flavonoids.[3,6] The rate of interconversion of (1) and (2) and the stabilities of forms (1) and (2) are largely dependent on the pH of the medium.[2] In spite of its biological and chemical importance, the mechanism of reaction (1) has so far received little


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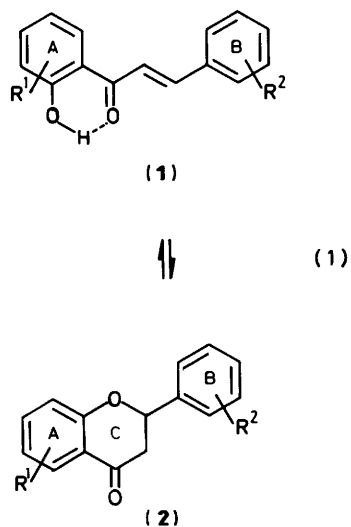
attention. Kinetic studies of the transformations undergone by the 4'-hydroxyflavylium ion in aqueous solution[7] and of the cyclization of 2'-hydroxychalcones[8,9] have recently been published. In our previous report[9] on the mechanism of reaction (1) we proposed a general attack by H^+ of the ionized form of (1) which produces rotation through the $CO-C_\alpha$ bond and concerted annellation to (2), a mechanism

which differs from the stepwise addition–elimination proposed by Old and Main.[8] In order to afford further evidence in support of the proposed mechanism a study of the influence of the medium permittivity upon the reaction rate is now reported. The effect of deuterium substitution in the reagent was also studied and the high isotope effects observed in the kinetics of several substituted 2'-hydroxychalcones confirm the existence of a general acid slow step.

Results and Discussion

Solvent Effects.—A great number of solvent parameters has been defined in an attempt to develop a general treatment applicable to the solvent effects,[10–12] but a fully satisfactory theory has not been attained yet. Although in previous studies of solvent effects on different systems we have used relatively new parameters[13] and even multi-parameter equations,[14,15] in this case we decided to use the more classical treatment based on the relative permittivity of the medium since other parameters are not available for the mixed solvents systems used in this work. The very well known Kirkwood's[16] relationship between the reaction rate constant and the medium relative permittivity, *D*, for bimolecular reactions given by equation (2) can be
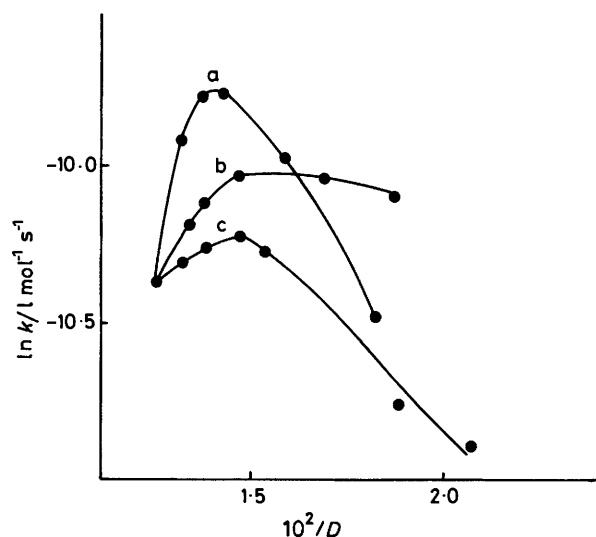

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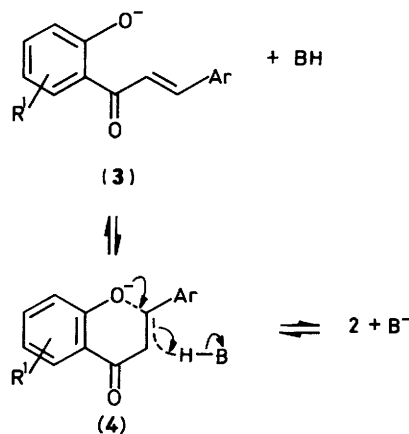
Scheme.

Table 1. Cyclization of 2'-hydroxychalcone in basic solution at 26 °C[a]

Solvent	$10^4 k_{obs.}/s^{-1}$	δ^b	[H − D][c]/ mol l⁻¹	$10^5 k/l$ mol⁻¹ s⁻¹	D^d	μ^e/D
Water	49.6	0.9982	55.45	8.94	80.37	1.82
Methanol	18.2	0.7914	24.73	7.36	32.35	1.71
Isopropyl alcohol	5.66	0.7855	13.07	4.33	18.62	1.67
t-Butyl alcohol	0.116	0.7887	10.64	1.09	10.2[f]	1.67

[a] Kinetics were measured at 420 nm. [OH⁻] ≃ 0.03 mol l⁻¹. [b] 20 °C; Ref. 18. [c] H⁺-donor–dipole concentration. [d] 20 °C; Ref. 19. [e] Data from A. L. McClellan, 'Tables of Experimental Dipole Moments,' Freeman, New York, 1963. [f] From the plot of D vs. T and D vs. % alcohol (ref. 19).

Table 2. Cyclization of 2'-hydroxychalcone in basic methanol–dioxane mixtures at 14.6 °C[a]

%Dioxane	$10^4 k_{obs.}/s^{-1}$	[H − D][b]/ mol l⁻¹	$10^5 k/l$ mol⁻¹ s⁻¹
0	4.70	24.87	1.89
5.19	4.78	23.87	2.00
8.35	4.84	23.24	2.08
31.5	4.85	18.37	2.64

[a] [OMe⁻] = 2.66 10⁻² mol l⁻¹. [b] H⁺-donor–dipole concentration.

Figure 1. Cyclization of 2'-hydroxychalcone in alkaline mixed solvents at 14.6 °C: a, water–methanol; b, water–dioxane; c, water–isopropyl alcohol

$$\ln k = \ln k_0 + \frac{e^2}{2 kT}\left(\frac{1}{D} - 1\right)\left[\frac{z_A^2}{r_A} + \frac{z_B^2}{r_B} - \frac{(z_A + z_B)^2}{r^\ddagger}\right] + \frac{3}{8 kT}\left(\frac{1 - D}{D + 1}\right)\left[\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} + \frac{\mu^{\ddagger 2}}{r^{\ddagger 3}}\right]. \quad (2)$$

substantially simplified in the present case. In fact, the proposed mechanism is depicted in the Scheme and since it implies the interaction between one ion and one dipole, equation (2) can be simplified to equation (3) neglecting the dipolar term.[17]

$$\ln k = \ln k_0 + \frac{e^2 z_A^2}{2 kTD}\left(\frac{r^\ddagger - r_A}{r^\ddagger r_A}\right) \quad (3)$$

Equation (3) predicts that, other effects being constant, the rate of the reaction should increase when the permittivity of the medium diminishes.

Cyclization of 2'-Hydroxychalcone.—The structural transformations undergone by the title compound were kinetically studied in the following mixtures: water–methanol, water–dioxane, and water–isopropyl alcohol. Since in these systems

the proton donor is the solvent, the second-order rate constant, k, was estimated as the rate constant per unit concentration of the protic species present in the solution. The experimental rate constants plotted against inverse relative permittivity[18,19] are shown in Figure 1. It can be observed in all the cases that ln k increases with small additions of organic solvent to water. Taking into account the various protic species present, only for the case of water–dioxane does the curve shown in Figure 1 represent strictly the variation of ln k with $1/D$: this is seen as a rate increase in the region of high D; for media containing larger aprotic solvent content the curve departs from the ideal behaviour [equation (3)].

Comparison of the different slopes of the curves in Figure 1 at high D-values allows an estimation of the relationship between the rate of reaction and the acidity of the protic species (which is a hypothetical species: an 'average' of the several types of hydroxylic species present in the medium). In the high-D region, the slopes of the curve ln k vs. $1/D$ decreases in the order water–methanol, water–dioxane, water–isopropyl alcohol, which is the order of the decreasing acidity of the protic agent present in each medium,[20] MeOH > water > Me₂CHOH.

In order to verify the influence that the acidity of the medium has on the rate of reaction (1), the cyclization of 2'-hydroxychalcone was then studied in some pure alcohols. The observed second-order rate coefficients of the reaction of 2'-hydroxychalcone carried out in dilute aqueous alkali, methanol, and isopropyl and t-butyl alcohols at 26 °C are presented in Table 1. It can be observed that the rate of the reactions in these alcohols decreases in the order of the decreasing acidity.

Finally, in order to confirm that the reaction in non-aqueous solvents implies also the interaction between one ion and one dipole, the cyclization of 2'-hydroxychalcone was studied in alkaline methanol–dioxane mixtures. The observed second-order rate coefficients for the reactions carried out in pure methanol and dioxane–methanol mixed solvents at 14.6 °C are shown in Table 2. An increase in rate is observed with increasing additions of dioxane to the medium, as would be expected for the decreased relative permittivity of the medium if equation (3) applies.

Cyclization of 2',4- and 2',4'-Dihydroxychalcones.—In order to verify whether the reactions of substituted 2'-hydroxychalcones are similarly influenced by the relative permittivity of the medium, the rates of the reactions of the title chalcones were determined in water–methanol mixtures and the results are plotted in Figure 2. In both cases an increase in rate is observed with a decrease in the medium's relative permittivity in the high D-region.

Although more significant mechanistic conclusions cannot be drawn for an analysis in terms of the bulk medium relative permittivities, all the above results are consistent with the proposed mechanism as it implies a reaction between one ion and one dipole.
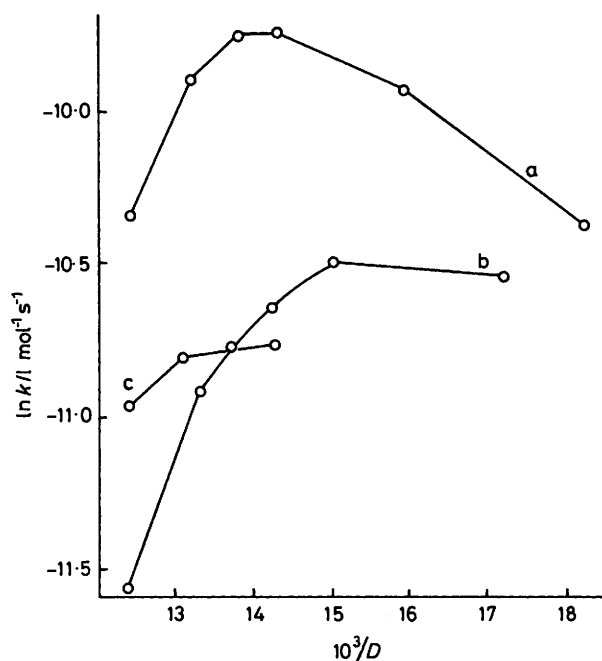
Figure 2. Cyclization of a, 2'-hydroxychalcone; b, 2',4-dihydroxychalcone; c, 2',4'-dihydroxychalcone in NaOH–water–methanol mixtures

Table 3. Cyclization of substituted 2'-hydroxychalcones at 25 °C studied in the pH-independent region[a]

Solvent	Substituent	λ/nm[b]	$10^5 k^c/\text{l}$ $\text{mol}^{-1}\,\text{s}^{-1}$	$\Delta H^{\ddagger}/\text{kJ}$ mol^{-1}	$-\Delta S^{\ddagger}/\text{J}$ $\text{mol}^{-1}\,\text{K}^{-1}$
Water	4-OH	400	0.58 ± 0.02	69.1	110
	4',4-(OH)₂	432	1.46	67.5	108
	4'-OH	410	3.91	61.7	120
	3'-OMe-4'-OH	410	3.59	62.9	116
	4'-OH-4-NO₂	425	1.70	73.3	87
	3-OH	400	5.68	60.4	120
	H	320 410	8.2 ± 0.3	62.1	112
Methanol	H	420	6.61	80.7	50
	4-NO₂	317	5.29	74.1	75
	5'-Me	430	7.35	70.0	85
	4-OH	440	2.0 ± 0.1[d]		
	3-OH	420	3.9 ± 0.2		
	4'-OH	400	4.0[e]		

[a] Error in $\Delta H^{\ddagger}$ ± 2.5 kJ mol⁻¹. $\Delta S^{\ddagger}$ ± 9 J mol⁻¹ K⁻¹. [b] Wavelength of the kinetic measurements. [c] Error in $k \leqslant 2\%$ unless otherwise stated. [d] At 22.5 °C. [e] Estimated values (experimental at [OMe⁻] ~ 0.2 mol l⁻¹).

Table 4. Isotope effects on the cyclization of substituted 2'-hydroxychalcones in the pH-independent region

Substituents	$T/°C$	k_H/k_D (water)	k_H/k_D (methanol)	$10^5 k_H{}^a/\text{l}$ $\text{mol}^{-1}\,\text{s}^{-1}$
4-OH	24.9	11		0.58
4-OH	22.5		9.3	2.00[b]
4,4'-(OH)₂	29.0	10.5		1.46
4'-OH	22.4	2.5		3.91
4'-OH, 4-NO₂	22.5	1.7		1.70
H	25.5	5.3		8.22
H	26.5		1.3	6.61
4-NO₂	24.4		1.2	5.29
5'-Me	26.1		1.25	7.25

[a] At 25 °C. [b] At 22.5 °C.

Substituent Effects.—In our previous work on this reaction we examined the effect of some substituents. A more thorough research of the substituent effects was then carried out and the results are shown in the Table 3. Since some compounds are only sparingly soluble in water the reactions were studied in methanol and the kinetics of the reactions of 2'-hydroxychalcone and of 2',4-dihydroxychalcone were determined in both solvents to allow rate comparisons. The most notable feature of the results is the small variations in rate coefficients throughout Table 3. It can be observed that the reactions in methanol are less sensitive to substituent effects that the reactions in aqueous media, but even in this solvent the rates are within one order of magnitude. It can also be observed that electron-donor (such as the oxyanion) as well as electron-acceptor (such as the nitro group) substituents diminish the rate irrespective of their positions in the rings. Old and Main[8] examined only the effect of electron-donor substituents in the A ring, and they observed a decrease in rate. Table 3 also shows that an oxyanion in the *para* position of ring B has almost the same effect as a nitro group in the same position. This lack of sensitivity to substituents effects is consistent with the concerted mechanism proposed in the Scheme: in fact, electron-donating substituents would favour the attack of H⁺ on C-α while electron-withdrawing substituents would facilitate the addition of phenoxide onto C-β. Although Old and Main[8] did not study the effect of substituents in the ring B, a unimolecular mechanism such as that proposed by them or by Panasenko *et al.*[21] would require the observation of an acceleration in rate by substituents that increase the electrophilicity of C-β, (*e.g.* 4-O⁻) when, in fact, the opposite effect was found. In fact, in both solvents, the reaction of the 2',4-dihydroxychalcone was the slowest of all the compounds studied: in this case it is clear that the conjugate nucleophilic displacement of B⁻ is a slow step.

Isotope Effects.—The reaction of 2'-hydroxychalcone has been previously studied in glycine–NaOH buffer[9] and the dependence of the reaction rate on the buffer concentration indicated general acid catalysis. In order to confirm that this

would imply some rate-determining proton transfer, such as that depicted in the Scheme, the reaction rates of several chalcones were studied in NaOD–D₂O or in NaOD–CD₃OD. Table 4 shows the observed isotope effects (k_H/k_D) and also the second-order rate coefficients for the reactions with the naturally abundant isotope, k_H. The isotope effects for 2'-hydroxychalcone and for 2',4-dihydroxychalcone were determined in alkaline aqueous and methanolic media to allow comparison.

The magnitude of the observed isotope effect is extremely important. The chalcones in which there is a hydroxy group at the *para* position of ring B exhibit the greater kinetic isotope effects, which are in the range expected for a rate-determining O–H rupture. On the basis of the observed substituent effects, the addition of water to form intermediate (4) and the conjugate nucleophilic displacement of B⁻ were proposed to have similar rates or to constitute a concerted process. In the reaction of 2',4-dihydroxychalcone the addition of BH is favoured by the electron-donating substituent at the 4-position and the slower step is the concerted oxyanion attack on C-β and rupture of the B–H bond which is responsible for the huge I.E. observed. By contrast, when an electron-withdrawing group (the nitro group) is in the 4-position, the first step (addition of BH) is relatively slower than the second and the observed I.E.s are, consequently, very small. Deuterium kinetic isotope effects are known to depend on two factors: one depending on the loss of zero-point

energy for OH and OD between the initial and the transition state, and the other concerned with the quantum-mechanical probability of tunnelling of the proton through the energy barrier. The former will depend on the 'symmetry' of the transition state[22] and the second has recently been attributed to the contribution of steric hindrance;[23] values of $k_H/k_D = 20$ have been observed when both factors are operative. Since there are no important steric differences between the compounds studied the large I.E. observed also for the 2'-hydroxychalcone may be considered as an indication of the degree of concertedness of the reactions involved, producing highly symmetric transition states.

The I.E. effects observed in methanol (Table 4) are smaller than those measured in water and these results are consistent with the lower sensitivity to substituent effects already mentioned and the levelling effect of this solvent in the reactions described resulting from its relatively high acidity.

It was observed that after the equilibrium shown in equation (1) had been reached the n.m.r. spectrum of 2',4'-dihydroxychalcone changed when it was allowed to stand in NaOD–D$_2$O solution for several hours (see the Experimental part). Since no report of this was found in the literature, the reaction of the base-catalysed aromatic hydrogen exchange was studied in aqueous and in methanolic media and the results are reported by us elsewhere;[24] the rate of this reaction is sufficiently low to have no effect on the cyclization kinetic isotope effects. When only one hydroxy group is present on ring A, aromatic isotope exchange is slow and less regiospecific. Compounds such as 2'-hydroxy-, 2',3-dihydroxy-, 2',4'-dihydroxy-, and 2'-hydroxy-4-nitrochalcones show an extremely slow isotope exchange randomly distributed among the various exchangeable phenyl protons. This additional study is further evidence that the kinetic isotope effects observed above are not artifacts but represent genuine and unperturbed values.

Experimental

M.p.s are uncorrected. U.v. and visible spectra were recorded with a Beckman DK-2A spectrophotometer. ^{1}H N.m.r. spectra were run with a Varian EM 360 A spectrometer using SiMe$_4$ as an internal standard. 2'-Hydroxy-, 2'-hydroxy-4-nitro-, 2',3-dihydroxy-, 2',4-dihydroxy-, and 2',4'-dihydroxy-, and 2',4'-dihydroxy-3-methoxychalcones were prepared as previously described.[9]

2'-Hydroxy-5-methylchalcone.—Benzaldehyde (2.0 g, 18.8 mmol) was mixed with 2'-hydroxy-5'-methylacetophenone (2.5 g, 16.7 mmol) and ethanolic NaOH (10%; 50 ml) and the reaction was allowed to proceed for 8 h at room temperature whereupon an orange solid precipitated. The reaction mixture was acidified (using 10% aqueous hydrochloric acid) and extracted with ethyl acetate. The organic extract was washed three times with water, dried (Na$_2$SO$_4$), and evaporated. Chromatographic purification of the residue on a Sephadex LH-20 column using methanol as the eluant gave the desired compound (1.9 g, 48%), m.p. 109—110 °C; $\lambda_{max.}$(MeOH) 315, 365, and 290 nm; $\lambda_{max.}$(HOMe–NaOMe) 303, 434, and 247 nm; δ(Cl$_3$CD) 12.65 (1 H, s, 2'-OH), 2.35 (3 H, s, 5'-Me), 6.90 (1 H, d, J 9 Hz, 3'-H), 7.95 (1 H, d, J 16 Hz, H$_\beta$), and 7.15—7.85 (8 H, m, H$_\alpha$, 4'-, 6'-H, and ring B protons).

2',4,4'-Trihydroxychalcone.—2',4'-Dihydroxyacetophenone (2.5 g, 16.4 mmol) and benzaldehyde (2.0 g, 16.4 mmol) were dissolved in ethanol (30 ml). Aqueous KOH (60%; 30 ml) was added dropwise and the mixture was allowed to react at 4 °C for 3 days. The solid material was worked up as described above and purified by column chromatography: first on Kieselgel 40 silica gel using benzene–ethyl acetate (8:2) as the

eluant and then on Sephadex LH-20 eluting with methanol. The pure yellow crystals had m.p. 179—181 °C (lit.,[25] 187—188 °C), $\lambda_{max.}$(MeOH) 370, 329, 310, and 249 nm; $\lambda_{max.}$(H$_2$O) 369, 310, and 235 nm; $\lambda_{max.}$(H$_2$O–NaOH) 430, 350, 260, and 240 nm; δ[(CD$_3$)$_2$CO] 13.65 (1 H, s, 2'-OH), 6.35—6.60 (2 H, m, 3'- and 5'-H), 6.95 (2 H d, J 9 Hz, 3-and 5-H), 7.75 (2 H, d, J 9 Hz, 2- and 6-H), 7.85 (2 H, s, H$_\alpha$ and H$_\beta$), and 8.10 (1 H, d, J 9 Hz, 6'-H).

2',4'-Dihydroxy-4-nitrochalcone.—4-Nitrobenzaldehyde (2.0 g, 13.2 mmol) and 2',4'-dihydroxyacetophenone (1.8 g, 13 mmol) were dissolved in ethanol (100 ml). A buffer of Na$_2$HPO$_4$–NaOH (pH 10) with a little glycine as catalyst was then added. The reaction was allowed to proceed at room temperature for 1 week. The reaction mixture was then worked up as usual. The residue was dissolved in methanol and purified on a Sephadex LH 20 column. The eluate was treated with 15% aqueous NaOH, acidified, extracted with ethyl acetate, dried, and evaporated. Further purification of the residue on a Sephadex LH-20 column eluting with methanol led to pure crystals of the title chalcone (0.04 g, 1.2%), m.p. 223—225 °C; $\lambda_{max.}$(H$_2$O) 300 and 340 nm; $\lambda_{max.}$(H$_2$O–NaOH) 240, 325, and 423 nm; $\lambda_{max.}$(MeOH) 290, 318, and 350 nm; δ[(CD$_3$)$_2$CO] 13.40 (1 H, s, 2'-OH), 6.25—6.60 (2 H, m, 3'- and 5'-H), and 7.50—8.65 (7 H, m, 6'-H, H$_\alpha$, H$_\beta$, and ring B protons).

Kinetic Measurements.—Kinetic determinations were performed spectrophotometrically as previously described.[9] In all cases kinetics were measured for the pH-independent region and pseudo-first-order kinetics were observed. The standard deviation in the specific rate-constant was $\leqslant 2\%$ and the temperature constancy was to within ± 0.1 °C.

The overall rate of the substrate disappearance is given by equation (4):

$$\frac{-d[(1)]}{dt} = k \, [(1)][HB] \qquad (4)$$

where k is the rate constant for the overall process. The permittivity values were calculated from a plot of D_{20} vs. %organic solvent (w/w) using the data given by Akerlöf.[19] The proton-donor–dipole concentration was estimated using equation (5) when both solvents are proton donors and equation (6) when only one solvent is a proton donor.

$$[H - D] = \frac{\%A/M_A + \%B/M_B}{\%A/\delta_A + \%B/\delta_B} \times 1\,000 \qquad (5)$$

$$[H - D] = \frac{\%A/M_A \times 1\,000}{\%A/\delta_A + \%B/\delta_B} \qquad (6)$$

where M is the molecular weight, δ the density, and A and B are the mixture components.

The n.m.r. spectrum of 2',4'-dihydroxychalcone changes when it is allowed to stand in NaOD–D$_2$O solution for several hours. Among other changes due to the cyclization process[9] the signals due to the 3'-H and 5'-H protons change with time while the ring B protons remain practically invariant. Doublets due to 6-H of flavanone and to 5'-H of the chalcone are both observed, but the signal for 3'-H of chalcone disappeared and also the signal due to the 8-H of the flavanone was absent. Consequently the respective coupling between 5'-H and of 6-H with the above mentioned protons also disappeared. For all the other chalcones studied the aromatic hydrogen exchange was extremely slow and not very regiospecific. The results have been confirmed by mass spectrometric measurements.[24]

Acknowledgements

References

1 J. Mirek and Z. Miara, *Synthesis*, 1981, 979.

2 D. N. Dhar, 'The Chemistry of Chalcones and Related Compounds,' Wiley, New York, 1981.

3 'The Flavonoids,' Part 2, eds. J. B. Harborne, T. J. Mabry, and H. Mabry, Academic Press, New York, 1975; 'Biochemistry of Phenolic Compounds,' Academic Press, London and New York, 1964.

4 L. Jurd, 'The Chemistry of Flavanoid Compounds,' C. O. Chichester Academic Press, New York, 1972, p. 123; *Recent Adv. Phytochem.,* 1972, 135.

5 J. Sallai, M. Gabor, and F. Kallay, *Acta Pharm. Hung.,* 1976, **46**, 49; J. Metzner, H. Bekemeier, M. Paintz, and E. Schneidewind, *Pharmazie*, 1979, **34**, 97; Y. B. Vibhute and S. S. Wadje, *Indian J. Exp. Biol.,* 1976, **14**, 739.

6 L. Jurd, 'The Chemistry of Plant Pigments,' C. O. Chichester, Academic Press, New York, 1972; J. B. Harborne, T. J. Mabry, and H. Mabry, 'The Flavonoids,' Part 1, Academic Press, New York, 1975.

7 R. A. McClelland and G. H. McGall, *J. Org. Chem.,* 1982, **47**, 3730.

8 K. Barry Old and L. Main, *J. Chem. Soc., Perkin Trans. 2,* 1982, 1309.

9 J. J. P. Furlong and N. S. Nudelman, *J. Chem. Soc., Perkin Trans. 2,* 1981, 633.

10 M. Begtrup, R. W. Taft, and M. J. Kamlet, *J. Org. Chem.,* 1986, **51**, 2130 and refs. cited therein.

11 C. Reichardt and E. Harbusch-Gornert, *Liebigs Ann. Chem.,* 1983, 721.

12 C. G. Swain, *J. Org. Chem.,* 1984, **49**, 2005.

13 P. M. E. Mancini, R. D. Martínez, L. R. Vottéro, and N. S. Nudelman, *J. Chem. Soc., Perkin Trans. 2,* 1984, 1133.

14 R. D. Martínez, P. M. E. Mancini, L. R. Vottero, and N. S. Nudelman, *J. Chem. Soc., Perkin Trans. 2,* 1986, 1427.

15 N. S. Nudelman, P. M. E. Mancini, R. D. Martínez, and L. R. Vottero, *J. Chem. Soc., Perkin Trans. 2,* 1987, 951.

16 J. S. Kirkwood, *J. Chem. Phys.,* 1934, **2**, 351.

17 E. A. Moelwyn-Hughes, 'Chemical Statics and Kinetics of Solutions,' Academic Press, London, 1971, p. 271.

18 'Handbook of Chemistry and Physics,' ed. R. C. Weast, 55th edn., CRC, Cleveland, Ohio, 1974—1975.

19 G. Akerlöf, *J. Am. Chem. Soc.,* 1932, **54**, 4125.

20 J. Hine and M. Hine, *J. Am. Chem. Soc.,* 1952, **74**, 5266.

21 A. I. Panasenko, O. I. Kachurin, and S. P. Starkov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.,* 1975, **18**, 1203.

22 L. Melander and W. H. Saunders Jr., 'Reaction Rates of Isotopic Molecules,' Wiley, New York, 1980.

23 P. Pruszynsky and A. Jarczewski, *J. Chem. Soc., Perkin Trans. 2,* 1986, 1117.

24 J. J. P. Furlong and N. S. Nudelman, *Acta Sud Am. Quim. (Chile),* 1984, **3**, 130.

25 'Atlas of Spectral Data and Physical Constants for Organic Compounds,' eds. J. G. Grasselli and W. M. Ritchey, 2nd. edn., CRC, Cleveland, Ohio, 1975, vol. 3, p. 45.