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Kinetics and Mechanism of the Cyclisation of Some 2'-Hydroxychalcone Epoxides and Subsequent Elimination Reactions of Aurone Hydrates

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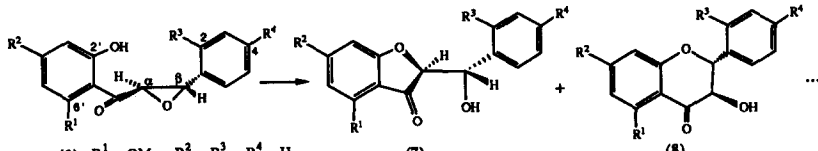
Abstract: Analysis of the pH-rate profile for the cyclisation of the monoanion of 2'-hydroxychalcone epoxide which gives 3-hydroxyflavanone and of some 6'-alkoxy-substituted analogues which give mostly aurone hydrate, gives rate coefficients which quantify the preference for α over β cyclisation when 6'-substituents are present. These are considered in terms of stereoelectronic factors which may be responsible for the preference. Also reported are rate coefficients for the subsequent reaction of aurone hydrates in which aurones and coumaranones are formed.

We recently described[1] the first synthesis of 2'-hydroxychalcone epoxides with 6'-substituents (**1-5**) and reported[2] on their preference to cyclise (equation 1) to aurone hydrates (**7**) rather than 3-hydroxyflavanones (**8**), the products expected in the absence of 6'-substituents by analogy with the cyclisation [**6**→**8**(R^1=R^2=R^3=R^4=H)] of the only previously known 2'-hydroxychalcone epoxide, the parent epoxide (**6**) itself[3,4]. The redirection of cyclisation away from the β-position to the α-position of the epoxide when a 6'-substituent is present was of course expected from previous product studies of some reactions in which such epoxides have been postulated as intermediates in aurone formation. These include the reactions of 6'-substituted 2'-hydroxychalcones with alkaline hydrogen peroxide (AFO reaction)[5,6,7,8] and of reactions with base of 6'-substituted 2'-hydroxychalcone dibromides[9] (Emilewicz-von Kostanecki reaction) and bromohydrins[10] (Rasoda reaction). The strongly alkaline conditions of all these reactions would preclude detection of chalcone epoxide intermediates, as we know from our earlier[4] kinetic study that even at pH 7 in water the parent epoxide (**6**) has a half-life of about 4 seconds and the rate increases in proportion with hydroxide concentration.



...Eq. 1

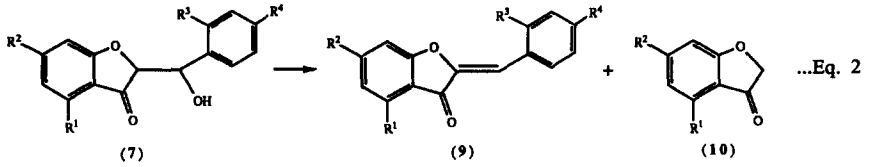
(1) R^1 = OMe; R^2 = R^3 = R^4 = H
(2) R^1 = O^{i}Pr; R^2 = R^3 = R^4 = H
(3) R^1 =OMe; R^2 = OMe; R^3 = R^4 = H
(4) R^1 = OMe; R^2 = R^4 = H; R^3 = CF_3
(5) R^1 = OMe; R^2 = R^3 = H; R^4 = Cl
(6) R^1 = R^2 = R^3 = R^4 = H

(7) (8)

Factors considered[2] as possibly determining the preference for α-cyclisation when the C=O group of the epoxide is forced by interaction with a 6'-substituent to lie out-of-plane with the aromatic ring were first that a conformation favourable to β-cyclisation becomes stereoelectronically disfavoured, and second that there is less delocalisation from the 2'-O^- group onto the C=O (steric inhibition of resonance), this having two interrelated effects. Not only is the 2'-O^- more nucleophilic but also the α-carbon to which it cyclises is more electrophilic because of the increased electron-withdrawing capacity of the carbonyl group when it is out-of-plane.

This question of whether the out-of-plane C=O results in α-cyclisation by restricting β-cyclisation (stereoelectronic deactivation) or by promoting α-cyclisation (electronic activation) might be expected to show up in rates of cyclisation of 6'-substituted *vs* non-6'-substituted epoxides. In the present study, rates of cyclisation measured as a function of pH give absolute rate coefficients for chalcone monoanion cyclisation. Knowledge[2] of the proportion of α- *vs* β-cyclisation for the epoxides under the conditions of the present study allows the calculation of rate coefficients for α- and β-cyclisation. A comparison in particular of the α-cyclisation rates as a function of aryl ring substituents will be seen to throw some significant light on the question of the factors controlling the preference for α- over β-cyclisation in the 6'-substituted cases.

Also reported are rate data for the subsequent elimination reactions at higher pH in which aurone hydrates form aurones (**9**) and coumaranones (**10**), the respective products of dehydration and dealdolisation (equation 2).



...Eq. 2

EXPERIMENTAL

Materials

The preparation of the chalcone epoxides has been previously described.[1]

Redistilled analytical grade acetonitrile and doubly glass-distilled deaerated water were used in the preparation of buffer solutions.

Kinetic Measurements

Kinetics were measured at 30°C in 1:1 v/v MeCN-H_2O solutions containing KCl to maintain ionic strength (μ = 0.20 mol l^{-1}). Buffering was achieved with low concentrations (< 0.01 mol $^{-1}$) of analytical grade acetate (pH 5.2 - 6.5), phosphate (6.8 - 7.9 and 10.0 - 12.0), trishydroxymethylaminomethane (7.9 - 9.4) and carbonate (9.9 - 11.5) reagents. Unbuffered KOH was used above pH 12.0.

Absorbance changes with time were monitored using Kontron Uvikon 810 and 860 spectrophotometers for reaction half-lives over about 20s, and for faster reactions using a Durrum D-110 stopped-flow instrument fitted with a Tektronix Oscilloscope R5103N and Biomation Waveform Recorder model 805. The instrument was calibrated with the standard ferric nitrate-potassium thiocyanate reaction. A narrow bore drive syringe was used for the chalcone epoxide solution in acetonitrile and a wide-bore syringe for a solution of KCl in MeCN-H_2O of volume ratio calculated to give a nett 1:1 v/v MeCN-H_2O ratio once mixed with the epoxide solution in the reaction chamber. The nett 1:1 volume ratio was confirmed by density measurements on the effluent solution from the reaction chamber.

Observed first order rate coefficients (k_{obs}) for epoxide cyclisations were calculated as the gradients of plots of $\ln(A_t - A_{infinity})$ versus time. Rate coefficients for duplicate runs for slower reactions on the spectrophotometers were routinely reproducible to within 3%. For faster reactions by stopped flow, variations of up to 5% were found and up to five duplicate runs were carried out in order to establish an accurate mean value for epoxide cyclisation. For some runs at pH values greater than about 11.5, the rate of the consecutive (post-

cyclisation) reaction occurring after the cyclisation (i.e. the reaction of aurone hydrate, which gives absorbance changes at the wavelength used to monitor the epoxide cyclisation reaction) becomes sufficiently fast relative to the epoxide cyclisation that a steady infinity absorbance could not be obtained for the latter. Computer analysis based on Moodie's treatment[11] for consecutive first order reaction kinetic analysis was used to obtain accurate rate coefficients for the cyclisation.

RESULTS

Electronic spectral changes

Figures 1 and 2 show repetitive scans for the cyclisation of 2'-hydroxychalcone epoxide (**6**) and 2'-hydroxy-6'-methoxychalcone epoxide (**1**) respectively. Absorbance changes can be seen to be maximum at 260 nm for **6** and 290 nm for **1**, the wavelengths at which absorbance changes were monitored for kinetic analysis. There is no post-cyclisation reaction for **6** which gives only 3-hydroxyflavanone (infinity spectrum in Figure 1).

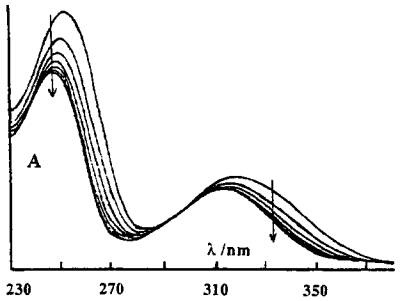


Figure 1: Repetitive scans for the cyclisation of 2'-hydroxy-6'-methoxychalcone epoxide (**6**) at pH 7.8; time interval 240 s.

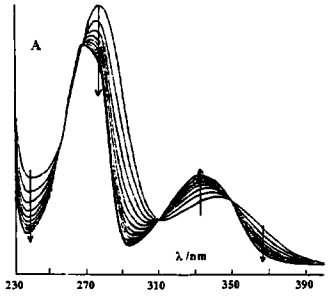


Figure 2: Repetitive scans for the cyclisation of 2'-hydroxychalcone epoxide (**1**) at pH 7.9; time interval 90 s.

For the slow subsequent reaction in which initially-formed aurone hydrate goes on to give both aurone and coumaranone (equation 2), the spectral changes have already been published for the aurone hydrate from epoxide **1**. They are similar to those for the aurone hydrate from 2-trifluoromethyl-2'-hydroxy-6'-methoxychalcone epoxide (**4**) which (Figure 3) indicate aurone formation (380 nm). The latter reaction was monitored at 245 nm for kinetic analysis. Similar suitable wavelengths were chosen for all other cyclisation and post-cyclisation reactions, repetitive scans for which are available on request from the authors.

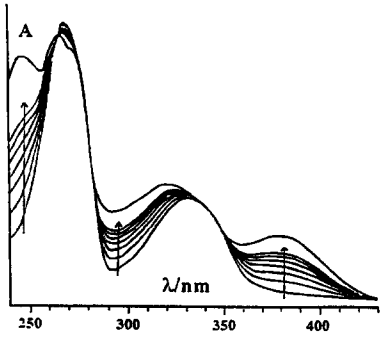


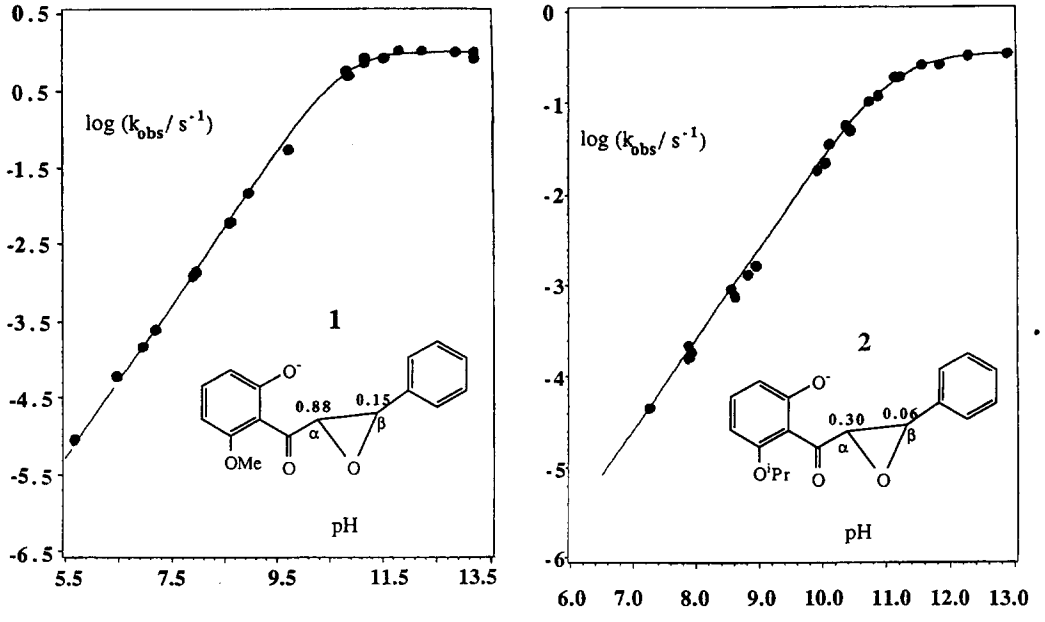
Figure 3: Repetitive scans for the post-cyclisation reaction for 2'-hydroxy-6'-methoxy-2-trifluoromethylchalcone epoxide (**4**) in which the aurone hydrate **16** undergoes elimination (aurone absorbance at 380 nm); pH 11.0; first seven scans at time interval of 120 s, then infinity scan.

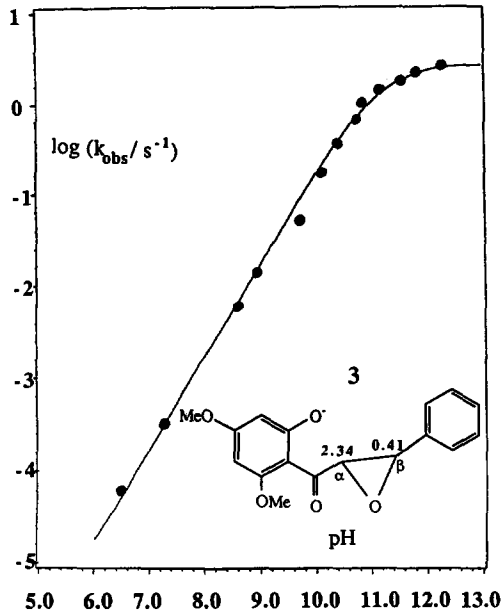
Cyclisation Kinetics

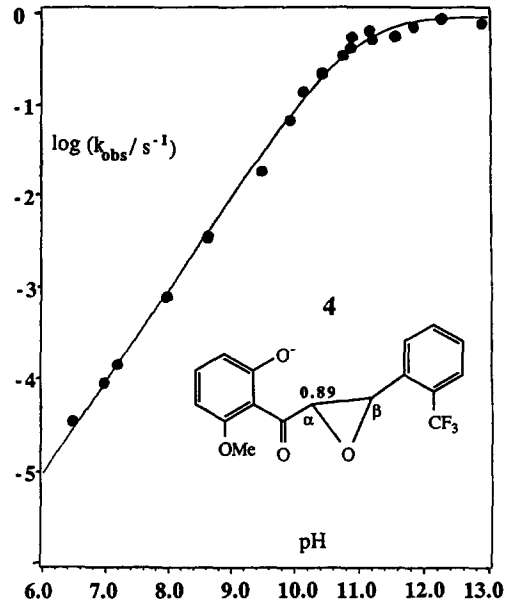
Figures 4 show experimental rate coefficients (points) as a function of pH for the six epoxides studied. The curves are theoretical and are based on the kinetic form $k_{obs} = f_A k_1$, where k_1 is the rate coefficient for unimolecular cyclisation of chalcone epoxide anion(2'-O^-) and f_A is the fraction of epoxide present in anionic form (2'-O^-) at each pH. Values of f_A are given in terms of the dissociation constant K_A for the 2'-OH group of the chalcone epoxide by the expression $K_A/(K_A + a_{H^+})$. Values of K_A which were determined to give the best fit to the experimental data, as shown in the plots, are listed in Table 1 alongside the values of k_1, which, in the plots, are the maximum plateau rates at high pH where the 2'-hydroxy group is fully ionised.

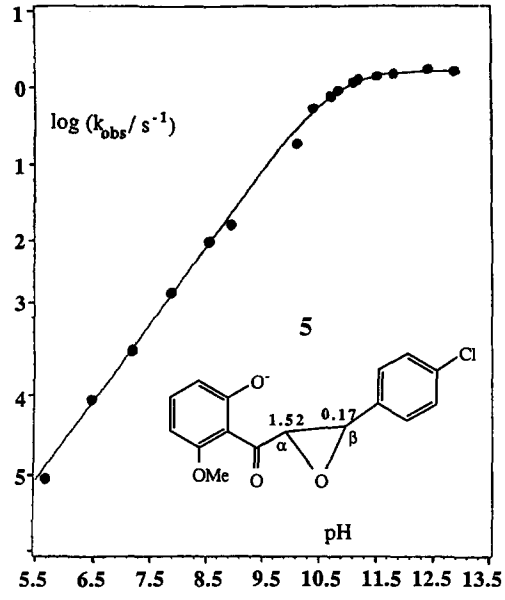
We previously reported[2] that in buffered 1:1 MeCN-H_2O solutions the 6'-substituted chalcone epoxides of the present study (**1**, **2**, **3**, **4** and **5**) give respectively 86%, 84%, 85%, 100% and 90% of α-cyclisation to form aurone hydrate, the remaining product being 3-hydroxyflavanone (14%, 16%, 15%, 0% and 10% respectively). It is on these figures that are based the proportionated rate coefficients k_1^{α} and k_1^{β} in Table 1.

Figures 4: pH-rate profiles for the cyclisation of chalcone epoxides **1** and **2** (this page) and **3-6** (opposite page) as labelled. Points are experimental and lines theoretical,based on the equation $k_{obs} = \{K_A / (K_A + a_{H^+})\}\ \{k_1\}$, where K_A is the acid dissociation constant for the 2'-OH group of the chalcone epoxide (see Table 1 for values) and k_1 is the rate coefficient for cyclisation of the chalcone epoxide monoanion (see Table 1 for values).The values of k_1^{α} and k_1^{β}, respectively the rate coefficients for cyclisation of the 2'-O^- group to the α and β positions of the chalcone epoxide monoanion, are given in units of s^{-1} on the structural diagram labels for the plots in this Figure as well as in Table 1.




log (k_{obs}/ s^{-1})
3
MeO
O⁻
2.34
0.41
α
β
OMe
O
O
pH
1
0
-1
-2
-3
-4
-5
5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0


log (k_{obs}/ s^{-1})
4
O⁻
0.89
α
β
CF3
OMe
O
O
pH
0
-1
-2
-3
-4
-5
6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0


log (k_{obs}/ s^{-1})
5
Cl
O⁻
1.52
0.17
α
β
OMe
O
O
pH
1
0
1
2
3
4
5
5.5 6.5 7.5 8.5 9.5 10.5 11.5 12.5 13.5

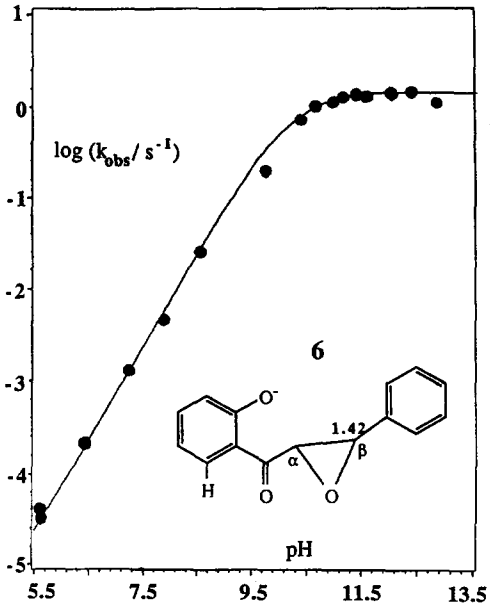

log (k_{obs}/ s^{-1})
6
O⁻
1.42
α
β
H
O
O
pH
1
0
-1
-2
-3
-4
-5
5.5 7.5 9.5 11.5 13.5

Table 1. Acid Dissociation Constants (K_A) for 2'-Hydroxychalcone Epoxides and Rate Coefficients* for Cyclisation of Their Monoanions (2'-O^-); 1:1 v/v MeCN/H_2O (μ = 0.2 (KCl); 30°C

Epoxide	pK_A	k_1/s^{-1}	$k_1\alpha/s^{-1}$	$k_1\beta/s^{-1}$
1	10.78	1.03	0.88	0.15
2	11.14	0.36	0.30	0.06
3	11.19	2.75	2.34	0.41
4	10.97	0.89	0.89	-
5	10.80	1.69	1.52	0.17
6	10.28	1.42	-	1.42

*Rate coefficients are defined as follows: k_1 is the nett first-order rate coefficient for monoanion cyclisation represented by the plateau at high pH in the pH-rate profiles (Figures 4); k_1^{α} is for cyclisation at the α–position to form aurone hydrate; k_1^{β} is for cyclisation at the β-position to form 3-hydroxyflavanone (based on product ratio: see text).

Post-cyclisation Kinetics

The 6'-substituted chalcone epoxides give mixtures of dehydration (aurone) and dealdolisation (coumaranone and aryl aldehyde) products[2] whose ratio has not been determined in each case. However, sharp isosbestic points in repetitive scans for 2'-hydroxy-6'-methoxychalcone epoxide[2] and its 2-trifluoromethyl derivative (Figure 3) indicate, as discussed[2] in the previous paper, that *erythro-threo* isomerisation of aurone hydrates is rapid in comparison with their elimination; clean first-order kinetics were observed for post-cyclisation reactions.

Measured first-order rate coefficients (k_{obs}) are plotted in Figure 5. Lines of best fit are of unit slope within experimental error as is consistent with a first-order dependence on hydroxide activity. Second-order rate coefficients given by $k_2 = k_{obs}/a_{OH^-}$ can not be calculated without a value for K_w for the 1:1 MeCN-H_2O solvent mixture but from k_{obs} values at pH 11.0, relative k_2 values are approximately 2.1 : 1.0 : 0.66 : 0.43 : 0.10 for **5**, **1**, **2**, **4** and **3** respectively (aurone hydrates **17**, **13**, **14**, **16** and **15** respectively in equation 3).

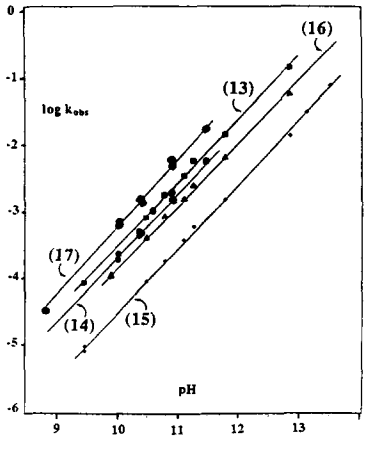


Figure 5: Plots of log k_{obs} *vs* pH for the post-cyclisation elimination reactions of aurone hydrates **13**-**17** (see equation 3 for key).

DISCUSSION

pK_A values of chalcone epoxides

These are discussed first as they bear upon the question of relative nucleophilic strengths of 2'-O^- groups in different epoxides, which in part determines relative rate coefficients for cyclisation as discussed below.

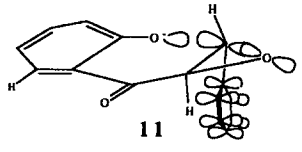
Table 1 shows that the 6'-OMe substituent of **1** increases the pK_A of the 2'-OH group to *ca* 10.8 from *ca* 10.3 for the 6'-H case (**6**), *i.e.* the basicity of 2'-O^- is enhanced. This may result in part from electron-donation from the alkoxy function into the ring and onto the C=O group, which would compete with and attenuate such electron-withdrawal from 2'-O^- ; the anionic conjugate base species (2'-O^-) is more dependent on such stabilisation than the neutral acid (2'-OH). The additional 4'-OMe in the 4',6'-dimethoxy case raises the pK_A further to *ca* 11.2.

The 6'-O^{i}Pr group (**2**; pK_A 11.14) increases the pK_A moreso than the 6'-OMe group (**1**; pK_A 10.78) as is consistent with a more effective electron-donation associated with the secondary versus primary alkyl group on 6'-O, and with the C=O oxygen being twisted further away from the larger O^{i}Pr group and out-of-plane with the aromatic ring to which it is attached, thereby reducing the extent of delocalisation of charge off the 2'-O^- onto the C=O and leaving the 2'-O^- group more basic.

The 4-Cl group is electronically remote from the 2'-O^- function and has little influence on basicity (**5**; pK_A 10.80). The highly polar 2-CF_3 group in **4** (pK_A 10.97) may have a long-range field effect destabilising the anionic 2'-O^- centre

Cyclisation Kinetics

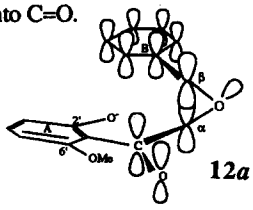
The rate coefficients for α-cyclisation (k_1^{α}; Table 1) of the series **6**, **1**, **3** and **2** give an insight into the factors governing the extent of α-cyclisation for 2'-hydroxychalcone epoxide monoanions. The parent epoxide (**6**; 6'-H) gives no detected α-cyclisation which as we have previously suggested, probably indicates that with the C=O in the plane of the aromatic ring and fully conjugated with 2'-O^- there is neither the enhanced nucleophilicity of the 2'-O^- nor the enhanced electrophilicity of the α-carbon expected when the C=O is forced out-of-plane with the ring, as in 6'-substituted epoxides. Substitution at the β-carbon to form 3-hydroxyflavanone is relatively more favoured electronically and it can occur also with normal[12] benzylic transition state stabilisation as the attainable conformation (**11**) indicates.



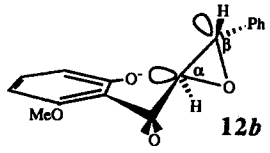
11

Conformation **11** can not easily be attained with the C=O forced out-of-plane as applies for 6'-substituted epoxides, and we have suggested that a conformation such as **12a** with the C=O forced somewhat out-of-plane would be stereoelectronically favoured in that it provides conjugation to C=O from the B-ring through the C_{α}-C_{β} σ-bond, an effect which is enhanced with the electron-withdrawing capacity of the C=O when it is out-of-plane with the ring and less tied up with accommodating negative charge to stabilise 2'-O^- (as would apply in **11**). The important characteristics of **12a**, redrawn in **12b**, are that it is ideally set up for optimised end-on S_N2 attack at

$C\alpha$ as the antibonding $C\alpha$-O orbital in **12b** indicates, and, importantly, in such a conformation the 2'-O^- is more nucleophilic because of reduced electron-withdrawal by the out-of-plane C=O through the aromatic ring and associated with this effect also is increased electrophilicity of the α-carbon because of enhanced inductive electron-withdrawal potential onto C=O.



12a



12b

The kinetic results for epoxides **3** and **2** throw further light on these stereoelectronic effects and the sensitivity of rate to substituent. First in the 4',6'-dimethoxy epoxide **3**, the steric effect of 6'-OMe with respect to C=O is essentially unchanged from **1** but the extra 4'-OMe donates more electron density into the ring and onto the C=O. This, as discussed under pK_A values above, accounts for the increased basicity of the 2'-O^- and this in turn the increased rate of α-cyclisation through a conformation similar to that in **12a/b**.

For the 6'-isopropoxy epoxide (**2**) in which the bulkier 6'-*O*-alkyl substituent is likely to twist the C=O group further out-of-plane with the aromatic ring (as consistent with the increased basicity of the 2'-O^-; pK_A 11.14; see above), the increased nucleophilicity of 2'-O^- should be increased to be rather more like that of the 4',6'-dimethoxy epoxide (pK_A 11.19). However, the rate coefficient for α-cyclisation is only 0.30 s^{-1}, about one eighth of that for **3**, and it is even smaller than that for the 6'-OMe epoxide (0.88 s^{-1}; pK_A 10.78). What this result suggests is that conformations such as **12b** become optimised for S_N2 α-substitution with a certain out-of-plane twist of the C=O, that if the enforced twist becomes too large the orientation of 2'-O^- with respect to the $C\alpha$-O bond gets so far from the optimum that the rate decreases, even though the 2'-O^- group should become even more nucleophilic and the α-carbon even more electrophilic the greater the out-of-plane twist.

In other words, the inherent reactivity with respect to α-substitution (2'-O^- nucleophilicity; α-carbon electrophilicity) increases with the angle of twist of the C=O, but the stereoelectronic requirements for S_N2 substitution determine that when the angle gets too large for optimal orientation for S_N2 the rate decreases with further increase in twist angle.

The presence of the 2-CF_3 group in the B-ring of the 6'-OMe epoxide has no effect on the rate of α-substitution. This suggests that any (general) through-bond inductive activation of nucleophilic attack on the epoxide by the strongly electron-withdrawing CF_3 group may be offset by repulsion of 2'-O^- via the through-space (field) effect of the electronegative F atoms. Certainly it is notable for this compound that β-substitution, which requires relatively close proximity of 2'-O^- and $CF_3{}^{\delta-}$ in the transition state, is not detected, though this might result alternatively from the absence of benzylic stabilisation of the transition state for β-substitution (*cf* **11**) if the steric effect of CF_3 is to twist the B-ring so that the π-orbital alignment of **11** is not attainable and/or if electronically the electron-withdrawal by CF_3 diminishes the π-electron donation from the B-ring implicit in the benzylic stabilisation. The 4-CF_3 compound, as yet not synthesised, may throw some light on this.

The 4-chloro group, which has minimal effect in other examples of benzylic substitution, has a negligible effect on the rate of β-substitution for **5** (0.17 s^{-1} *vs* 0.15 s^{-1} for 6'-OMe-4-H) but for α-substitution the rate is almost doubled. Perhaps this represents slight activation of the α-carbon through electron-withdrawal to Cl transmitted through the $C\alpha$-$C\beta$-aryl π-system of **12a**, but study of other substituent effects would be required to understand this small rate effect.

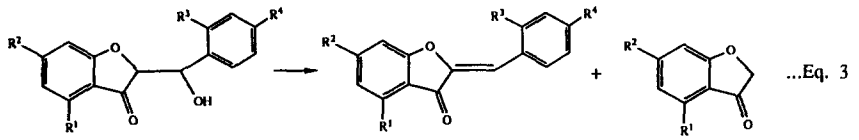
In summary, then, the results of the present study are consistent with the following reactivity considerations:

(i) for non-6'-substituted epoxides the "planar" conformation **11** can be attained and then benzylic transition state stabilisation for β-substitution dominates reactivity such that α-substitution is unimportant;

(ii) for 6'-substituted epoxides, the out-of-plane twist of the C=O increases reactivity by the tandem effect of increasing nucleophilicity of 2'-O^- and electrophilicity of $C\alpha$ and by favouring a conformation (**12b**) in which the stereoelectronic requirement for optimal S_N2 substitution can be approached. If the twist gets too large in spite of increased inherent reactivity (2'-O^- and $C\alpha$) the angle of the 2'-O^-..Cα-O is forced too far from optimal linearity and the rate drops away again.

Post-cyclisation Kinetics

The relative rates of reaction of aurone hydrates to form aurone and coumaranone are *ca* 1.0 : 0.7 : 0.1 : 0.4 : 2.0 respectively for the aurone hydrates **13, 14, 15, 16** and **17** (equation 3). There is no detectable reaction of 3-hydroxyflavanones under these conditions on the time-scale of the aurone hydrate reaction.

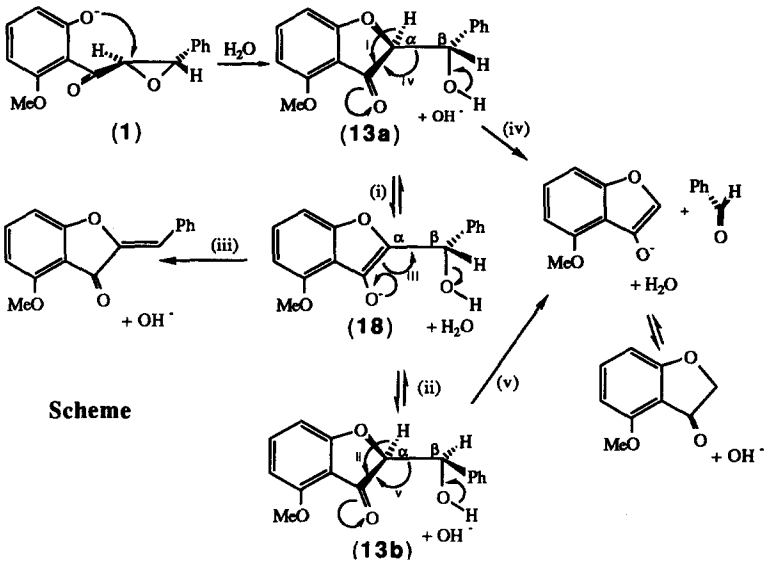


...Eq. 3

(13) R^1 = OMe; $R^2 = R^3 = R^4$ = H
(14) R^1 = O^{i}Pr; $R^2 = R^3 = R^4$ = H
(15) R^1 =OMe; R^2 = OMe; $R^3 = R^4$ = H
(16) R^1 = OMe; $R^2 = R^4$ = H; R^3 = CF_3
(17) R^1 = OMe; $R^2 = R^3$ = H; R^4 = Cl

As discussed previously,[2] equilibration of *erythro* (*e.g.* **13a**; Scheme) and *threo* (**13b**) aurone hydrates *via* the enolate (**18**) is rapid relative to elimination. As far as aurone formation (step iii; Scheme) is concerned, therefore, the rate will be dependent on concentration of enolate (**18**) and this will in turn be dependent on α-proton acidity in aurone hydrate. It is therefore the capacity of the C=O to stabilise the electron pair withdrawn from the $C\alpha$-H bond (steps i and ii; Scheme) as the enolate (**18**) which determines the concentration of the enolate and thus the nett rate of elimination of water to form aurone. For coumaranone formation (steps (iv) and/or (v); Scheme), the rate will again be dependent directly on the capacity of the C=O to stabilise an electron pair, in this case that withdrawn from the $C\alpha$-$C\beta$ bond as the coumaranone enolate. Therefore, irrespective of the proportion of aurone and coumaranone products formed (and these proportions are not known for very dilute solution as employed for the kinetic study) any effect which reduces the electron-withdrawing capacity of the C=O relative to $C\alpha$-H or $C\alpha$-$C\beta$ would cause the rate to diminish. Thus for **15** in which there is an extra (4') OMe group delocalising electrons onto the C=O from the A-ring, the rate is about ten times slower than for **13** in which only the 6'-OMe group is so acting. The 6'-O^{i}Pr group in **14** may be slightly more electron-donating with its secondary alkyl function on 6'-O and it is slightly less reactive than **13**.

As for substituents on the other ring, 4-Cl accelerates the reaction of **17** over **13** by a factor of two which may be associated with a weak +R effect stabilising developing π-bond formation in the transition state for aurone formation ($C\alpha$-$C\beta$ π-bond) and/or in the transition state for benzaldehyde formation ($C\beta$-O π-bond)) in the dealdolisation reaction. By contrast, it appears for **16** that strong inductive electron-withdrawal by the CF_3 group from the $C\beta$ centre limits loss of anionic leaving groups (OH^- in aurone formation and/or coumaranone anion in



Scheme

dealdolisation) so that the rate is depressed by a factor of about two. However, these B-ring substituent effects are very small and it appears from the effects of the 4'-OMe group in **15** that in general 4' and 6' A-ring substituents will be found to influence the rate much more.

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