Reactions in Strongly Basic Media. Part 10.[1] Base-catalysed Isomerisation of Z- to E-substituted Chalcones

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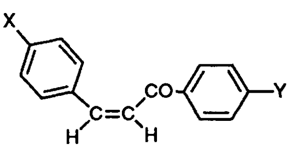
The rate coefficients for the methoxide-catalysed isomerisation of substituted (*Z*)-chalcones have been measured in methanolic dimethyl sulphoxide (DMSO) at 30.0 °C, as well as for (*Z*)-chalcone at several temperatures. The reactions are first order in substrate and base. Further, $\log k_1$ for the reaction of (*Z*)-chalcone and (*Z*)-4-nitrochalcone correlate with an acidity function, H_{R^-}, having slopes equal to 0.53 and 0.45, respectively. The effect of substitution has been assessed using the Hammett equation, with ρ equal to 1.99 for the β-phenyl group and 1.93 for the benzoyl group. For the (*Z*)-chalcone, the enthalpy and entropy of activation are 14.2 kcal mol^{-1} and −14 cal mol^{-1} K^{-1}, respectively, and the kinetic solvent isotope effect, $k_2^{\mathrm{MeOD}}/k_2^{\mathrm{MeOH}}$, is *ca.* 2.0. The rate coefficients for the amine-catalysed isomerisation of (*Z*)-chalcone and (*Z*)-4-nitrochalcone in DMSO have been measured at 30.0 °C. The amino bases are a series of secondary aliphatic amines and the Brønsted coefficients, β, are given as 0.39 and 0.38, respectively. The isomerisation is considered to proceed by rate-determining attack of the base at the β-carbon of the (*Z*)-chalcone to form a carbanion. The '*cis*'-conformer of the carbanion then rotates to form the '*trans*'-conformer, which eliminates the base to give the (*E*)-chalcone.

Chalcones can occur as *Z*- and *E*-isomers, **1** and **2**, respectively. Normally, the *E*-isomers are the more thermodynamically stable.[2,3] The isomerisation of a number of (*Z*)-chalcones to the *E*-isomers catalysed by aqueous acids has been studied.[3]



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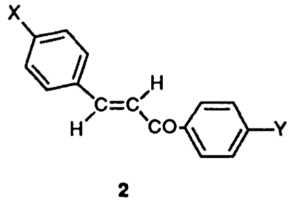

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Nucleophilic reagents can react with carbon–carbon double bonds which are activated by strongly electron-withdrawing groups to result in a number of products.[4] One of the simplest reactions of this type for activated double bonds to undergo is *Z*–*E* isomerisation. The nucleophile apparently adds to the double bond of the *Z*-isomer to form a carbanion. The latter is free to rotate and, after elimination of the nucleophile, the *E*-isomer is formed. In an important study, Kroeger and Stewart[5] investigated the kinetics of the base-catalysed isomerisation of (*Z*)-α-cyanostilbenes in methanolic and ethanolic dimethyl sulphoxide (DMSO). The rates of reaction were correlated with an acidity function, H_{R^-},[6] constructed from the equilibrium addition of alkoxide anions, OR$^-$, to α-cyanostilbenes, A, as indicators, and defined in eqn. (1) below. The slopes of the

$$H_{R^-} = \mathrm{p}K_a + \log([\mathrm{AOR}^-]/[\mathrm{A}]) \qquad (1)$$
$$= -\log \frac{a_{\mathrm{H}^+} f_{\mathrm{AOR}^-}}{a_{\mathrm{ROH}} f_{\mathrm{A}}}$$

correlation of $\log k_1$ in methanolic DMSO with H_{R^-} range from 0.43 to 0.64. The Hammett ρ value for the effects of substitution in the α-phenyl ring on the rates in methanolic DMSO is *ca.* 2.8. This agrees with the mechanism outlined above, with the attack of methoxide anion on the β-carbon of the *Z*-stilbene as the rate-determining step.

Maccarone *et al.*[7] have studied the isomerisation of (*Z*)-1,2-diarylacrylonitriles catalysed by potassium t-butoxide in decahydronaphthalene. The Hammett ρ values at 190 °C for the effects of substitution in the α- and β-phenyl groups on the rates were 1.05 and −2.25, respectively. The isomerisation of (*Z*)-chalcone catalysed by pyrrolidine and piperidine in n-heptane has been studied by Kinastowski *et al.*[8] They found the isomerisation to be first-order in substrate and base, and a subsequent slow addition of the base to the *E*-isomer occurred.

Our interest in the reactivity of chalcones arose from studies of their biological activity.[9] For the latter we have speculated and modelled activity on the basis of nucleophilic addition to the ketovinyl group.[9] In order to gain further information on the chemical reactivity of such systems we have studied the base-catalysed isomerisation of (*Z*)-chalcones, which is reported here.

Results

The rate coefficients, k_2, for the methoxide-catalysed isomerisation of 4- and 4′-substituted *Z*-chalcones in methanolic DMSO at 30.0 °C are shown in Table 1. The reaction was found to be first order both in the substrates and in methoxide. The products of the reactions, the corresponding *E*-isomers, were found to be formed in yields of >98% under the conditions of the reactions (see the Experimental section). Table 2 shows the rate coefficients for (*Z*)-chalcone itself at three temperatures, and the activation parameters calculated from these results. The first-order rate coefficients, k_1, for the methoxide-catalysed isomerisation of (*Z*)-chalcone itself in methanolic DMSO containing 0.01 mol dm^{-3} sodium methoxide at 30.0 °C are shown in Table 3, together with the interpolated H_{R^-} values.[6] The latter results were correlated using eqn. (2) below and

$$\log k_1 = lH_{R^-} + \text{constant} \qquad (2)$$

the relations derived are shown in Table 4. The kinetic solvent isotope effect has been measured in 19.7 mol% DMSO and is shown in Table 3. The Hammett equation (3) can be used to

$$\log(k/k_0) = \rho\sigma \qquad (3)$$

Table 1 Rate coefficients (k_2) for the catalysed isomerisation of substituted Z-chalcones at 30.0 °C[a]

	$k_2/10^{-1}$ dm^3 mol^{-1} s^{-1}			
Substituent[b]	Methoxide in 57.1 mol% methanolic DMSO	Piperidine in DMSO	Morpholine in DMSO	λ/nm
H	3.60	1.85	0.320	307, 313
4'-Me	1.94			310
4'-OMe	1.03			318
4'-F	4.67			315
4'-Cl	10.0			313
4'-CN	69.4			318
4'-NO_2	105			320
4-OMe	1.01	0.619	0.0981	343
4-F	4.08	2.10	0.396	315
4-Cl	14.2	6.76	1.26	315
4-NO_2	119	59.0	10.1	320

[a] Rate coefficients were reproducible to within ±3%. [b] 4'- or 4-substituents are in the β-phenyl and benzoyl rings, respectively.

Table 2 Rate coefficients (k_2) for the methoxide-catalysed isomerisation of (Z)-chalcone in 57.1 mol% methanolic DMSO at several temperatures[a] and the activation parameters[b] at 30.0 °C

$k_2/10^{-1}$ dm^3 mol^{-1} s^{-1}				
At 30 °C	45 °C	60 °C	$\Delta H^‡$/kcal mol^{-1}	$\Delta S^‡$/cal mol^{-1} K^{-1}
3.60	11.7	32.4	14.2(±0.3)	−14(±1)

[a] See Table 1. [b] Standard deviations are shown in parentheses.

Table 3 Rate coefficients (k_1) for the methoxide-catalysed isomerisation of (Z)-chalcone and (Z)-4-nitrochalcone in methanolic DMSO containing 0.01 mol dm^{-3} sodium methoxide at 30.0 °C[a]

	$k_1/10^{-3}$ s^{-1}		
Mol% DMSO	(Z)-chalcone	(Z)-4-nitrochalcone	H_{R^-}[b]
19.7	0.0556[c]	3.79	13.79
27.6	0.176	10.8	14.47
36.3	0.442	19.1	15.22
46.1	1.02	53.6	16.07
57.1	3.60	119	17.03
69.5	14.7	340	18.13
83.7	79.3	2150	19.63

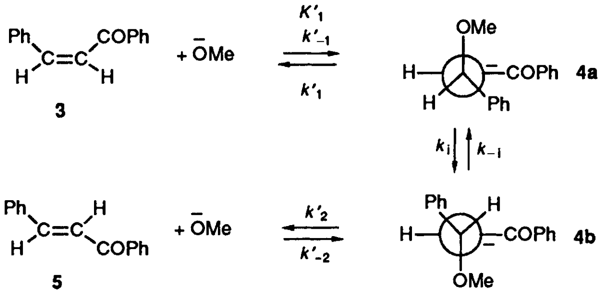
[a] See Table 1. [b] Interpolated from reference 6. [c] In 19.7 mol% [O-^{2}H]methanol-[$^2H_6$]DMSO, k_1 = 0.111 s^{-1}.

assess the effects of substitution in both phenyl rings of the chalcones using *para*-σ-values.[10] Excellent correlations were obtained as shown in Table 4, without need to resort to the use of σ^- values, *cf.* reference 5. The rate coefficients, k_2, for the secondary aliphatic amine-catalysed isomerisation of the Z-chalcones in DMSO at 30.0 °C are shown in Tables 1 and 5.[11] The Brønsted equation (4) can be used to correlate such base-catalysed reactions and the results are shown in Table 4.

$$\log k_b = \beta \log K_b + \log G_b \qquad (4)$$

Discussion

Methoxide-catalysed Isomerisation.—The methoxide-catalysed isomerisation of the substituted Z-chalcones is first order both in substrate and methoxide anion. A reaction pathway for the isomerisation is shown in Scheme 1 and is similar to that proposed by Kroeger and Stewart[5] for a *closely* related system. Thus, the methoxide anion adds to the β-carbon atom of the double bond of the Z-isomer to form the '*cis*' conformer of the carbanion (**4a**). This conformer can rotate to the '*trans*' carbanionic conformer (**4b**), which eliminates methoxide to form the E-isomer. The activation parameters, shown in Table 3, are typical of a bimolecular reaction and can be compared to the values of $\Delta H^‡$ and $\Delta S^‡$ of 16.0 kcal mol^{-1} and −13 cal mol^{-1} K^{-1}, respectively, found for the isomerisation of (Z)-α-cyanostilbene under similar conditions.[5]



Scheme 1

Substituent Effects.—The Hammett ρ values for substitution in both the β-phenyl and benzoyl group, as shown in Table 4, indicate the need for stabilisation of developing negative charge on the α-carbon atom of the double bond. The ratio of the ρ values for substitution in the benzoyl group to that in the β-phenyl group is *ca.* 0.97. This agrees with the ratio of the transmission coefficients for the links, *i.e.* C(sp^2 carbonyl)/C(sp^3), tabulated by Bowden,[12] which is equal to 0.90. This demonstrates consistent stabilisation of the developing anionic centre. Both links act to insulate the substituted phenyl groups from the reactive centre and block any 'exalted' resonance effects. Thus, normal substituent effects are observed here for the *para*-nitro groups. The rather surprising result of Maccarone *et al.*,[7] having a negative ρ value for a β-phenyl group, may arise from the conditions of their study in which ion pairing would be expected.

The ρ value for substitution in the α-phenyl group in the methoxide-catalysed isomerisation of (Z)-α-cyano stilbenes[5] at 25 °C of *ca.* 2.82 has been compared with that observed for the α-phenyl group in the equilibrium addition of methoxide to α-cyanostilbenes,[13] which is equal to about 4.62. The comparison of rate to equilibrium ρ values for the α-phenyl group was considered to indicate for the transition state an approximately half-formed carbanion,[5] which agreed with the results for the rate–acidity function correlation. The ρ value for the latter equilibrium reaction, for substitution in the β-phenyl group,[13] is

Table 4 Regression analyses for the isomerisation of the Z-chalcones in 57.1 mol% methanolic DMSO at 30.0 °C[a]

	Gradient	*s*	Intercept	*r*	*n*
In methanolic DMSO	*l*				
log k_1 *vs.* H_{R^-} (H)	0.53	0.01	−11.50	0.998	7
log k_1 *vs.* H_{R^-} (4-NO_2)	0.45	0.01	−8.60	0.998	7
In 57.1 mol% methanolic DMSO	ρ		log k_0		
log k_2 *vs.* σ (4-)(benzoyl)	1.994	0.116	−0.439	0.995	5
log k_2 *vs.* σ (4′-)(β-phenyl)	1.933	0.028	−0.436	0.999	7
In DMSO	β		log G_b		
log k_2 *vs.* pK_a (H)	0.39	0.01	−4.90	1.000	5
log k_2 *vs.* pK_a (4-NO_2)	0.38	0.01	−3.28	0.999	5
In DMSO	ρ		log k_0		
log k_2 *vs.* σ (4-)(benzoyl) for piperidine	1.936	0.10	−1.469	0.996	5
log k_2 *vs.* σ (4-)(benzoyl) for morpholine	1.932	0.10	−0.711	0.996	5

[a] *s* is the standard deviation, *r* the correlation coefficient and *n* the number of substituents or points.

Table 5 Rate coefficients (k_2) for the secondary aliphatic amine-catalysed isomerisation of substituted (*Z*)-chalcones in DMSO at 30.0 °C[a]

	$k_2/10^{-1}$ mol^{-1} s^{-1}		
Base	(*Z*)-chalcone	(*Z*)-4-nitrochalcone	lit.[11] pK_a
Imidodipropiononitrile	0.0112	0.417	5.0
Morpholine	0.320	10.1	8.6_5
Diethanolamine	0.603	19.5	9.5
Diethylamine	1.38	43.6	10.4
Piperidine	1.85	59.0	10.6

[a] See Table 1.

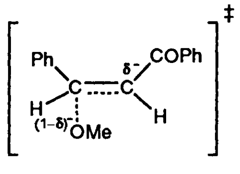
ca. 2.2. Unfortunately, for the present study, the ρ value for equilibrium addition is not known. If the relevant ρ value for the β-phenyl group from the study of α-cyanostilbenes by Stewart and Kroeger[13] is used, a very 'advanced' carbanionic transition state is indicated.

Kinetic Solvent Isotope Effect.—The kinetic solvent isotope effects, k_2^{MeOD}/k_2^{MeOH}, in 19.7 mol% DMSO is *ca.* 2.0 at 30.0 °C, as shown in Table 3. This can be compared with those found for the methoxide-catalysed methanolysis of aryl esters in methanol at 25 °C which are equal to 1.4–2.1.[14] The present result indicates a transition state composed of the substrate and methoxide. The decreased solvation requirement of the transition state relative to the initial state gives rise to the increase in rate.

Rate–Acidity Function Correlations.—The slopes of the correlation between log k_1 and H_{R^-} for (*Z*)-chalcone and (*Z*)-4-nitrochalcone are 0.53 and 0.45, respectively, as shown in Table 4. This is a Brønsted-type correlation and the values of such coefficients have been considered to be a 'rough' measure of 'advance' of the transition state.[15] These results indicate an approximately half-formed carbanion and agree with the results for similar correlations for substituted (*Z*)-α-cyanostilbenes.[5] However, these results contrast with that from the ρ values, as discussed above.

Bernasconi[16] has discussed a principle of nonperfect synchronisation of bond formation/cleavage, development of charge, *etc.* Previous studies[11,17] have noted the discrepancies between evidence from substituent effects and rate–acidity function correlations.

Mechanistic Pathway.—All the evidence indicates that the mechanistic pathway shown in Scheme 1 operates, with k'_1 as the rate-determining step. The transition state for k'_1 will be of higher energy than that for k'_2 due to the steric 'bulk' interactions present in the former, as well as in **3**. The barrier to rotation for **4a** to **4b** would appear to be much lower than the enthalpy of activation for this reaction based on related studies.[18] The transition state suggested is shown as **6** below, with an incompletely formed carbanionic structure.



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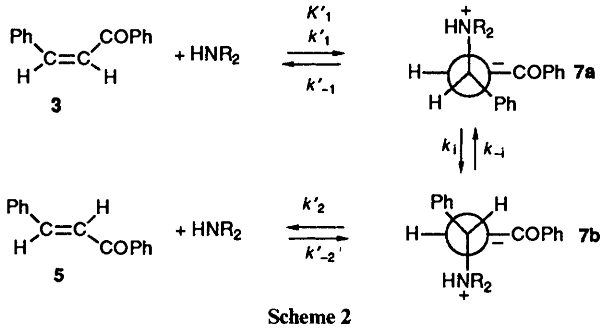
Amine-catalysed Isomerisation.—The rate coefficients, k_2, for the secondary aliphatic amine-catalysed isomerisation of the (*Z*)-chalcones in DMSO at 30.0 °C are shown in Tables 1 and 5, together with the known pK_a values of the amines.[11] The reaction was found to be first order both in the substrates and in amines. Scheme 2 shows the suggested mechanistic pathway, which is closely related to Scheme 1.



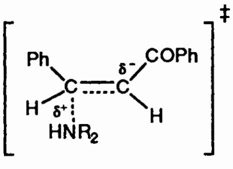
Scheme 2

Substituent Effects.—The Hammett ρ values for substitution in the β-phenyl group, as shown in Table 5, indicate the need for stabilisation of developing negative charge on the α-carbon atom of the double bond, and compare closely to that for the methoxide-catalysed reaction in methanol. This is despite the concurrent development of positive charge at the nitrogen of the secondary aliphatic amine as **7a** is formed *via* the transition state **8**. Thus the rate-determining step appears to be k'_1 in Scheme 2.

Table 6 The physical constants of the previously unreported substituted *Z*-chalcones

		Found (%)				Calc. (%)		
Substituent	M.p./°C	C	H	Other	Formula	C	H	Other
4′-Me	*a*	86.0	6.1		$C_{16}H_{14}O$	86.5	6.3	
4′-OMe	30–32	80.7	5.9		$C_{16}H_{14}O_2$	80.7	5.9	
4′-F	53–55	79.7	4.8	8.6 (F)	$C_{15}H_{11}FO$	79.6	4.9	8.4 (F)
4′-Cl	61–63	74.1	4.6	14.4 (Cl)	$C_{15}H_{11}ClO$	74.2	4.6	14.6 (Cl)
4′-CN	73–75	82.2	4.7	6.0 (N)	$C_{16}H_{11}NO$	82.4	4.7	6.0 (N)
4′-NO_2	78–80	70.9	4.4	5.5 (N)	$C_{15}H_{11}NO_3$	71.1	4.4	5.5 (N)
4-F	58–60	79.7	4.8	8.6 (F)	$C_{15}H_{11}FO$	79.6	4.9	8.4 (F)

[a] Deep yellow oil.



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Brønsted Coefficients.—The Brønsted coefficients for the reaction catalysed by secondary aliphatic amines in DMSO are shown in Table 4. The β values of 0.39 and 0.38 found are somewhat similar to those of 0.53 and 0.45 found for the slopes of the correlation between $\log k_1$ and H_{R^-} in methanolic DMSO containing methoxide. As previously this indicates an approximately half-formed carbanion in the transition state. Further analysis of these results is impossible without a reliable estimate of the values of K'_1 for the equilibrium addition in Schemes 1 and 2.

In agreement with previous studies,[11,19] there appears to be no evidence for correlation between reactivity and selectivity in the present study. The nature of the transition state seems to be comparatively 'set' and does not vary significantly with the nature of 'distant' substituents or the nucleophile.

Experimental

Materials.—The substituted *Z*-chalcones were prepared from the corresponding *E*-chalcones, prepared as described elsewhere,[9] by the method of Lutz.[20] The *E*-chalcones, dissolved in n-pentane in a Pyrex Erlenmeyer flask, were exposed to sunlight for 10 days. Fractional crystallisation gave separate crystals of *E*- and *Z*-isomers, which were colourless and deep yellow, respectively. After mechanical separation, the products were subjected to column chromatography on alumina with benzene as the eluent. After evaporation under reduced pressure, the *Z*-isomers were recrystallised from pentane at −20 °C. The yields were from 1 to 3%, with recovery of the *E*-isomer. The identity and purity of the *Z*-chalcones were investigated by a number of techniques, especially as dimers can be formed.[2] Bromination of the *Z*- and *E*-isomers gave the chalcone dibromides (*n.b.* the dimers do not add bromine). The *Z*-isomers are quantitatively isomerised by base catalysis to the *E*-isomers (*n.b.* the dimers are inert). The ^1H NMR spectra of the *Z*-chalcones had signals for the α-hydrogen at about 6.6 ppm $\{J_{\alpha,\beta} = 12.6(\pm 0.4)$ Hz, $[^2H_6]$DMSO$\}$, whereas, the *E*-chalcones had signals at about 7.25 ppm ($J_{\alpha,\beta} = 16.0(\pm 0.4)$ Hz, $[^2H_6]$DMSO). The signals for the β-hydrogens were submerged in those for the aromatic hydrogens for both isomers. All the compounds had IR and mass spectra in accord with the stated structure. The m.p.s and elemental analyses of the unreported *Z*-chalcones are shown in Table 6. The others agreed well with literature values.[3,20] The solvents and bases for the kinetic studies were prepared as previously described.[11,13,17,19,21]

Measurements.—Rate coefficients for the methoxide-catalysed isomerisation were determined spectrophotometrically by use of a Unicam SP800 spectrophotometer. The reactions were followed at the wavelengths shown in Table 1. The products of the reactions were found to be the corresponding *E*-isomers in quantitative yield, both by comparison of the UV–VIS spectra of authentic samples with the result of kinetic runs (98–102%), and isolation. The kinetic procedure was as described previously.[11,17,21]

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