Reactions of Carbonyl Compounds in Basic Solutions. Part 11.[1] The Baker–Venkataraman Rearrangement

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The detailed mechanism of the Baker–Venkataraman rearrangement has been studied. The kinetics of the rearrangement of a series of 2-acetylphenyl 3- or 4-substituted benzoates and acetylnaphthyl benzoates catalysed by a basic 'non-nucleophilic' buffer in dimethyl sulphoxide have been measured. Studies of substituent effects, kinetic isotope effects, and acidity function correlations indicate a pathway involving pre-equilibrium formation of the carbanion, followed by rate-determining intramolecular nucleophilic attack. The methanolysis of the 2-acetylphenyl benzoates catalysed by methoxide in methanolic dimethyl sulphoxide has been similarly investigated. In this case the pathway appears to involve neighbouring group participation by the ketonic carbonyl group.

The transformation of 2-acetylphenyl benzoates into 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones, catalysed by base under aprotic conditions (the Baker–Venkataraman rearrangement),[2,3] has been used fairly widely in synthesis.[4] The only mechanistic study published is that of Burrows and Topping[5] on the closely related rearrangement of 2-acetylphenyl mesitoate, catalysed by t-butoxide in t-butyl alcohol, to give the corresponding β-diketone. These authors also showed that 1-acetyl-2-naphthyl mesitoate with potassium hydroxide in 47.5% ethanol–water gave 35% of the product as the corresponding β-diketone. The mechanism they offered was one in which the acetyl group suffered proton abstraction by base to give the enolate anion, which then acted as a carbanionic nucleophile, attacking the ester group. The alkaline hydrolysis and methoxide-catalysed methanolysis of *o*-acetylphenyl benzoate appeared to involve ketonic carbonyl group participation,[5] as has been observed for other systems.[6]

In the present study the base-catalysed rearrangement and methoxide-catalysed methanolysis of a series of 2-acetylphenyl 3- or 4-substituted benzoates and related compounds have been investigated. Substituent effects, kinetic isotope effects, and rate–acidity function correlations have been employed to elucidate mechanisms.

Results and Discussion

Baker–Venkataraman Rearrangement.—Preliminary experiments showed that the substituted 2-acetylphenyl benzoates gave quantitative yields of the rearrangement products (the substituted diphenylpropanediones), with potassium t-butoxide in dimethyl sulphoxide (DMSO). However, this reaction was too fast to be followed spectrophotometrically with ease. A 'non-nucleophilic' buffer was constructed from a series of four 4-substituted 2,6-dimethylphenols partially neutralised with potassium t-butoxide. The acidity function of the medium (H_-) can be calculated from equation (1). The chosen degree of

$$H_- = pK_a - \log [HA]/[A] \quad (1)$$

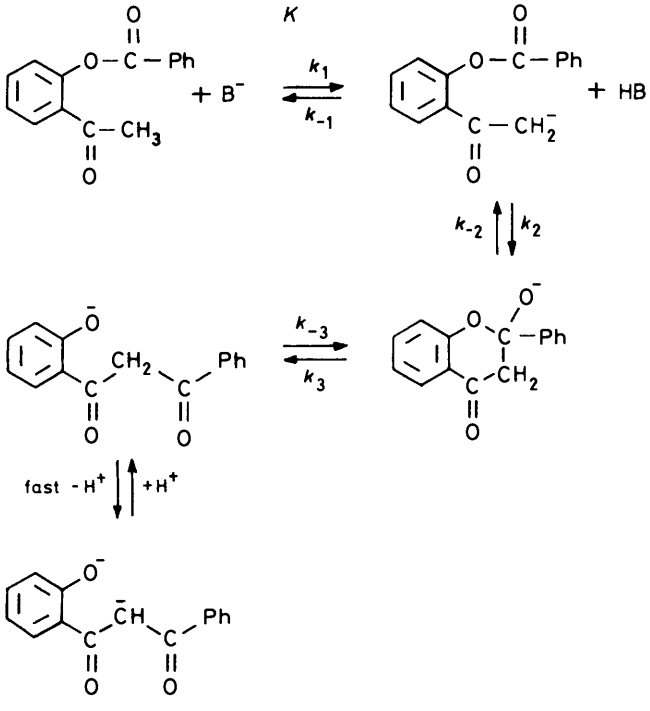
neutralisation was 90%; therefore H_- was equal to the pK_a − log 9.0 (*i.e.* pK_a − 0.95). The pK_a values of the phenols were measured in DMSO (see later).

The rearrangement reactions were found to be first-order in substrate. The rate coefficients for the base-catalysed rearrangement of 2-acetylphenyl benzoate are shown in Table 1. The observed rate coefficients can be correlated with the calculated H_- values to give a linear relation with a slope of about 1.0. The slope of near unity can be considered to indicate

Table 1. Rate coefficients (k_{obs}) for the rearrangement of 2-acetylphenyl benzoate in DMSO containing buffer at 30.0 °C[a]

4-Substituent in 2,6-dimethylphenol	$10^3 k_{obs}/s^{-1}$
Me	49.5
H	14.7
Cl	1.52
Br	1.32

[a] Buffer composed of potassium t-butoxide (2×10^{-2} M) and a 4-substituted 2,6-dimethylphenol (2×10^{-1} M). Rate coefficients reproducible to within ±3%.



Scheme 1.

a transition state for the reaction corresponding closely to the carbanionic product of the ionisation step. The suggested mechanism is shown in Scheme 1. Equilibrium ionisation is followed by intramolecular nucleophilic attack. The step corresponding to k_3 would be expected to be fast in comparison

Table 2. Rate coefficients (k_{obs}) for the rearrangement of 2-acetylphenyl substituted benzoates in DMSO containing buffer at 30.0 °C[a]

Substituent	$10^4 k_{obs}/s^{-1}$
p-NO_2	505
m-NO_2	438
m-Cl	66.0
m-Br	64.2
p-Br	25.9
p-Cl	25.5
H	5.53
m-Me	2.71
p-Me	2.12
p-OMe	0.958

[a] Buffer composed of potassium t-butoxide (1×10^{-3}M) and 2,4,6-trimethylphenol (2×10^{-1}M). Rate coefficients reproducible to within ±3%.

Table 3. Hammett reaction constants (ρ) for the base-catalysed reactions of 2-acetylphenyl substituted benzoates at 30.0 °C[a]

	ρ	log k_0/s^{-1}	*r*	*s*	*n*
Rearrangement in DMSO	2.667	−3.259	0.994	0.072	10
Methanolysis in 30 mol % methanolic DMSO	1.92	−1.02	0.985	0.096	8
pK_a Values of 4-subst. 2,6-dimethylphenols in DMSO	3.79	15.84	0.953	0.50	4

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

with k_{-2}, as the former involves the much better leaving group phenoxide. Thus k_{obs} can be equal to either k_1 or Kk_2. Table 2 shows the rate coefficients for the rearrangement of 2-acetylphenyl 3- or 4-substituted benzoates.

The effect of the substituents is well correlated with σ values, ρ being about 2.7 (Table 3). A number of reactions which involve a rate-determining attack by a negatively charged oxygen nucleophile on an ester carbonyl group directly bonded to the substituted phenyl group have reaction constants of this type, *e.g.* ρ for the alkaline hydrolysis of benzoate esters is in the range 2—3,[7] and for the methoxide-catalysed methanolysis of methyl benzoates at 60.0 °C is *ca.* 2.0.[8] This clearly indicates k_2 as the rate coefficient of the rate-determining step. The coefficient k_1 would be expected to have a greatly reduced susceptibility to polar substituent effects, which would be greatly decreased by transmission either through bonds of through space.

Kinetic isotope effects were obtained by measuring the rates of rearrangement of 2-[$^2H_3$]acetylphenyl and 2-acetylphenyl benzoate under identical conditions (Table 4). The value of k_H/k_D found (about 1.5) clearly precludes ionisation (k_1) as the rate-determining step, as this would require a primary isotope effect of about 6—8. However, the value found here is quite different from the value (0.7—0.9) for the closely related rearrangement of methyl *o*-acetylbenzoate.[1] The difference may lie in the five-membered-ring transition state of the latter as compared with the six-membered-ring transition state in the present study.

In Table 5 are shown the rates of rearrangement of the 2-acetylphenyl, 2-acetyl-1-naphthyl, and 1-acetyl-2-naphthyl benzoates under identical conditions at a series of temperatures. Table 6 shows the activation parameters for the reactions. Thus the 2-acetyl-1-naphthyl ester reacts about three times and the 1-acetyl-2-naphthyl ester about ten times faster than 2-acetylphenyl benzoate. Steric interactions between the proximate acetyl and ester groups will cause deconjugation in the initial state. Further, these steric effects themselves will be relieved in forming the less crowded transition state (for k_2). Thus both effects will cause rate increases with increasing steric 'bulk' interactions. Study of Catalin models suggests that steric interactions decrease in the order 2-acetylphenyl < 2-acetyl-1-naphthyl < 1-acetyl-2-naphthyl, which is the order of increasing rate of reaction. The effect seems to be mainly in the enthalpy of activation term. The activation parameters are of the type expected for a transition state formed from the substrate and a base.

Table 4. Kinetic isotope effect for 2-[$^2H_3$]acetylphenyl and 2-acetylphenyl benzoates at 30.0 °C[a]

Reaction	k_H/k_D
Rearrangement in DMSO[b]	1.4_5
Methanolysis in 10 mol % methanolic DMSO	0.9_2

[a] k_H/k_D Measured under identical conditions simultaneously and considered to be reproducible to within ±5%. [b] Buffer composed of potassium t-butoxide (2×10^{-2}M) and 2,4,6-trimethylphenol (2×10^{-1}M).

Table 5. Rate coefficients ($10^3 k_{obs}/s^{-1}$) for the rearrangement of aryl benzoates in DMSO containing buffer at various temperatures[a]

	Aryl group		
T/°C	2-Acetylphenyl	2-Acetyl-1-naphthyl	1-Acetyl-2-naphthyl
18.4	0.591	1.75	5.80
22.4	0.906	2.44	8.60
26.0	1.17	3.33	11.4
30.0	1.66	4.73	15.3
33.3	2.22	5.81	19.2
35.0	2.57	6.64	21.5
38.3	3.20	8.32	26.8
40.2	3.71	9.34	30.4

[a] Buffer composed of potassium t-butoxide (2×10^{-3}M) and 2,4,6-trimethylphenol (7×10^{-2}M). Rate coefficients reproducible to within ±3%.

Table 6. Activation parameters for the rearrangement of aryl benzoates in DMSO containing buffer at 30.0 °C[a]

Aryl group	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
2-Acetylphenyl	15 200 (±200)	−18.6 (±0.8)
2-Acetyl-1-naphthyl	14 000 (±200)	−20.4 (±0.9)
1-Acetyl-2-naphthyl	13 600 (±200)	−19.5 (±0.9)

[a] As Table 5.

Table 7. pK_a Values of 4-substituted 2,6-dimethylphenols in DMSO at 30.0 °C[a]

Substituent	pK_a
4-Me	16.4
4-H	16.0
4-Cl	15.1
4-Br	14.8

[a] pK_a Values are reproducible to within ±0.1.

Table 8. Rate coefficients (k_{obs}) for the methanolysis of 2-acetylphenyl 3- or 4-substituted benzoates in methanolic DMSO containing 3.26 × 10^{-3}M-sodium methoxide at 30.0 °C[a]

		Substituents							
mol % DMSO	H_-	*p*-OMe	*p*-Me	*m*-Me	H	*p*-Cl	*p*-Br	*m*-Cl	*m*-Br
0.00	11.34	5.09_5	7.67_5	12.6_5	17.9_5	59.5	62.8	76.2	82.2
5.00	11.74	5.75_5	12.2	16.3	27.4_5	56.6	66.2_5	$115._5$	$116._5$
10.00	12.08	8.05	16.6	21.5	27.6	94.4	106.0	150.0	$156._5$
15.00	12.44	9.99	19.9	27.0_5	$40.0._5$	$131._5$	155.0	173.0	$221._5$
20.00	12.78	13.6	26.6	37.2	60.2	185.0	200_5	261.0	$276._5$
25.00	13.10	19.3	35.1	$47.3._5$	75.1	187.0	262.0	$353._5$	$355._5$
30.00	13.41	25.5_5	48.9	66.0	$107._5$	$286._5$	$324._5$	$440._5$	$472._5$
35.00	13.68	37.4	$71.5._5$	96.4	$145._5$	331.0			
40.00	13.95	48.9_5	102.0	$128._5$	174.0				
45.00	14.25	74.2	143.0	$190._5$	$268._5$				
50.00	14.54	105.0	$198._5$	257.0	$368._5$				
55.00	14.91	$165._5$	304.0	408_5					
60.00	15.27	$249._5$	409.0						
65.00	15.54	351.0							
70.00	15.81	499.0							

[a] Rate coefficients reproducible to within ±3%. The *m*- and *p*-nitro esters reacted too rapidly to be studied by this method.

Table 9. Slopes (l) of the rate–acidity function correlation for methanolysis of 2-acetylphenyl substituted benzoates

Substituent	l
p-OMe	0.54
p-Me	0.52
m-Me	0.52
H	0.48
p-Cl	0.35
p-Br	0.33
m-Cl	0.34
m-Br	0.36

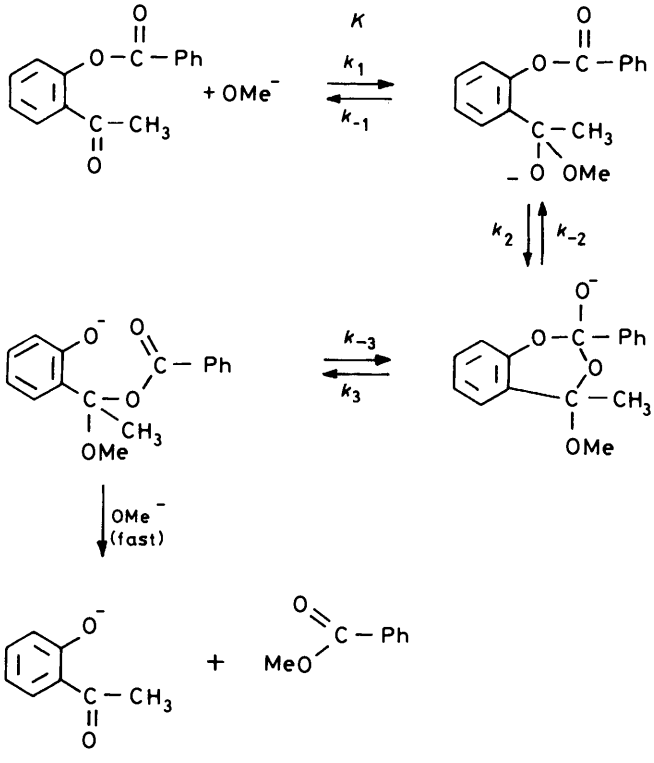
Table 10. Rate coefficients (k_{obs}) for the methanolysis of 2-acetylphenyl benzoate in 10 mol % methanolic DMSO containing 6.52 × 10^{-3}M-sodium methoxide at various temperatures[a]

T/°C	$10^2 k_{obs}$/s^{-1}
25.2	3.99
30.0	5.30
35.3	7.21_5
39.1	8.96
42.0	10.4
45.1	12.2_5
49.5	15.5
53.2	18.3

[a] Rate coefficients reproducible to within ±3%.

Table 11. Activation parameters for the methanolysis of 2-acetylphenyl benzoate in 10 mol % methanolic DMSO containing 6.52 × 10^{-3}M-sodium methoxide at 30 °C

$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
9 900 (±100)	−31.5 (±0.2)



Scheme 2.

pK_a *Values of the* 4-*Substituted* 2,6-*Dimethylphenols.*—The pK_a values of the 4-substituted 2,6-dimethylphenols were measured in DMSO at 30 °C by a potentiometric method, as described later. The results are shown in Table 7. The pK_a values can be correlated with σ values as shown in Table 3. The ρ value is about 3.8 and may be compared with the values obtained by Fischer *et al.*[9] for the half-neutralisation potentials of 4-substituted 2,6-dimethylphenols in propan-2-ol (4.23), acetone (5.55), chlorobenzene (4.32), and benzene (4.74).

Methanolysis.—Preliminary experiments showed that the substituted 2-acetylphenyl benzoates gave quantitative yields of the substituted methyl benzoates with sodium methoxide in methanolic DMSO. The reactions were found to be first-order in both substrate and methoxide. The rate coefficients for the methoxide-catalysed methanolysis of 2-acetylphenyl benzoates are shown in Table 8. Following Burrows and Topping,[5] we suggest that ester exchange occurs with neighbouring group participation by the ketonic carbonyl group,[6] with k_{obs} equal to k_1 or Kk_2 (in Scheme 2). The effect of the substituents can be correlated with σ as shown in Table 3, ρ being about 1.9. For the

Table 12. Physical constants of substrates and products

Substituent	2-Acetylphenyl 3- or 4-substituted benzoate			1-(2-Hydroxyphenyl)-3-(3- or 4-substituted phenyl)-propane-1,3-dione		
	M.p. (°C)	Lit. m.p. (°C)	Ref.	M.p. (°C)	Lit. m.p. (°C)	Ref.
4-NO_2	90—92	91—92	14	200	200—201	16
3-NO_2	103	*a*		186—188	*a*	
3-Br	84—85	*a*		118	*a*	
4-Br	95—97	*a*		128—129	*a*	
3-Cl	80	80	15	113—114	115	15
4-Cl	92	92—93	16	124—125	122—124	16
3-OMe	104—106	*a*		64—65	*a*	
H	92	87—88	2	118	121	2
4-Me	102—103	101	17	108—110	109—110	17
3-Me	61—62	62.5	17	63	63	17
4-OMe	112—114	113—114	18	108—109	111	18
2-Acetyl-1-naphthyl	130—131	131.5	19	145—147	147	21
1-Acetyl-2-naphthyl	86—87	85—86	20	134—135	136—137	21

[a] New compound.

same reasons as previously stated for the rearrangement (regarding the size of ρ), the rate-determining step will be cyclisation (k_2), *i.e.* that involving nucleophilic attack on the ester carbonyl group.

The rate coefficients for the methanolysis can be correlated with the acidity function, H_-, giving linear relations, the slopes of which are shown in Table 9. The values of the slope (l = 0.3—0.5) probably reflect the marked requirement for protic solvation of the transition states for methanolysis as compared with the reference state, the indicators used in constructing H_-.

The rate coefficients for the methanolysis of 2-acetylphenyl benzoate at various temperatures are shown in Table 10. Table 11 shows the activation parameters. The value of $\Delta S^{\ddagger}$ is negative and rather large; it is similar to those observed for alkaline hydrolysis of esters involving neighbouring group participation by a carbonyl group.[6]

Experimental

Materials.—The 3- and 4-substituted benzoyl chlorides were prepared from the corresponding benzoic acids and thionyl chloride. Rearrangements of phenyl, 1-naphthyl, and 2-naphthyl acetates with aluminium chloride in carbon disulphide gave 2′-hydroxyacetophenone, 2-acetyl-1-naphthol, and 1-acetyl-2-naphthol, respectively. 2′-Hydroxy[2,2,2-$^2H_3$]acetophenone was prepared by exchanging the ketone itself several times with a solution of sodium deuterioxide in deuterium oxide. The exchange was monitored by ^1H n.m.r. spectroscopy and found to give >98% deuteriation in the side chain. The synthesis of the substituted 2-acetylphenyl benzoates, 1-acetyl-2-naphthyl benzoate, and 2-acetyl-1-naphthyl benzoate was completed by Baker's method,[2] in which the benzoyl chloride and phenol react together in the presence of pyridine. The 1-(2-hydroxyphenyl)-3-(3- or 4-substituted phenyl)propane-1,3-diones, as well as the corresponding naphthyl derivatives, were prepared either by reaction with a mixture of potassium carbonate and toluene[2] or by treatment with potassium t-butoxide in DMSO. Solvents were purified as described previously,[10,11] as were sodium methoxide[12] and potassium t-butoxide (KOBu^t–Bu^{t}OH).[13] After repeated recrystallisation and drying under vacuum (P_2O_5), the substrates and products had m.p.s in good agreement with the literature values,[2,14–21] or gave satisfactory results in elemental analysis. Details are shown in Table 12. 2,6-Dimethylphenol and 2,4,6-trimethylphenol were obtained commercially. Bromination and chlorination of the former phenol gave 4-bromo- and 4-chloro-2,6-dimethylphenol, respectively. The phenols were either recrystallised or sublimed under reduced pressure.

Kinetic Procedure.—A u.v.-visible spectroscopic method was used as previously described.[22] The reactions were first-order in substrate and, for the methanolysis, in methoxide. The buffer solutions were prepared immediately prior to the kinetic run and were as stated in the relevant Tables. The base in methanolysis was 3.26 × 10^{-3}M-sodium methoxide, unless the order with respect to the base was being studied. The values of the acidity function in methanolic DMSO were interpolated from literature values[23] and corrected for the change in base concentration.[24] The λ values used in the kinetic measurements were normally those showing the greatest differences between the substrate and product. The products (propane-1,3-diones or *o*-hydroxyacetophenones and substituted methyl benzoates) were obtained in quantitative yield from preparative-scale reactions. Their identities were confirmed by spectral comparison with products of kinetic runs under the same conditions and by t.l.c.

pK_a *Values.*—The pK_a values of the 4-substituted 2,6-dimethylphenols were measured by a potentiometric method in DMSO at 30.0 (±0.1) °C (essentially that of Ritchie and Uschold,[25] except with KOBu^t as base). A direct-reading pH meter was used (Pye Unicam PW 9409), together with a glass electrode (401 E07) and reference electrode (AgCl–DMSO).[26] The electrode's behaviour was checked and found to be reversible. The pH scale was checked before and after use with 0.1N-sulphuric acid in DMSO. The phenol concentrations were 5 × 10^{-3}M in DMSO and the titrant was 0.6M-KOBu^t–Bu^{t}OH in DMSO. The titrations were carried out under nitrogen.

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Received 9*th April* 1986; *Paper* 6/699