Reactions of Carbonyl Compounds in Basic Solutions. Part 10.[1] Methoxide-catalysed Cyclisation of Methyl 2-Acylbenzoates and 8-Acyl-1-naphthoates

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The detailed mechanism of the methoxide-catalysed rearrangement of both normal and pseudo methyl *o*-acylbenzoates and 8-acyl-1-naphthoates to form indane-1,3-diones and phenalene-1,3-diones, respectively, has been studied. Rate–acidity function correlations for the reactions in methanolic dimethyl sulphoxide give linear relations. The kinetic isotope effects have been observed with k_H/k_D equal to 0.7—0.9 and 5—7 for methyl *o*-acetylbenzoate and normal methyl 8-acetyl-1-naphthoate, respectively. The effect of substituents and ring–chain tautomerism on the rates has been considered. For the *o*-acylbenzoates the initial state is the ring–chain tautomeric equilibrium mixture and the rate-determining step is the intramolecular attack of the anion of the normal ester. For normal 8-acyl-1-naphthoates the rate-determining step is the ionisation of the normal esters; for the corresponding pseudo esters, the rate-determining step is the isomerisation of the psuedo to the normal ester.

In the preceding paper we examined the detailed mechanism of the methoxide-catalysed cyclisation of benzylidenephthalides and both normal and pseudo methyl *o*-phenylacetylbenzoates to form 2-phenylindane-1,3-diones.[1] Bowden and Last,[2] while examining the alkaline hydrolysis of normal methyl 8-acyl-1-naphthoates, showed that the reaction proceeded with neighbouring group participation by the carbanion derived from the 8-acetyl, -propionyl, or -isobutyryl derivative. This cyclised to form the phenalene-1,3-dione before giving the final product of hydrolysis by cleavage of the intermediate.

The present report details a full investigation of methoxide-catalysed rearrangement of methyl *o*-acylbenzoates and 8-acyl-1-naphthoates in methanolic dimethyl sulphoxide (DMSO) using rate–acidity function correlations and kinetic isotope, substituent, and other effects. In methanolic methoxide, the equilibrium between normal and pseudo ester is accessible and, in contrast to the situation in water, the products are not finally trapped as carboxylate anions.

Results and Discussion

The mechanism suggested[3] for the rearrangement of methyl 2-acylbenzoates and 8-acyl-1-naphthoates is that shown in the Scheme.

Attack by methoxide on the normal ester (**1**) can give either the pseudo ester (**2**) or the anion of the normal ester (**3**). The latter can lose methoxide to give the dione (**5**), which is rapidly ionised under basic conditions to give (**6**).

The kinetic studies have been carried out in methanol and methanolic DMSO containing methoxide. The reaction is first-order both in substrate and in methoxide. For the 2-acetyl-, 2-propionyl-, and 2-isobutyryl-benzoate esters both normal and pseudo ester react at the same rate; for the 8-acetyl- and 8-propionyl-1-naphthoate esters, the normal esters react much faster than the pseudo esters. Thus the initial state for the benzoate esters must be the tautomeric equilibrium mixture of normal and pseudo esters, *i.e.* equilibration between tautomers is faster than cyclisation. Similarly, the normal naphthoate esters react by cyclisation before equilibration has time to occur. The pseudo naphthoate esters slowly tautomerise to the corresponding normal esters before cyclising relatively rapidly. The rates of rearrangement are shown in Table 1 as first-order rate coefficients, k_{obs}, for a stated DMSO content and H_- value. For the normal naphthoate esters, the simple first-order behaviour deviated after 7—8 'half-lives' of the reaction. For these normal esters, tautomerisation will still occur, albeit slowly relative to cyclisation. The rate coefficients of the second and slower process were measured; they correspond roughly to the rate coefficients for cyclisation of the corresponding pseudo esters extrapolated to these low DMSO content systems. This is reasonable, as the equilibrium mixtures of tautomeric esters will be almost completely pseudo ester (see ref. 4 and Experimental section). It is considered that the relative stabilities of five- or six-membered rings for the pseudo esters play no role other than 'determining' the initial state.

Correlation of Reaction Rates with the Acidity Function.—The rates of rearrangement of the various substrates to either indane-1,3-diones or phenalene-1,3-diones in methanolic DMSO containing methoxide can be related to the acidity function, H_-, for the medium. A fairly linear correlation between log k_{obs} and H_- is observed for all substrates. The slopes (l) for the correlations are shown in Table 2. Such linear correlations do not allow us reliably to assign the details of the mechanism. However, Bell and Cox[5] found a slope of 0.48 for the inversion (ionisation) of (−)-menthone in aqueous DMSO containing base. This slope is similar to the smaller slopes observed here for the two normal naphthoate esters, in marked contrast to the values of about 1 found for the normal/pseudo esters of the methyl 2-acylbenzoates.

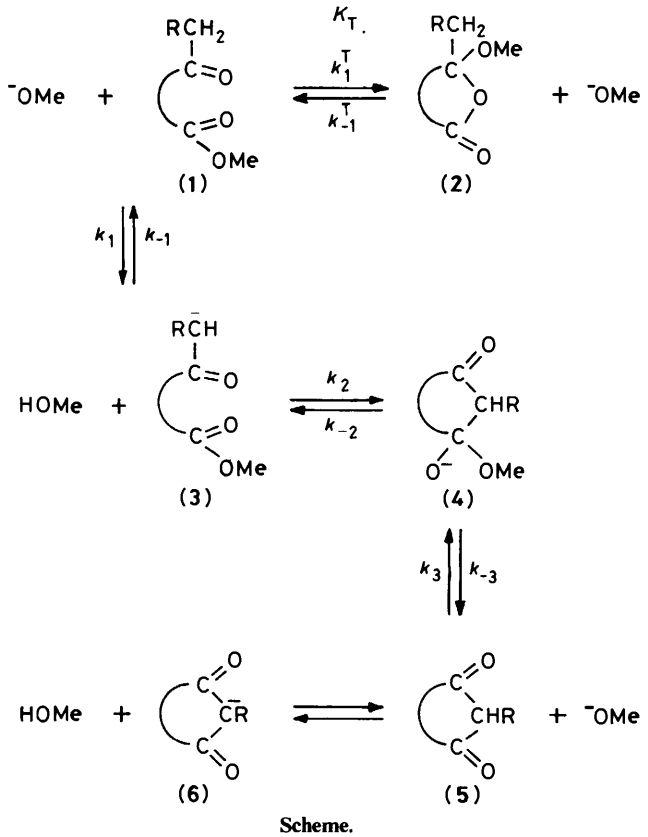
Isotope Effect.—The kinetic isotope effects (k_H/k_D) observed for the rearrangement of normal/pseudo methyl 2-acetylbenzoate and normal methyl 8-acetyl-1-naphthoate are shown in Table 3. The values are between 0.7 and 0.9 over the range of basicity studied for the benzoate ester. This clearly excludes the ionisation step (k_1) as rate-determining. The small reverse value, as observed for the phenylacetyl ester,[1] is compatible with either a small steric effect or a change in hybridisation of carbanion carbon from sp^2 to sp^3 (ref. 6) which occurs in the cyclisation step and arises from the (partial) exchange of dueterium in the substrate. Thus this confirms that the rate-determining step is cyclisation (k_2) for the benzoate esters, as for the *o*-phenylacetyl system in low DMSO content solutions.

For the 8-acetyl ester, k_H/k_D changes from 5.0 in methanol to 4.8 in 36.3 mol% methanolic DMSO, with a maximum value of 6.7 in 12.5 mol% methanolic DMSO. Cox and Gibson[7] have commented on the variation of isotope effects with DMSO composition. However, this result clearly indicates a large primary kinetic isotope effect with k_1 rate-determining. The

Table 1. Rate coefficients for the cyclisation of methyl esters in methanolic DMSO containing 3.5 × 10^{-2}M-sodium methoxide at 30.0 °C*

		$10^3k_{obs}/s^{-1}$						
		8-Acetyl-1-naphthoate		8-Propionyl-1-naphthoate		2-Acetyl-benzoate	2-Propionyl-benzoate	2-Isobutyryl-benzoate
mol% DMSO	H_-	normal	pseudo	normal	pseudo	normal/pseudo	normal/pseudo	normal/pseudo
0.00	12.38	1.45		0.710				
7.20	12.93	2.57		0.830				
13.90	13.39	3.86		1.14				
25.10	14.25	7.45		2.05				
36.30	14.80	15.5		4.20				
72.20	16.94					3.00	3.38	
75.00	17.15					3.41	5.58	
77.80	17.35		0.480		0.0900	4.88	9.67	
83.20	17.86		0.970		0.200	15.3	34.4	0.550
86.80	18.18		1.63		0.250	29.2	77.0	1.32
93.20	19.07							5.44

* Reproducible to within ±3%.



Scheme.

transition state appears to be that with the proton lost fairly symmetrically placed with regard to methoxide and the carbanion.[8] The present result is similar to that for the alkaline hydrolysis of the ester (proceeding by rate-determining ionisation)[2] and for (−)-menthone inversion (again proceeding by rate-determining ionisation).[5]

Effect of Pre-equilibrium on the Rates.—The equilibria between normal and pseudo ester will only affect k_{obs} for the 2-acylbenzoates by reducing the concentration of the normal ester. The 'true' rate coefficient, k^T_{obs}, for this reduction is related to k_{obs} as in equation (1). The equilibrium constant (K_T) has

$$k^T_{obs} = k_{obs}(1 + 1/K_T) \quad (1)$$

Table 2. The slopes (l) of the rate–acidity function correlations

	l
Normal methyl 8-acetyl-1-naphthoate	0.4_4
Normal methyl 8-propionyl-1-naphthoate	0.3_8
Normal/pseudo methyl 2-acetylbenzoate	1.0_8
Normal/pseudo methyl 2-propionylbenzoate	1.1_2
Normal/pseudo methyl 2-isobutyrylbenzoate	0.9_3

Table 3. Kinetic isotope effect (k^H_{obs}/k^D_{obs}) for the cyclisation of normal/pseudo methyl *o*-acetylbenzoate and normal methyl 8-acetyl-1-naphthoate in methanolic DMSO at 30.0 °C

mol% DMSO	k_H/k_D
	Normal/pseudo methyl *o*-acetylbenzoate
75.0	0.8_1
77.8	0.7_0
80.7	0.9_4
83.7	0.9_5
86.8	0.8_8
89.9	0.7_1
93.2	0.7_8
	Normal methyl 8-acetyl-1-naphthoate
0.0	$5._0$
5.96	$5._3$
12.48	$6._7$
27.55	$5._6$
36.32	$4._8$

been studied previously for these esters.[9] In this study, analysis of the mixture of the 2-acrylbenzoates when the reaction was stopped immediately after initiation showed the initial state to be the equilibrium mixture of ester tautomers. The latter did not vary in composition over the range of solvent compositions studied. The values of K_T and the values of k^T_{obs} in 80 mol% methanolic DMSO are shown in Table 4. As the pK_a values of acetophenone (24.7), propiophenone (24.4), isopropyl phenyl ketone (26.3), and phenylacetophenone (17.7) are known,[10] it is possible to correct the observed rates for the relative acidity of the substrate and, thus, for the effects of ionisation pre-equilibrium on the observed rate. These corrected relative rates are shown in Table 4 and refer to the intramolecular nucleophilic step (k_2). They demonstrate the increase in nucleophilicity with increase in availability of the electrons on the carbanion.

Table 4. Tautomeric equilibrium constants (K_T) and 'true' relative rates for the rearrangement (k^T_{obs}) and for the intramolecular process (k_2) for methyl 2-acylbenzoates in 83.2 mol% methanolic DMSO at 30.0 °C

Acyl substituent	K_T	Relative 'true' rate	Relative rate for intramolecular attack
Acetyl	0.56	1.0	1.0
Propionyl	0.43	2.7	5.4
Isobutyryl	0.21	0.074	3.0
Phenylacetyl[1]	0.35	20	2.0×10^{-6}

Rearrangement of the Pseudo Methyl 8-Acyl-1-naphthoates.—As has been indicated earlier, the pseudo naphthoate esters react much more slowly than the corresponding normal esters. The pseudo esters appear to undergo base-catalysed tautomerisation in the rate-determining step. By analogy with the study of Bowden and El-Kaissi[11] of the base-catalysed isomerisation of methyl 8-benzoyl-1-naphthoates, the rate-determining step is considered to be decomposition by dissociation of methoxide anion from the tetrahedral adduct of the pseudo ester and methoxide to give the normal ester. The normal ester then rearranges less rapidly to form the product.

Some general conclusions from this and our previous study[1] are as follows. (1) Stereochemical control of reactivity can be achieved so that a switch can be made from rate-determining intramolecular nucleophilic attack to formation of the carbanionic nucleophile. The innate high nucleophilicity of the carbanion is then exposed *when* it is correctly orientated for ready reaction subsequent to its formation. (2) Substituent effects on the reactivity of carbon acids can be reversed as the stabilisation of the carbanion reduces its reactivity as a nucleophile *but* increases its ease of formation. (3) Solvent effects on the reactivity of carbon acids can be reversed as they increase the ease of formation of the carbanion *but* decrease its nucleophilicity.

Experimental

Materials.—The normal and pseudo methyl 2-acylbenzoates and 8-acyl-1-naphthoates were prepared as previously described,[2,9,12] as was 8-[$^2H_3$]acetyl-1-naphthoic acid.[2] 2-[$^2H_3$]Acetylbenzoic acid was prepared by exchanging the acid itself several times with a solution of sodium deuterioxide in deuterium oxide. The deuteriation (monitored by ^1H n.m.r. spectroscopy) occurred >97% in the side chain. Preparative g.l.c. was used to purify the pseudo esters.[13] The substituted indane-1,3-diones and phenalene-1,3-diones were made by base-catalysed rearrangement of the corresponding normal methyl 2-acylbenzoates and 8-acyl-1-naphthoates. 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. Solvents were purified as described previously[14,15] as was sodium methoxide.

Kinetic Procedure.—A u.v.–visible spectroscopic method was used, as previously described.[1,16] The reactions were first-order in both substrate and base and were carried out at 3.5×10^{-2}M-sodium methoxide concentration, unless the order with respect to the base was being studied. The values of the acidity function, H_-, were those interpolated from literature values[17] and corrected for change in base concentration.[18] The λ values used in the kinetic measurements were normally those showing the greatest differences between the substrate and product. The products, the anions of the corresponding indane-1,3-diones or phenalene-1,3-diones, were obtained in quantitative yield from preparative-scale reactions and their identities were confirmed by spectroscopic comparison with the diones in basic solution.

Tautomeric Equilibrium Procedure.—Either a g.l.c. or a ^1H n.m.r. method was used, as previously described.[9] For the benzoate esters, both tautomers were detected. For the normal naphthoate esters in the presence of methoxide, only the normal ester, together with the rearrangement product, was detected. For the normal naphthoate ester in the presence of hydrogen chloride and the pseudo ester under both conditions, only the pseudo ester was detected.

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