

# Reactions of Carbonyl Compounds in Basic Solutions. Part 9.<sup>1</sup>

## Methoxide-catalysed Cyclization of Benzylidenephthalides and Methyl *o*-Phenylacetylbenzoates

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The detailed mechanism of the methoxide-catalysed rearrangement of substituted benzylidenephthalides and both normal and pseudo methyl *o*-phenylacetylbenzoates to form 2-phenylindane-1,3-diones has been studied. A rate-acidity function correlation for the reactions in methanolic dimethyl sulphoxide (DMSO) shows a linear increase in rate with increasing  $H_-$  to reach a maximum in rate before decreasing, except for the *p*-nitro substrate. This derivative shows a rate decrease throughout the  $H_-$  range. The  $\rho$  values in methanol and in 94 mol % methanolic DMSO are 1.7 and  $-1.6$ , respectively. The kinetic isotope effect has been observed with  $k_H/k_D$  0.8–1.0. The equilibrium constants for ring-chain tautomerism of the methyl *o*-phenylacetylbenzoates have been determined and shown to be independent of substituent and solvent composition. The rate-determining step is the intramolecular attack of the anion of the normal ester on the ester carbonyl group. In methanol and methanolic DMSO of high methanol content this is preceded by the ionization equilibrium of the normal ester. In methanolic DMSO of low methanol content and for the *p*-nitro substrate, the initial state is the anion itself.

A number of studies<sup>2,3</sup> have been made of the mechanism of the base-catalysed cyclization of benzylidenephthalides and both the normal and pseudo methyl *o*-phenylacetylbenzoates to form 2-phenylindane-1,3-diones. Eskola *et al.*<sup>2</sup> concluded from their investigations that the reaction passed through the anion of the pseudo ester. More recently Creamer *et al.*<sup>3</sup> have shown convincingly that all the substrates react *via* the anion of the normal ester. They considered from their studies of substituent and other effects that, in methanolic methoxide, the rate-determining step involves a transition state of structure close to that of the anion of the normal ester.

We report a comprehensive investigation of the detailed mechanisms of such rearrangements in methanolic methoxide and in methanolic methoxide containing dimethyl sulphoxide (DMSO) using rate-acidity function correlations and substituent, kinetic isotope, and other effects. The significance of these studies in methanolic methoxide is the accessibility of the equilibria involved and that the products are not finally trapped as the carboxylate anions, as would be the case in water. The employment of DMSO enables the switch in the relative stabilities of the substrate and its anion to be made.

### Results and discussion

The mechanism suggested<sup>3,4</sup> for the rearrangement of benzylidenephthalides and the normal and pseudo methyl *o*-phenylacetylbenzoates is that shown in the Scheme.

Initial attack by methoxide at the phthalide (1) carbonyl group gives the anion of the normal ester (2). The latter can either capture a proton to give the normal ester (3) or intramolecularly attack the ester group to form the cyclic intermediate (5). The normal ester (3) is in tautomeric equilibrium with the pseudo ester (4). The cyclic intermediate (5) can lose methoxide to give the indanedione product (6), which is rapidly ionized under basic conditions to give (7).

The kinetic studies have been carried out in methanol or methanolic DMSO containing methoxide. The reaction is always first-order in the substrate or a species derived from it. The reaction is first-order in base in media of low DMSO content. Creamer *et al.*<sup>3</sup> have shown that benzylidenephthalide rearranges in methanol at the same rate as both normal and pseudo methyl *o*-phenylacetylbenzoate. We have re-examined

this system for both unsubstituted and *m*-chloro substrates over the range of methanolic DMSO studied, and verified this observation. This indicates that the equilibria between phthalide and both esters are established much more rapidly than the rate at which the rearrangement occurs. The actual composition of the 'true' substrate is considered later.

In Table 1 are shown the rates of rearrangement of a series of substituted substrates in a range of solvents of various compositions. These are given as first-order rate coefficients,  $k_{\text{obs}}$ , for a stated DMSO content and  $H_-$  value.

*Correlation of Reaction Rates with the Acidity Function.*—The rates of rearrangements of the substrate to 2-phenylindane-1,3-

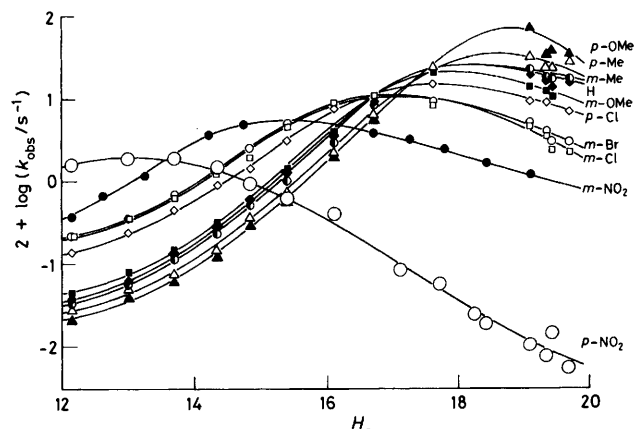
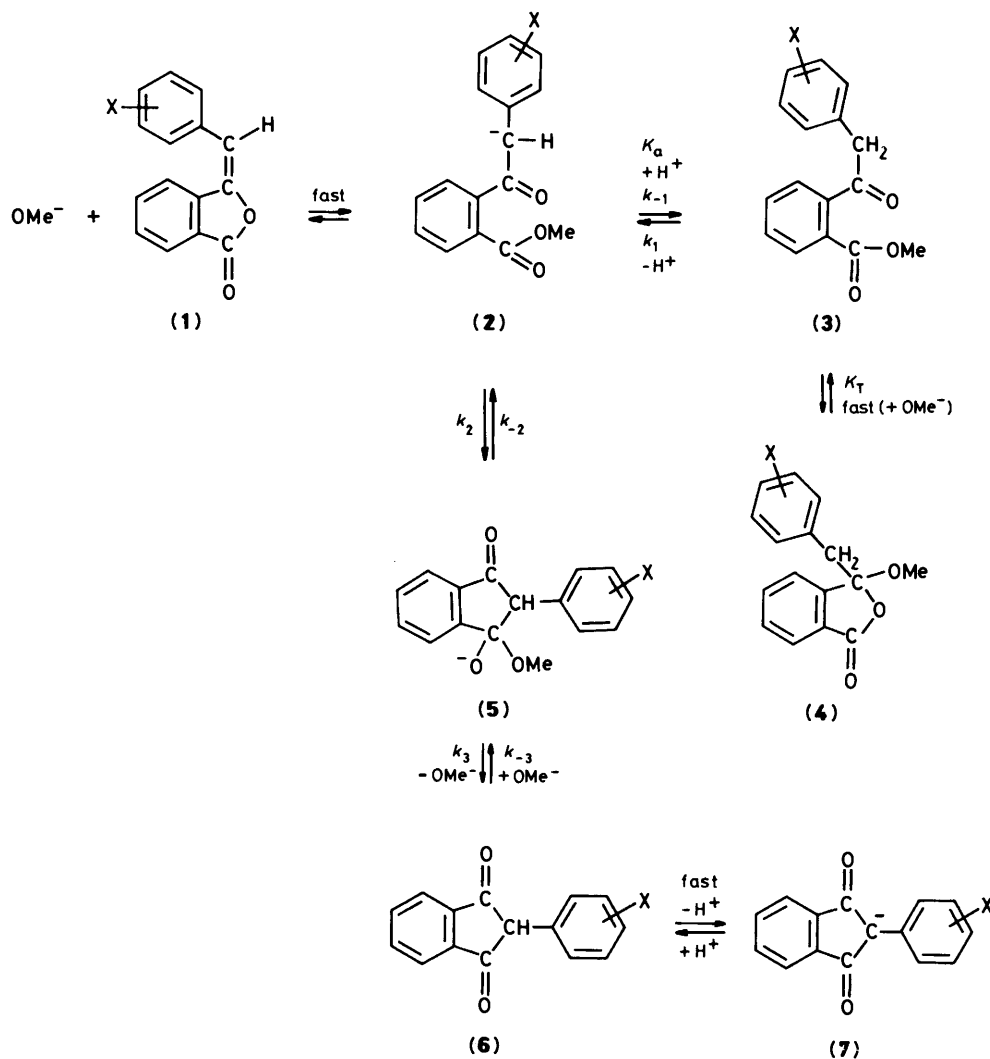


Figure. Relation between  $k_{\text{obs}}$  for the intramolecular cyclisation of benzylidenephthalides and methyl *o*-phenylacetylbenzoates with  $H_-$ .

diones in methanolic DMSO containing methoxide can be related to the acidity function  $H_-$  for the medium as shown in the Figure. A linear correlation between  $\log k_{\text{obs}}$  and  $H_-$  is observed until a value of ca. 17 for  $H_-$  for all substituents except *p*-nitro. The slopes ( $\rho$ ) for these linear portions (Table 2) range from 0.48 to 0.68. Linear correlations, while indicating the likely importance of carbanionic-type species in the pathway, do not define the rate-determining step as either the ionization of the ketonic carbon acid or a step subsequent to its production. Thus  $k_{\text{obs}}$  could be equal to  $k_1$  or  $Kk_2$ , etc. Slopes of 0.4–0.5



**Table 1.** Rate coefficients for the cyclization of substituted benzylidene-naphthalides in methanolic DMSO containing  $2.5 \times 10^{-2}$ M-sodium methoxide at 30.0 °C

| mol %<br>DMSO | $H_-$ | $10^3 k_{\text{obs}}/s^{-1}^a$ |              |              |       |               |              |              |              |                           |                           |
|---------------|-------|--------------------------------|--------------|--------------|-------|---------------|--------------|--------------|--------------|---------------------------|---------------------------|
|               |       | <i>p</i> -OMe                  | <i>p</i> -Me | <i>m</i> -Me | H     | <i>m</i> -OMe | <i>p</i> -Cl | <i>m</i> -Cl | <i>m</i> -Br | <i>m</i> -NO <sub>2</sub> | <i>p</i> -NO <sub>2</sub> |
| 0.00          | 12.16 | 0.216                          | 0.260        | 0.327        | 0.391 | 0.440         | 1.30         | 2.07         | 2.20         | 5.83                      | 16.6                      |
| 5.96          | 12.70 |                                |              |              |       |               |              |              |              | 6.59                      |                           |
| 10.00         | 13.00 | 0.377                          | 0.460        | 0.651        | 0.554 | 0.760         | 2.32         | 3.71         | 3.74         |                           | 18.7                      |
| 12.48         | 13.20 |                                |              |              |       |               |              |              |              | 11.5                      |                           |
| 20.00         | 13.70 | 0.608                          | 0.711        | 1.08         | 1.31  | 1.43          | 4.29         | 6.24         | 6.78         |                           | 18.2                      |
| 27.55         | 14.18 |                                |              |              |       |               |              |              |              | 34.8                      |                           |
| 30.00         | 14.35 | 1.15                           | 1.70         | 2.28         | 2.74  | 3.00          | 8.97         | 13.4         | 13.1         |                           | 10.0                      |
| 36.32         | 14.60 |                                |              |              |       |               |              |              |              | 47.7                      |                           |
| 40.00         | 14.84 | 2.77                           | 3.46         | 5.02         | 5.79  | 5.70          | 16.0         | 22.1         | 25.1         |                           | 9.87                      |
| 50.00         | 15.40 | 5.73                           | 7.36         | 10.40        | 13.1  | 14.0          | 39.7         | 46.9         | 48.8         |                           | 5.96                      |
| 60.00         | 16.10 | 17.8                           | 22.7         | 28.3         | 36.4  | 39.1          | 74.3         | 91.3         | 92.2         |                           | 3.89                      |
| 69.52         | 16.68 |                                |              |              |       |               |              |              |              | 35.4                      |                           |
| 70.00         | 16.70 | 53.8                           | 65.5         | 86.4         | 105   | 108           | 166          | 119          | 108          |                           | 2.22                      |
| 75.00         | 17.10 |                                |              |              |       |               |              |              |              | 33.5                      | 0.804                     |
| 80.00         | 17.60 | 209                            | 239          | 213          | 210   | 223           | 171          | 93.2         | 81.4         |                           | 0.477                     |
| 81.50         | 17.80 |                                |              |              |       |               |              |              |              | 25.1                      |                           |
| 94.00         | 19.10 | 711                            | 303          | 212          | 194   | 132           | 92.6         | 50.5         | 46.1         | 16.5                      | 0.122                     |
| 96.35         | 19.35 | 358                            | 230          | 161          | 176   | 121           | 77.9         | 35.7         | 39.6         |                           | 0.0790                    |
| 97.40         | 19.43 | 395                            | 240          | 174          | 136   | 104           | 80.2         | 23.0         | 30.4         |                           | 0.101                     |
| 98.76         | 19.72 | 360                            | 255          | 173          | 156   | 132           | 58.9         | 22.6         | 29.3         |                           | 0.0550                    |

<sup>a</sup> Reproducible to within  $\pm 3\%$ .

**Table 2.** Slopes ( $l$ ) of the rate-acidity function correlations

| Substituent               | $l$              |
|---------------------------|------------------|
| <i>p</i> -OMe             | 0.6 <sub>8</sub> |
| <i>p</i> -Me              | 0.6 <sub>6</sub> |
| <i>m</i> -Me              | 0.6 <sub>3</sub> |
| H                         | 0.6 <sub>4</sub> |
| <i>m</i> -OMe             | 0.6 <sub>2</sub> |
| <i>p</i> -Cl              | 0.5 <sub>3</sub> |
| <i>m</i> -Br              | 0.5 <sub>1</sub> |
| <i>m</i> -Cl              | 0.5 <sub>1</sub> |
| <i>m</i> -NO <sub>2</sub> | 0.4 <sub>9</sub> |

have been found for correlations of the reaction of ketones in aqueous DMSO containing base where the rate-determining step is considered to be ionization of the keto carbon acid.<sup>5,6</sup>

The addition of the substrate to the reaction media (containing base) results in colouration on initial mixing. This is a transient phenomenon at low [DMSO] for most substrates, but the coloured species become increasingly persistent with increasing DMSO content and are distinct from the products. For the *p*-nitro substrate the coloured intermediate is formed even at very low DMSO content, is comparatively stable, and appears to be the 'true' initial state. For all the other substrates the rates increase with increasing  $H_-$  to reach a maximum before decreasing. For the *p*-nitro substrate these rates decrease with increasing DMSO content over the whole range. The region of change in slope is that where the reaction ceases to be first-order in base and the coloured intermediate persists, becoming the 'true' initial state. This switch appears to arise from a change in the initial state arising from the formation of a relatively stable carbanionic intermediate, the latter being the anion of the normal ester (**2**) (see later). Then  $k_{\text{obs}}$  would be equal to  $k_2$  or the rate coefficient for a subsequent step. The value of  $k_3$  is expected to be greater than that of  $k_{-2}$ , as the methoxide anion will be a better leaving group than the keto carbanion in protic solvents. The increase in rate generally observed with increasing  $H_-$  (i.e. increasing DMSO content) is mainly a function of the increasing activity of the base. However, the decrease in rates shown with increasing  $H_-$  (i.e. increasing DMSO content) by the *p*-nitro derivative and the other substrates in a medium of high DMSO content appears to arise from the solvating ability of DMSO for charge-extended structures<sup>7</sup> and the decreased availability of the protic solvating species, methanol, in these systems. Here the initial state, the carbanion, will require less protic solvation than the transition state for  $k$ , where the charge is more localized on oxygen.

**Effect of Pre-equilibrium on the Rates.**—The equilibria involving phthalide and normal and pseudo ester will only affect  $k_{\text{obs}}$  at low DMSO content and then by reduction of the concentration of the normal ester. The 'true' rate coefficient,  $k_{\text{obs}}^T$ , can be found by correcting  $k_{\text{obs}}$  for this reduction. Analysis of the mixture when the reaction was stopped prior to completion showed that the phthalide had, in all cases, disappeared immediately after initiation of the base-catalysed reaction. The initial substrate was normally found to be the equilibrium mixture of tautomeric normal and pseudo esters. The experimental rate coefficient ( $k_{\text{obs}}$ ) can be related to  $k_{\text{obs}}^T$  in terms of equation (1).<sup>8</sup> Here  $k^T$  for all the substrates varies significantly neither with the composition of the solvent nor with the substituent (see later).

$$k_{\text{obs}}^T = k_{\text{obs}} (1 + 1/K_T) \quad (1)$$

**Substituent Effects.**—The effect of substituents in the phenyl group has been studied in methanol and in methanolic DMSO

**Table 3.** Hammett reaction constants ( $\rho$ ) for the base-catalysed rearrangement<sup>a</sup>

| Solvent                      | $\rho$ | $\log k_0/s^{-1}$ | $n$ | $r$   | $s$   |
|------------------------------|--------|-------------------|-----|-------|-------|
| Methanol (a)                 | 1.587  | -3.338            | 9   | 0.964 | 0.116 |
| (b)                          | 1.750  | -3.395            | 9   | 0.981 | 0.092 |
| 94 mol % methanolic DMSO (a) | -1.564 | -0.704            | 9   | 0.983 | 0.078 |
| (b)                          | -1.659 | -0.659            | 9   | 0.925 | 0.179 |

<sup>a</sup> (a) Based on  $\sigma$  values; (b) based on  $\sigma^-$  values;  $n$  = number of substituents;  $r$  = correlation coefficient;  $s$  = standard deviation

**Table 4.** Kinetic isotope effects ( $k_{\text{H}}/k_{\text{D}}$ ) for the rearrangement of methyl *o*-phenylacetylbenzoate in methanolic DMSO at 30.0 °C

| DMSO mol % | $k_{\text{H}}/k_{\text{D}}$ |
|------------|-----------------------------|
| 20         | 1.0 <sub>5</sub>            |
| 25         | 0.9 <sub>6</sub>            |
| 30         | 0.9 <sub>9</sub>            |
| 40         | 0.8 <sub>2</sub>            |
| 94         | 0.8 <sub>3</sub>            |

<sup>a</sup> Measurements of  $k_{\text{H}}$  and  $k_{\text{D}}$  made simultaneously, i.e. under identical conditions; the ratio is considered to be reproducible to within  $\pm 5\%$ .

and assessed by using the Hammett equation with  $\sigma$  and  $\sigma^-$ .<sup>9,10</sup> Except for the *p*-nitro substrate, good linear correlations are given as shown in Table 3, with  $\rho$  in methanol and in 94 mol % methanolic DMSO being about 1.7 and -1.6, respectively. The observed rate coefficient ( $k_{\text{obs}}$ ) in 94 mol % methanolic DMSO appears to be  $k_2$  in the reaction scheme. The  $\rho$  value for such a process would be expected to be negative, as electron-withdrawing substituents decrease the nucleophilicity of the carbanion, thus inhibiting the reaction, and *vice versa*. Furthermore,  $k_{\text{obs}}$  in methanol could be either  $k_1$  or  $Kk_2$  in the reaction scheme. The reaction constant is not affected by pre-equilibrium tautomerization between normal and pseudo ester; the latter appears to be almost independent of the substituent (see later). The value found for  $\rho$  would appear to be *very* small if  $k_{\text{obs}}$  were equal to  $k_1$ . Thus it would appear that  $k_{\text{obs}}$  equals  $Kk_2$ .

The *p*-nitro substrate has not been included in the correlations. While a  $\sigma^-$  substituent constant would be suitable to correlate the result in methanol, in 94 mol % methanolic DMSO even  $\sigma^-$  is inadequate to account for the enhanced electron-withdrawing effect of the *p*-nitro group. This might be expected if we consider that (**4**) is the fully developed carbanion.

**Isotope Effect.**—The kinetic isotope effect ( $k_{\text{H}}/k_{\text{D}}$ ) observed for the rearrangement of normal methyl *o*-phenylacetylbenzoate in methanolic DMSO is shown in Table 4. The values are between 0.8 and 1.0 over the whole range of basicity and clearly exclude ionization ( $k_1$ ) as the rate-determining step. The small reverse value is compatible with either a small steric effect or a change in hybridization of the carbanion carbon from  $sp^2$  to  $sp^3$  which occurs in the cyclization step,<sup>11</sup> arising from only partial exchange of deuterium in the substrate. This confirms that the rate-determining step is cyclization ( $k_2$ ).

**Equilibrium Constants for the Ring-Chain Tautomerization of Methyl Phenylacetylbenzoates.**—Methyl phenylacetylbenzoates can exist in two forms (normal and pseudo esters) as shown in the Scheme. Both forms can be isolated in the pure state.<sup>12,13</sup> The equilibrium constant ( $K_T$ ) was measured by an indirect method as described later. Equilibrium can be established by either base- or acid-catalysis. The  $K_T$  value was found to be

0.35  $\pm$  0.05 for all substituents and in 0–50 mol% methanolic DMSO. Thus the equilibrium constant is almost independent of the substituent and of the solvent composition. This does not apply to higher DMSO contents in the presence of base. The apparent change in  $K_T$  at higher  $H_-$  values appears to arise from the ionization of the normal ester, increasing the observed concentration of the normal ester on analysis. Thus at very high  $H_-$  values all the ester is in the normal form. The  $pK_a$  value of normal methyl *o*-phenylacetylbenzoate can be calculated as 15.2  $\pm$  0.2 in an approximate manner by using  $K_T$  to give the ionization ratio. Bordwell<sup>14</sup> has measured the  $pK_a$  of PhCH<sub>2</sub>COPh in pure DMSO as 17.7.

We conclude that the rearrangement proceeds with a rate-determining cyclization step ( $k_2$ ). In methanol or methanolic DMSO of high methanol content this is preceded by the ionization step. The initial state here is the equilibrium tautomeric mixture of normal and pseudo esters with  $k_{obs}$  equal to  $Kk_2$ . In methanolic DMSO of high DMSO content the initial state is the anion of the normal ester, and  $k_{obs}$  equals  $k_2$ .

### Experimental

**Materials.**—The substituted benzylidenephthalides were prepared by condensation of the appropriately substituted phenylacetic acids with phthalic anhydride, using sodium acetate as catalyst.<sup>15</sup> The substituted 2-phenylacetylbenzoic acids were prepared by heating the appropriate benzylidenephthalides with aqueous potassium hydroxide.<sup>16</sup> The normal methyl 2-phenylacetylbenzoates were synthesized by esterification of the acids with diazomethane in ether. 2-Phenyl[<sup>2</sup>H<sub>2</sub>]acetylbenzoic acid was prepared by exchanging the acid itself several times with a solution of sodium deuterioxide in deuterium oxide. The exchange was monitored by <sup>1</sup>H n.m.r. spectroscopy and found to give >98% deuteration in the side chain. The pseudo methyl 2-phenylacetylbenzoates were synthesized by reaction of the appropriate benzylidenephthalides with methanolic hydrogen chloride. The substituted 2-phenylindane-1,3-diones were made by base-catalysed rearrangement of the corresponding benzylidenephthalides in methanol. The solvents were purified as described previously,<sup>17,18</sup> as was sodium methoxide.<sup>12</sup> After repeated recrystallization and drying under vacuum (P<sub>2</sub>O<sub>5</sub>), the substrates and products had m.p.s in good agreement with the literature values.

**Kinetic Procedure.**—A u.v.–visible spectroscopic method was used, as previously described.<sup>19</sup> The substrate concentration was 5  $\times$  10<sup>-5</sup> to 1  $\times$  10<sup>-4</sup>M. The reactions were first-order in substrate and were carried out at 2.5  $\times$  10<sup>-2</sup>M-sodium methoxide concentration, unless the order with respect to the base was being studied. The values of the acidity function,  $H_-$ , were interpolated from literature values<sup>20</sup> and corrected for the

change in base concentration.<sup>21</sup> The  $\lambda$  values used in the kinetic measurements were normally those showing the greatest differences between the substrate and products. The products, the anions of the corresponding 2-phenylindane-1,3-diones, were obtained in quantitative yield from preparative-scale reactions and their identities were confirmed by spectral comparison with the indanediones in basic solution.

**Tautomeric Equilibrium Procedure.**—A solution of the 3- or 4-substituted benzylidenephthalide in methanolic DMSO containing sodium methoxide was set aside for a few minutes before addition of an excess of aqueous *N*-hydrochloric acid. The mixture was extracted with carbon tetrachloride. The extract was dried (MgSO<sub>4</sub>), filtered, and then evaporated under reduced pressure at 25 °C. The product was analysed by either g.l.c. (unsubstituted compound) or <sup>1</sup>H n.m.r. (all compounds).<sup>12</sup> The procedure was repeated on the benzoate esters with methanolic DMSO containing hydrogen chloride.

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