

# Isotope Effects in Proton-transfer Reactions. VIII.\* Isotope Effects in the Proton-transfer from (–)-Menthone to Methoxide Ion in Methanol and Methanol–Dimethyl Sulfoxide Solutions

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The primary kinetic and solvent isotope effects on the proton transfer from (–)-menthone to methoxide ion in methanol and methanol–dimethyl sulfoxide have been determined. The primary isotope effect at 25 °C is somewhat stronger in methanol ( $k_{\text{H}}/k_{\text{D}} = 7.15 \pm 0.09$ ) than in 10 mol % methanol–90 mol % dimethyl sulfoxide ( $k_{\text{H}}/k_{\text{D}} = 5.96 \pm 0.08$ ) but no clear maximum in the primary kinetic isotope effect is observed when the amount of DMSO in the solvent is varied. The kinetic solvent isotope effect at 25 °C varies from  $k^{\text{MeOD}}/k^{\text{MeOH}} = 2.04$  in methanol to 1.43 in 10 mol % methanol–90 mol % dimethyl sulfoxide. The variation is explained in terms of the fractionation theory with a gradual decrease of the fractionation factors and the number of solvating molecules when the amount of dimethyl sulfoxide in the solution is increased.

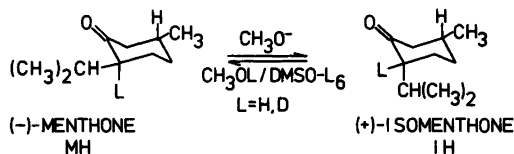
Solvent effects on proton-transfer reactions have recently been subject to a considerable interest. The influence of the solvent on the magnitude of the primary kinetic isotope effect and Brønsted's  $\beta$  for simple proton-transfer reactions have been explored.<sup>1,2</sup> Solvent motions coupled to the proton-transfer have been considered both in connection with experimental results<sup>3</sup> and from a theoretical point of view.<sup>4</sup>

Since the discovery of the exceptional properties of the non-hydroxylic solvent dimethyl sulfoxide (DMSO) in the solvation of ionic species this solvent

is frequently used in order to change the degree of solvation in a reaction.

The present paper presents an investigation of the change of the kinetic primary isotope effect and of the kinetic solvent isotope effect of a proton-transfer reaction in mixtures of a hydroxylic (methanol) and a non-hydroxylic (DMSO) solvent. The model reaction which has been studied is the methoxide-ion catalyzed epimerization of (–)-menthone–(+)-isomenthone (Scheme 1). This reaction has been rather extensively studied and a very recent investigation treats the kinetics of the reaction in the given media in detail.<sup>6</sup>

A study of the reaction in water–DMSO mixtures showed that the primary kinetic isotope effect for the reaction passes through a maximum ( $k_{\text{H}}/k_{\text{D}} = 6.45$ ) at about 35 mol % DMSO–65 mol % water.<sup>7</sup>



Scheme 1.

## RESULTS

The rate constants for the epimerization of (–)-menthone in mixtures of methanol and DMSO are given in Table 1. The rate of epimerization is increased by a factor of about 200 over the interval

\* For Part VII of this series see: Bergman, N.-Å. and Källsson, I. *Acta Chem. Scand.* A 30 (1976) 421.

Table 1. Epimerization of (–)-menthone in mixtures of methanol and dimethyl sulfoxide. Temperature  $25.00 \pm 0.05$  °C. Substrate concentration  $\sim 3 \times 10^{-5}$  M.

mol % DMSO	[MeONa]/M	$k/M^{-1}s^{-1}$ <sup>a</sup>
0	0.154–0.187	$(8.670 \pm 0.050) \times 10^{-3}$
14.9	0.151, 0.152	$(1.413 \pm 0.015) \times 10^{-2}$
27.0	0.0290	$(2.310 \pm 0.047) \times 10^{-2}$
28.0	0.0946	$(2.411 \pm 0.019) \times 10^{-2}$
41.3	0.0709	$(4.696 \pm 0.058) \times 10^{-2}$
50.3	0.0228	$(7.333 \pm 0.080) \times 10^{-2}$
57.6	0.0473	$(1.203 \pm 0.011) \times 10^{-1}$
59.7	0.0154	$(1.303 \pm 0.006) \times 10^{-1}$
70.0	0.00542	$(2.552 \pm 0.028) \times 10^{-1}$
74.5	0.0073	$(3.775 \pm 0.150) \times 10^{-1}$
79.8	0.00343	$(5.942 \pm 0.023) \times 10^{-1}$
80.0	0.00344	$(6.073 \pm 0.034) \times 10^{-1}$
90.0	0.00207	$2.108 \pm 0.037$
91.0	0.0029	$1.996 \pm 0.145$

<sup>a</sup>The values are weighted averages from at least 3 runs and the error limits are  $\pm 2\sigma$ . Uncertainty in the concentration of the base is included.

0–90 mol % DMSO. This increase is somewhat less than for the same reaction in corresponding mixtures of water–DMSO.<sup>7</sup>

The second-order rate constants for epimerization of deuterated (–)-menthone are given in Table 2. Most of these rate constants were obtained by running a 50:50 mixture of (–)-menthone and (–)-menthone-*d*. (In fact, deuterated (–)-menthone

Table 2. Epimerization of (–)-menthone-*d* in mixtures of methanol and dimethyl sulfoxide. Temperature  $25.00 \pm 0.05$  °C. Substrate concentration  $\sim 3 \times 10^{-5}$  M.

mol % DMSO	[MeONa]/M	$k/M^{-1}s^{-1}$ <sup>a</sup>
0	0.164–0.187	$(1.213 \pm 0.008) \times 10^{-3}$
14.9	0.151	$(2.004 \pm 0.027) \times 10^{-3}$
28.0	0.0946	$(3.481 \pm 0.030) \times 10^{-3}$
41.3	0.0709	$(6.649 \pm 0.117) \times 10^{-3}$
50.3	0.0228	$(1.058 \pm 0.016) \times 10^{-2}$
59.7	0.0154	$(1.921 \pm 0.008) \times 10^{-2}$
70.0	0.00542	$(3.697 \pm 0.056) \times 10^{-2}$
79.8	0.00343	$(8.993 \pm 0.022) \times 10^{-2}$
80.0	0.00344	$(9.052 \pm 0.042) \times 10^{-2}$
90.0	0.00207	$(3.534 \pm 0.055) \times 10^{-1}$

<sup>a</sup>The values are weighted averages from at least 3 runs and the error limits are  $\pm 2\sigma$ . Uncertainty in the concentration of the base is included.

contains deuterium in the 6 position too, but the influence of these deuterium atoms is neglected and deuterated (–)-menthone will be referred to a (–)-menthone-*d*.) The change in optical rotation as a function of time was then analyzed using the computer program PROGAEXP to determine the best fit of a two-exponential expression to the experimental data. Provided that the reaction is followed long enough to get good accuracy in  $k_D$  this is a convenient method in as much as  $k_H/k_D$  could be obtained without interexperimental errors.

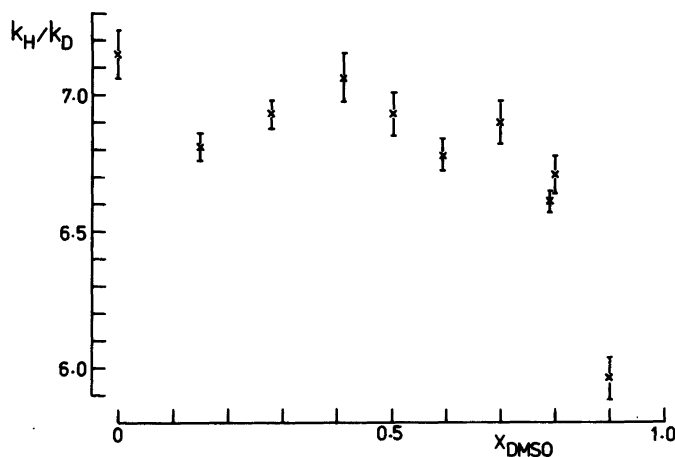


Fig. 1. Primary kinetic isotope effect for proton abstraction from (–)-menthone in mixtures of methanol–DMSO. Temperature  $25.00 \pm 0.05$  °C.

Table 3. Epimerization of (–)-menthone in mixtures of methanol-*O-d* and dimethyl sulfoxide-*d*<sub>6</sub>. Temperature 25.00 ± 0.05 °C. Substrate concentration ~ 3 × 10<sup>-5</sup> M.

mol % DMSO- <i>d</i> <sub>6</sub>	[MeONa]/M	<i>k</i> /M <sup>-1</sup> s <sup>-1</sup> <sup>a</sup>
0	0.1456	(1.835 ± 0.031) × 10 <sup>-2</sup>
0	0.119	(1.696 ± 0.035) × 10 <sup>-2</sup>
15.4	0.0683	(2.767 ± 0.036) × 10 <sup>-2</sup>
24.2	0.0534	(3.684 ± 0.054) × 10 <sup>-2</sup>
27.0	0.0287	(4.445 ± 0.096) × 10 <sup>-2</sup>
50.1	0.0152	(1.282 ± 0.023) × 10 <sup>-1</sup>
68.6	0.00435	(3.963 ± 0.070) × 10 <sup>-1</sup>
74.5	0.0051, 0.0072	(6.570 ± 0.190) × 10 <sup>-1</sup>
90.1 <sup>b</sup>	0.00163	2.988 ± 0.083
90.2 <sup>b</sup>	0.00166	2.974 ± 0.090
90.4 <sup>b</sup>	0.00157	3.127 ± 0.222
91	0.00224	2.664 ± 0.080

<sup>a</sup>The values are weighted averages from at least 3 runs and the error limits are ± 2σ. Uncertainty in the base concentration is included. <sup>b</sup>DMSO-*h*<sub>6</sub> was used since DMSO-*d*<sub>6</sub> of good quality was not available at the time for these runs. The rate of exchange of protons in the DMSO is believed to be slow in comparison to the rate of the reaction studied.

The method was checked by running (–)-menthone and (–)-menthone-*d* separately, giving the same result.

As has been shown,<sup>6</sup> the rate of enolate ion formation for (–)-menthone in methanol-*O-d* is somewhat higher than the corresponding rate for

(+)-isomenthone. This implies that *k*<sub>obs</sub> in light media starting with (–)-menthone is not exactly equal to the rate constant for formation of the enolate ion but as the deviation amounts to only some few percent no correction for this has been made in the present investigation. The *k*<sub>H</sub>/*k*<sub>D</sub> values in methanol–DMSO are given in Fig. 1.

The reaction was also studied in mixtures of methanol-*O-d*–DMSO-*d*<sub>6</sub> and the rate constants are given in Table 3. The kinetic solvent isotope effect was calculated directly for runs with the same methanol–DMSO composition. For runs with nearly the same composition, linear interpolation was performed in order to adjust the rate constants to an intermediate composition. The variation of the solvent isotope effect with increasing content of DMSO is shown in Fig. 2.

## DISCUSSION

As can be seen from Table 1 the rate increase in the inversion of menthone going from methanol to a mixture containing 90 mol % DMSO amounts to a factor of about 200. This is rather normal for ketones in mixtures of a hydroxylic solvent and DMSO. It is, however, somewhat less than the corresponding factor for, *e.g.*, cyanocarbon acids over the corresponding composition range.<sup>8,9</sup> The reason for this could at least qualitatively be explained by a possible destabilization of the developing enolate ion in the transition state<sup>10</sup> analogous to the known destabilization of the

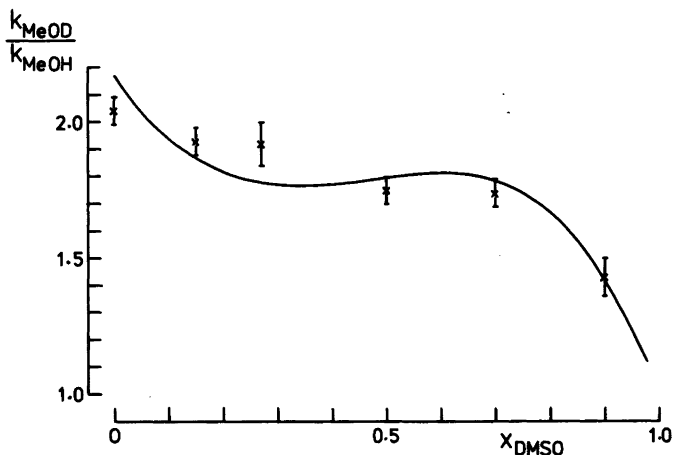
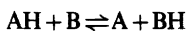


Fig. 2. Kinetic solvent isotope effect for proton abstraction from (–)-menthone in mixtures of methanol–DMSO. The solid line shows the theoretical curve (see text). Temperature 25.00 ± 0.05 °C.

methoxide ion in DMSO mixtures with hydroxylic solvents.

The primary kinetic isotope effect is determined by the properties of the isotopic reactants and the corresponding transition states of the rate-determining step.<sup>11</sup> A maximum in the isotope effect will be observed when cancellation of the zero-point energy difference between the isotopic reactants is at a minimum in the transition state. This has been suggested to occur for a reaction



when  $\Delta pK = pK_{\text{HA}} - pK_{\text{HB}}$  equals zero, i.e.,  $\Delta G^\circ = 0$ .<sup>12</sup>

For the present system there is no straightforward way of obtaining  $\Delta pK$  in different mixtures of methanol and DMSO. One way to estimate  $\Delta pK$  is to use the  $H_-$ -function.<sup>7,13</sup>

The use of the  $H_-$ -function in determining Brønsted's  $\beta$  for a reaction in mixtures of DMSO and water has been questioned by Cox and Gibson<sup>1</sup> who found that both rates and isotope effects for simple proton-transfer reactions varied considerably as the solvent composition was altered. No correlation between the kinetic isotope effects and the overall energy changes for the reactions could be established.

The range of  $\Delta pK$  for the present system could, however, be estimated to about 7 pK units ranging from  $\Delta pK = 4$  in methanol to  $\Delta pK = -3$  in DMSO. These figures could be obtained by assuming a  $pK_a = 22$  of menthone in methanol and  $pK_a = 18.3$  of methanol in methanol.<sup>14</sup> The corresponding values in DMSO being for menthone  $pK_a = 26$  (cf.  $pK_a = 26.3$  for phenyl isopropyl ketone in DMSO<sup>15</sup>) and for methanol  $pK_a = 29.1$ .

These figures mean that in terms of  $\Delta pK$  the transition state for the proton transfer changes from being slightly product-like in methanol to slightly reactant-like in DMSO.

As can be seen from Fig. 1 there is, however, no clear maximum in the  $k_{\text{H}}/k_{\text{D}}$  values but rather a somewhat irregular decrease as the amount of DMSO in the solvent is increased. Nevertheless, the rather strong isotope effect is an indication that the proton must be about half transferred in the transition state. The largest  $k_{\text{H}}/k_{\text{D}}$  values in the present investigation are found at positive  $\Delta pK$  values and it is interesting to note that also in the epimerization of menthone in water–DMSO the isotope-effect maximum lies at about  $\Delta pK = +2$ .<sup>7</sup> It

seems thus rather plausible that the  $k_{\text{H}}/k_{\text{D}}$  curve obtained in the present investigation could be part of an isotope-effect maximum curve.

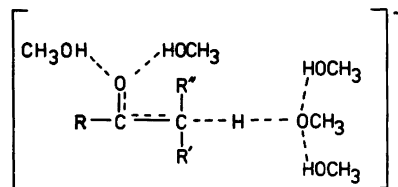
The solvent isotope effect as depicted in Fig. 2 shows a dramatic change from methanol to pure DMSO.

Solvent isotope effects are most conveniently discussed in terms of fractionation theory.<sup>16</sup> For the present case the expression for the limiting rate constant ( $k^{\text{OD}}$ ) in heavy medium relative to the one ( $k^{\text{OH}}$ ) in light medium will be

$$k^{\text{OD}}/k^{\text{OH}} = \prod_i \phi_i^* / \prod_i \phi_i^{\text{R}}$$

where  $\phi_i^*$  and  $\phi_i^{\text{R}}$  denote the fractionation factor for an exchangeable hydrogen in the transition and reactant states, respectively. The only positions with exchangeable hydrogens in the reactant are the OH-positions in the solvation shell of the methoxide ion, the fractionation factor of which is usually denoted  $\phi_{\text{OMe}}$ . The number of methanol molecules solvating the methoxide ion in methanol is usually assumed to be three.

Very little is known about the relative importance of functional-group solvation in the transition-state but one model of the transition state which should be considered is shown in Scheme 2.



Scheme 2.

The solvation of the two partly negatively charged oxygen atoms is thought to take place via two methanol molecules on each oxygen atom. The transition state could, according to the magnitude of the primary kinetic isotope effect, be considered as rather symmetric and a partial negative charge on the carbonyl oxygen atom is thus likely.

The resulting expression for the solvent isotope effect should thus be,

$$k^{\text{OD}}/k^{\text{OH}} = (\phi^*)^4 / \phi_{\text{OMe}}^3$$

under the assumption of four equal fractionation factors in the transition state and three for the methoxide ion. This expression is valid for pure methanol-*O-d*-methanol and gives with the experimental value  $k^{\text{OD}}/k^{\text{OH}}=2.04$  and  $\phi_{\text{OMe}}$  the result  $\phi^{\ddagger}=0.95$ .

For analysis of the results in mixtures of methanol and DMSO the fractionation factor of methoxide ion in these mixtures has to be known. A very recent investigation<sup>17</sup> has shown that there is a decrease from  $\phi_{\text{OMe}}=0.74$  in methanol to  $\phi_{\text{OMe}}=0.38$  in 75 mol % DMSO–25 mol % methanol. The change of  $\phi_{\text{OMe}}$  over the studied solvent composition is given by:

$$\phi_{\text{OMe}} = -0.40x^2 - 0.20x + 0.75$$

The expression is obtained by a least-squares fit to the experimental data<sup>17</sup> and  $x$  denotes the mol fraction of DMSO. It is reasonable to assume a decrease even in the  $\phi^{\ddagger}$  value when the DMSO content in the mixture is increased. This decrease could, however, be estimated to be somewhat less pronounced. Assuming a second-degree dependence of  $\phi^{\ddagger}$  (as well as of  $\phi_{\text{OMe}}$  above) and assuming linear change with  $x$  of the number of methanol molecules solvating the methoxide ion and the transition state gives the general expression (1). From this expression and the experimental values for  $k^{\text{OD}}/k^{\text{OH}}$  ( $ax^2 + bx + c$ ) can be calculated for a number of  $x$ -values. The so determined points are fitted to a

second-degree polynomial (with the method of least squares). This procedure yields  $a=0.21$ ,  $b=-0.35$  and  $c=0.98$  which, inserted in expression (1), gives the theoretical curve in Fig. 2.

$$k^{\text{OD}}/k^{\text{OH}} = \frac{(ax^2 + bx + c)^{4(1-x)}}{(-0.40x^2 - 0.20x + 0.75)^{3(1-x)}} \quad (1)$$

It is important to realize that the precise course of the theoretical solvent isotope effect curve is very sensitive to small deviations in the measured rate constants. However, the general shape is judged as reliable because test calculations with reasonably altered values, around the experimental ones, produce curves of similar shape.

It is also possible to construct curves of a similar shape using other assumptions regarding the form of  $\phi^{\ddagger}$  as well as of the solvation of the activated complex. Our assumptions, though, seem natural and are not contradicted by the experimental results.

The denominator in (1) has the attractive feature of being essentially constant over the interval  $x=0-0.5$  (Fig. 3). Neglecting any "medium" effect, a deviation from the value in methanol of  $k^{\text{OD}}/k^{\text{OH}}$  in this region would have to be attributed to fractionation in the solvating positions surrounding the transition state. The numerator of (1) gives the contribution from the transition state and is given in Fig. 3. It might be argued that the drop in  $k^{\text{OD}}/k^{\text{OH}}$  is

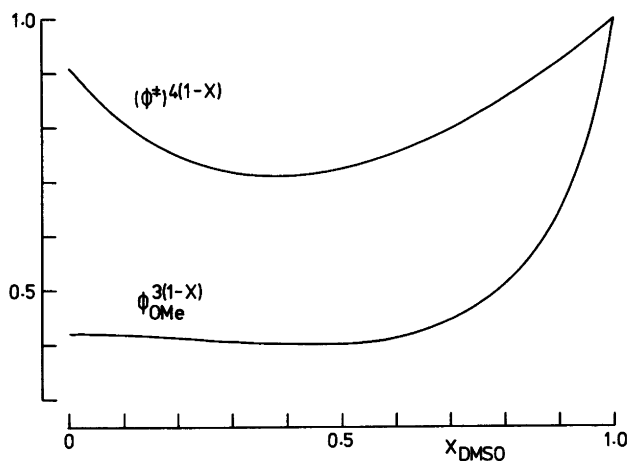


Fig. 3. Variation of the contributions from the transition state and the methoxide ion to the kinetic solvent isotope effect.

not a transition-state contribution but is merely reflecting the error limits in  $\phi_{\text{OMe}}$  or reflecting the crudeness in our assumption that the methoxide ion is linearly desolvated with  $x$ . However, to account for the decrease in the isotope effect at, for instance,  $x_{\text{DMSO}}=0.4$ , a  $\phi_{\text{OMe}}$  of 0.68 would have to be used instead of 0.61 or a mean solvation number for methanol of 1.28 instead of 1.80 and, in view of the large errors that would have to be assumed, our interpretation is presented with some confidence. A "medium" effect on the isotope effect may also be suggested but it has been shown that medium effects are small in proton-transfer reactions.<sup>18</sup>

The increase in fractionation of the transition state is probably an effect of desolvation. The number of occupied hydrogen-bonding sites is decreased, but at the same time the fractionation factors deviate more from unity. The result is that the product of  $\phi^*$ 's gives a lower value in 50 mol % DMSO than in methanol. The balance between the numerical values of the fractionation factors and the number of sites gives for the methoxide-ion fractionation, as mentioned above, a constant contribution to the overall isotope effect in the range  $x_{\text{DMSO}}=0-0.5$ . For the transition state the fractionation factor product goes through a minimum at roughly 40 mol % DMSO. An analogous increase in fractionation caused by desolvation has been observed in the case of sterically hindered oxyanions.<sup>19</sup> Although the interpretation of the isotope effects is complicated under these conditions, we believe that the magnitude of the drop of the numerator of eqn. (1) is a measure of the strength of the interactions between the solvent and the transition state.

From Fig. 3 it is obvious that a solvent of about 40 mol % of DMSO in methanol should provide a potential source for studying such effects for methoxide-catalyzed reactions.

It would be interesting to carry the analysis one step further, trying to ascribe the contribution from solvation to different parts of the transition state.

In general, substrates exhibiting similar degree of steric hindrance would be expected to give rise to a larger contribution from solvation of the methoxy oxygen the more reactant-like the transition state. The functional-group contribution would be more conspicuous the more product-like the transition state is, although large differences between different functional groups are anticipated. If solvation of the transition state is on the whole unimportant the kinetic solvent isotope effect would be expected to

Table 4. Kinetic solvent isotope effects on the methoxide-catalyzed proton abstraction from (-)-menthone and (+)-2-methyl-3-phenylpropionitrile in methanol and in 54 mol % DMSO in methanol.

Substrate	$k^{\text{OD}}/k^{\text{OH}}$	
	Methanol	54 mol % DMSO
Menthone (25 °C)	2.04	1.75
2-Methyl-3-phenylpropionitrile (60 °C)	2.09 <sup>a</sup>	1.76

<sup>a</sup>From Ref. 20.

be of a constant magnitude on going from 0 to 50 mol % of DMSO in methanol.

For the present system it is reasonable to assume a rather symmetric transition state making both functional-group solvation and methoxy-oxygen solvation of some importance.

For a reaction with a very unsymmetric transition state such as the methoxide-catalyzed proton-abstraction from 2-methyl-3-phenylpropionitrile in methanol<sup>8</sup> the situation is somewhat different. The highly product-like transition state in this reaction would suggest functional-group solvation to be of main importance.

In order to compare the two reactions we have therefore measured the kinetic solvent isotope effect of 2-methyl-3-phenylpropionitrile in 54 mol % of DMSO in methanol, and the results are presented in Table 4.

The results for the two very different reactions are virtually the same showing a pronounced drop in the kinetic solvent isotope effect when the solvent is changed from methanol to 54 mol % of DMSO in methanol. A compensation for the difference in temperature will change the values only slightly. In the case of 2-methyl-3-phenylpropionitrile dominant methoxy solvation is ruled out by the very unsymmetric transition state and the drop in the kinetic solvent isotope effect must thus be assigned to the functional group.

Clearly, more work is needed before our understanding of solvent fractionation is complete but we suggest that determination of kinetic solvent isotope effects at the two solvent compositions mentioned above may be a useful tool for elucidating in detail the solvation of transition states.

## EXPERIMENTAL

(-)-Menthone was synthesized and separated from the small amounts of (+)-isomenthone also formed according to Ref. 21.

Deuterated (-)-menthone and (+)-isomenthone were prepared from (-)-menthone by equilibration in methanol-*O-d* with sodium methoxide as catalyst. The solution was poured out onto ice with enough hydrochloric acid to neutralize the methoxide. The equilibrium mixture was extracted with ether. The ether layer was dried with CaSO<sub>4</sub> (Sikkon, Fluka AG) and the ether was evaporated. The procedure was repeated until NMR showed complete deuteration in position 2. The deuterated (-)-menthone and (+)-isomenthone were separated by HPLC in the same way as undeuterated material according to Ref. 21.

The solvents of listed quality were obtained from the following manufacturers and used without further purification.

*Methanol*. Anhydrous, H<sub>2</sub>O < 0.01 % w/w, May & Baker.

*Dimethyl sulfoxide*. H<sub>2</sub>O < 0.01 %, Riedel-de Haën AG.

*Methanol-O-d*. > 99.5 atom % D, CIBA.

*Dimethyl sulfoxide-d<sub>6</sub>*. > 99.5 atom % D, CIBA.

All handling of the solvents was carried out under nitrogen in order to avoid uptake of moisture.

Base solutions were made by dissolving sodium in methanol under nitrogen. The concentration of sodium methoxide was determined by titration against potassium hydrogen phthalate using phenolphthalein as indicator.

All glass apparatus was cleaned with chromic acid, washed with water, dilute ammonia, and then carefully rinsed with distilled water and finally dried at 120 °C for at least 24 h.

The polarimeter cell was rinsed with anhydrous methanol and then flushed with a stream of nitrogen prior to each kinetic run.

*Kinetic runs* were performed on a Zeiss OLD 5 digital polarimeter which can be read to 0.001°. The reactions were carried out in a thermostatted 10 cm polarimeter cell. The temperature was maintained by a Hetotherm Ultrathermostat 02 Pt 623 UO together with a Hetofrig cooling bath. The temperature in the thermostat bath was read on a thermometer, which could be read to 0.01 °C. In the circulation water, immediately after the cell, was mounted a REC Platinum resistance sensing element connected to a Fluke 8300 A digital voltmeter/ohmmeter readable to 0.01 ohm corresponding to 0.03 °C in the temperature range around 25 °C. This system was calibrated against a Hewlett-Packard quartz thermometer 2801 A which was calibrated against the resistance thermometer normal of National Testing Institute, Borås,

Sweden. Data from the polarimeter and from the voltmeter were collected on discettes in a CompuCorp 625 Mark II desktop computer interfaced on line. The data were then analyzed using the computer program PROGAEEXP.

*Acknowledgements*. The authors wish to thank Professor Lars Melander for his interest in the present work and for reading the manuscript prior to publication. Technical assistance by Dr. Inger Källsson with some of the polarimeter measurements is gratefully acknowledged. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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