

Epimerization of (–)-Menthone in Methanol-*O-d**

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The methoxide catalyzed epimerization of (–)-menthone and (+)-isomenthone has been studied in methanol-*O-d*. The rate constant for enolate ion formation from (–)-menthone has been shown to be somewhat larger (6%) than the corresponding rate constant for (+)-isomenthone. The same is also true for a mixture of 25 mol % methanol-*O-d* and 75 mol % dimethyl sulfoxide-*d*₆. The kinetics of the epimerization are treated in detail.

The isomerization of (–)-menthone** and (+)-isomenthone** catalyzed by both acids and bases has been subject to many investigations.

The reaction was discovered by Beckmann.¹ The first kinetic study was made by Vorländer² but the most exhaustive investigation was made by Tubandt³ who studied the influence of solvent, catalysts and temperature on the reaction. He was also able to show that the same equilibrium was reached from a menthone of $[\alpha]_D^{20} -27.75^\circ$ and from a "Rechtsmenthon" of $[\alpha]_D^{20} +27.79^\circ$ (in fact a mixture of (–)-menthone and (+)-isomenthone) and that the reaction velocity is the same in both cases.

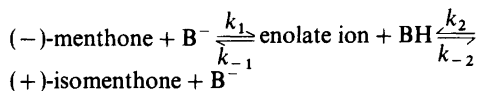
Acid-catalyzed epimerization has been most investigated. Besides the very first investigations there are investigations made by Bell and Caldin⁴ and Weissberger⁵ on the epimerization in aprotic solvents.

Base-catalyzed epimerization has been studied by Bunnett and Retallick⁶ who investigated the

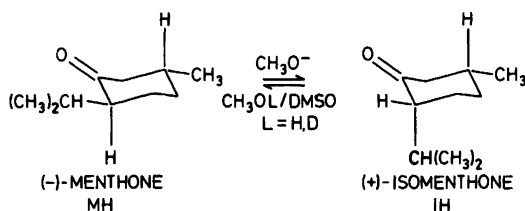
effectiveness of methoxide and thioethoxide as catalysts in the epimerization of (–)-menthone in methanol.

Recently Bell and Cox⁷ made an investigation of the kinetic isotope effect in the inversion of (–)-menthone in mixtures of water and dimethyl sulfoxide.

The usually assumed reaction scheme for the epimerization is



Bell and Cox⁷ found no deviation from first-order kinetics in studying the epimerization of (–)-menthone-*d* in water–dimethyl sulfoxide and thus concluded that $k_1 = k_2$ and that the rate-determining step in the inversion is the formation of the enolate ion.



We have been interested in studying the epimerization of (–)-menthone in mixtures of methanol and dimethyl sulfoxide and in the corresponding deuterated media in order to evaluate the kinetic solvent isotope effect on the reaction. The runs in methanol-*O-d* and mixtures of methanol-*O-d* and dimethyl sulfoxide-*d*₆ gave deviations from first-order kinetics which led us to look at the reaction in more detail. These deviations indicate that k_1 is

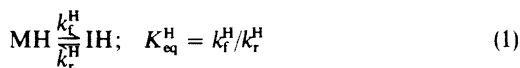
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** The systematic names for (–)-menthone and (+)-isomenthone according to Chemical Abstracts are (5*R*,2*S*)-*trans*-5-methyl-2-(1-methylethyl)-cyclohexanone and (5*R*,2*R*)-*cis*-5-methyl-2-(1-methylethyl)-cyclohexanone, respectively.

not exactly equal to k_2 . According to the findings of Bell and Cox⁷ for water–dimethyl sulfoxide, however, it is safe to conclude that k_1 cannot be very different from k_2 because they should have otherwise observed deviations from first-order kinetics in runs with (–)-menthone-*d* in light medium.

The present method of studying the inversion starting with (–)-menthone or (+)-isomenthone in heavy medium (methanol-*O-d*) is advantageous in detecting small deviations from first-order kinetics because the equilibration between the two deuterated epimers is slower than the reaction of the light epimer which is the reactant.

Epimerization of (–)-menthone in methanol. The kinetic analysis for the reaction in methanol is simple and straight-forward. Using MH and IH for (–)-menthone and (+)-isomenthone, respectively, the phenomenological scheme (1) can be



written. The superscript indicates that the reaction takes place in methanol. The observed first-order rate constant which, of course, is dependent on the concentration of base present in the system, is given by (2). This rate constant could be obtained

$$k_{\text{obs}}^H = k_f^H + k_r^H \quad (2)$$

from polarimetric measurements and it can be shown that if we start with MH the observed optical rotation α_{obs} at time t is given by (3), where $[\alpha]$

$$\alpha_{\text{obs}} = \delta \exp(-k_{\text{obs}}^H t) + \alpha_{\infty} \quad (3)$$

$$\delta = -\frac{K_{\text{eq}}^H}{1 + K_{\text{eq}}^H} ([\alpha]^{\text{IH}} - [\alpha]^{\text{MH}})[\text{MH}]_0$$

$$\alpha_{\infty} = \frac{[\alpha]^{\text{MH}} + [\alpha]^{\text{IH}} K_{\text{eq}}^H}{1 + K_{\text{eq}}^H} [\text{MH}]_0$$

denotes specific rotation and $[\text{MH}]_0$ is the initial concentration of (–)-menthone in g/ml.

Assuming that the epimerization takes place *via* an enolate ion, E, the mechanistic scheme (4) can



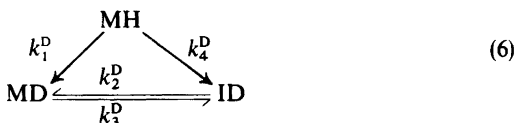
be written; the values of the first-order rate constants depend on the concentration of base present in the system.

If the steady-state approximation holds for E it can be shown that

$$k_{\text{obs}} = \frac{k_a^H k_{-d}^H + k_{-a}^H k_d^H}{k_{-a}^H + k_{-d}^H} \quad (5)$$

which means that only if $k_a^H = k_d^H$, will (5) yield $k_{\text{obs}} = k_a^H$.

*Epimerization of (–)-menthone in methanol-*O-d*.* For the reaction of (–)-menthone in methanol-*O-d* the phenomenological scheme (6) can be written;



MD and ID indicate deuterated (–)-menthone and deuterated (+)-isomenthone, respectively. The reactions from MH to the two deuterated epimers are written as irreversible since they are carried out in great excess of methanol-*O-d* compared with menthone. The superscript indicates that the reaction takes place in methanol-*O-d*.

Using the matrix method by Bergson⁸ it can be shown that if we start with optically pure MH the observed optical rotation at time t will be given by (7), where

$$\alpha_{\text{obs}} = \beta \exp(-\lambda_1 t) + \gamma \exp(-\lambda_2 t) + \alpha_{\infty} \quad (7)$$

$$\beta = \left\{ [\alpha]^{\text{MH}} + [\alpha]^{\text{MD}} \frac{k_1^D - k_2^D}{\lambda_2 - \lambda_1} + [\alpha]^{\text{ID}} \frac{k_4^D - k_3^D}{\lambda_2 - \lambda_1} \right\} [\text{MH}]_0 \quad (8)$$

$$\gamma = \frac{k_1^D k_3^D - k_2^D k_4^D}{\lambda_2 (\lambda_2 - \lambda_1)} ([\alpha]^{\text{ID}} - [\alpha]^{\text{MD}})[\text{MH}]_0 \quad (9)$$

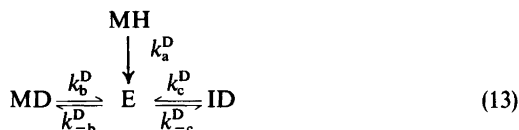
$$\alpha_{\infty} = ([\alpha]^{\text{MD}} + [\alpha]^{\text{ID}} K_{\text{eq}}^D)[\text{MH}]_0 / (1 + K_{\text{eq}}^D)$$

$$\lambda_1 = k_1^D + k_4^D \quad (10)$$

$$\lambda_2 = k_2^D + k_3^D \quad (11)$$

K_{eq}^D is the equilibrium constant for the equilibrium between deuterated menthone and isomenthone in methanol-*O-d*. $[\alpha]$ denotes as before specific rotation and $[\text{MH}]_0$ is the initial concentration of (–)-menthone in g/ml.

Before looking at the factors β and γ we shall consider the mechanistic scheme which corresponds to the phenomenological scheme (6). Using the same assumptions as before the scheme (13) can be written.



Using the matrix method⁸ the relations (14)–(19) between mechanistic rate constants in (13) and the phenomenological rate constants in (6) can be derived.

$$k_1^D = k_a^D k_{-b}^D / (k_{-b}^D + k_{-c}^D) \quad (14)$$

$$k_2^D = k_{-b}^D k_c^D / (k_{-b}^D + k_{-c}^D) \quad (15)$$

$$k_3^D = k_b^D k_{-c}^D / (k_{-b}^D + k_{-c}^D) \quad (16)$$

$$k_4^D = k_a^D k_{-c}^D / (k_{-b}^D + k_{-c}^D) \quad (17)$$

$$\lambda_1 = k_1^D + k_4^D = k_a^D \quad (18)$$

$$\lambda_2 = k_2^D + k_3^D = (k_{-b}^D k_c^D + k_b^D k_{-c}^D) / (k_{-b}^D + k_{-c}^D) \quad (19)$$

It can now be of some interest to look at the factors β and γ . Assuming $[\alpha]^{\text{MD}} = [\alpha]^{\text{MH}}$ (see also Table 1), β can be rewritten as (20).

$$\beta = \frac{k_4^D - k_3^D}{\lambda_2 - \lambda_1} ([\alpha]^{\text{ID}} - [\alpha]^{\text{MD}}) [\text{MH}]_0 \quad (20)$$

As the inversion of (-)-menthone in methanol is subject to a rather normal primary kinetic isotope effect⁹ $k_4^D > k_3^D$ and as $k_4^D/k_3^D = k_a^D/k_b^D \sim k_a^D/k_c^D = k_1^D/k_2^D$ it is obvious that β (20) will always be less than zero.

We can now derive an expression for γ in terms of the mechanistic rate constants and λ_1 and λ_2 . Using the relations (14)–(17) it can be shown that

$$\gamma = \frac{k_a^D k_{-b}^D k_{-c}^D (k_b^D - k_c^D)}{\lambda_2 (\lambda_2 - \lambda_1)} \cdot \frac{1}{(k_{-b}^D + k_{-c}^D)^2} \times ([\alpha]^{\text{ID}} - [\alpha]^{\text{MD}}) [\text{MH}]_0 \quad (21)$$

As the denominator in (21) is less than zero (see above) the sign of γ will be determined by the relative magnitudes of k_b^D and k_c^D .

It is easily seen that $\gamma=0$ if $k_b^D = k_c^D$, i.e. if the rate constant for enolate-ion formation from MD is the same as from ID. In such a case (7) will become a single-exponential expression and $\ln(\alpha_{\text{obs}} - \alpha_{\infty})$ vs. t will give a straight line with $-\lambda_1$ as the slope, and according to (18) $\lambda_1 = k_a^D$. As the experiments in deuterated media (see further below) show that α_{obs} vs. t cannot be represented by a single-exponential expression one may infer that $k_b^D \neq k_c^D$.

If we make the assumption that the primary kinetic isotope effect on the rate constant for enolate formation from (-)-menthone is the same as for (+)-isomenthone, i.e.,

$$k_b^D/k_c^D = k_a^D/k_d^D$$

where k_d^D is the rate constant for formation of E starting from IH in a scheme like (13), it should be possible to evaluate the ratio k_b^D/k_c^D from two experiments starting with optically pure (-)-menthone and optically pure (+)-isomenthone, giving k_a^D and k_d^D , respectively. For a reaction starting with optically pure IH an expression similar to (7) is valid. It can be shown, however, that in such a case $\beta > 0$. The expression for γ contains the factor $(k_b^D - k_c^D)$. As $\lambda_2 < \lambda_1$ it will be true that $\gamma < 0$ provided $k_b^D > k_c^D$.

RESULTS

The runs of (-)-menthone in methanol gave good first-order kinetics with plots of $\ln(\alpha_{\text{obs}} - \alpha_{\infty})$ vs. t which were linear for at least four half-lives. As data for this reaction have been published elsewhere^{3a,6} and as our data are in reasonable agreement with them no data will be given here, but some data could be found in Ref. 9 in connection with a discussion of the isotope effects on the reaction.

Using High Performance Liquid Chromatography (HPLC) the two epimers could easily be obtained in optically pure form.¹⁰ The specific rotations of the two epimers at different wavelengths in methanol are given in Table 1. Experiments of the type outlined above could thus be performed.

The results from some experiments in methanol-*O-d* are given in Table 2. They clearly show that $k_a^D > k_d^D$. If the assumption made above is valid this implies that $k_b^D > k_c^D$. We should therefore expect that in experiments starting with IH the observed

Table 1. Specific rotations of (–)-menthone (MH), (+)-isomenthone (IH) and the corresponding deuterated epimers MD and ID, respectively, in methanol at 25 °C.

Wavelength (λ)/nm	$[\alpha]_{\lambda}^{25}/^{\circ}$			
	MH (8.54 mg/ml)	MD (8.82 mg/ml)	IH (9.43 mg/ml)	ID (8.54 mg/ml)
589	–24.24	–23.59	+100.2	+100.9
578	–25.41	–24.72	+105.8	+106.7
546	–29.04	–28.12	+125.1	+126.1
436	–50.59	–49.67	+272.7	+275.1
365	–79.98	–80.06	+657.8	+664.8

Table 2. Rate constants for enolate-ion formation from (–)-menthone (MH) and (+)-isomenthone (IH) in methanol-*O-d* at 25.00 ± 0.05 °C.

Run	Substrate ^a	$k_{\text{obs}}/10^{-3}\text{s}^{-1}$ ^b	$k^{\text{MH}}/k^{\text{IH}}$
1	IH	2.674 ± 0.004	1.060 ± 0.007
2	IH	2.675 ± 0.004	
3	MH	2.836 ± 0.014	
4	MH	2.394 ± 0.014	1.060 ± 0.008
5	IH	2.239 ± 0.004	
6	MH	2.351 ± 0.012	
7	MH	3.240 ± 0.018	1.069 ± 0.007
8	IH	3.030 ± 0.004	
Mean value			1.063 ± 0.007

^a Substrate conc. 6.0×10^{-2} M. ^b $k_{\text{obs}} = \lambda_1$ in expression (7). Base concentration 0.13–0.18 M. The same base solution is used within each group. Errors listed are ± 2σ obtained from the analysis.

rotation α_{obs} should pass through a minimum since $\beta > 0$, $\gamma < 0$ and $\lambda_1 > \lambda_2$. This is also observed and two typical runs are shown in Fig. 1.

The results are thus consistent with the assumption that the rate constant for enolate-ion formation from (–)-menthone is larger than that from (+)-isomenthone. The same is true also in a mixture of methanol-*O-d* and dimethyl sulfoxide-*d*₆ as can be seen from Table 3.

That the present method is advantageous in detecting small deviations from first-order kinetics was confirmed by running (–)-menthone in a mixture of 80 mol % D₂O and 20 mol % DMSO-*d*₆, a mixture where no deviation from first-order kinetics could be detected by running (–)-menthone-*d* in light medium.⁷ The experimental curve (α vs. t) obtained in the present experiment describes a two-

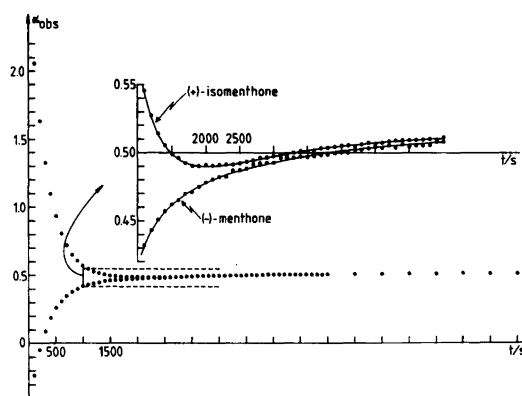


Fig. 1. Typical runs of (–)-menthone and (+)-isomenthone in methanol-*O-d*. The solid curves are theoretical curves for the two epimers.

Table 3. Rate constants for enolate-ion formation from (-)-menthone (MH) and (+)-isomenthone in 25 mol % methanol-*O-d*-75 mol % DMSO-*d*₆ at 25.00 ± 0.05 °C.

Run	Substrate ^a	$k_{\text{obs}}/10^{-3} \text{ s}^{-1}$ ^b	$k^{\text{MH}}/k^{\text{IH}}$
9	MH	5.093 ± 0.024	1.090 ± 0.007
10	IH	4.674 ± 0.010	
11	MH	4.881 ± 0.048	1.078 ± 0.017
12	IH	4.526 ± 0.026	
Mean value			1.084 ± 0.012

^a Substrate conc. 6.0×10^{-2} M. ^b $k_{\text{obs}} = \lambda_1$ in expression (7). Base concentration 7×10^{-3} M. The same base solution is used within each group. Errors listed are ± 2σ obtained from the analysis.

Table 4. Equilibrium constant (K_{eq}^{H}) for the epimerization of (-)-menthone to (+)-isomenthone in methanol at 25.00 ± 0.05 °C. Concentration of sodium methoxide 0.15 M.

Run	Wavelength of light used/nm	α_{∞}	$10^3 \cdot (\text{Conc. of MH})$ g ml ⁻¹	K_{eq}^{H} ^a
13	436	0.837	18.17	0.425
14	546	0.342	18.44	0.447
15	436	0.904	18.25	0.449
Mean value				0.440 ± 0.015 ^b

^a Calculated using the specific rotations given in Table 1. ^b The equilibrium mixture, according to Ref. 11, contains 30 % of (+)-isomenthone and 70 % of (-)-menthone.

exponential curve and it was not possible to fit a one-exponential expression to it.

If the results obtained in methanol-*O-d* are transferable to ordinary methanol, i.e., $k_a^{\text{H}} > k_d^{\text{H}}$, this implies that in methanol the rate constant (k_a^{H}) for breaking the C-H bond to form the enolate ion is somewhat different from the observed rate constant. Since the equilibrium constant for the epimerization could be measured (Table 4) it is, however, possible by means of the present results to calculate k_a^{H} from the observed rate constant. The expression for k_{obs} in (5) may be rewritten as

$$k_a^{\text{H}} = k_{\text{obs}} (k_a^{\text{H}}/k_d^{\text{H}} + K_{\text{eq}}^{\text{H}}) / (1 + K_{\text{eq}}^{\text{H}})$$

Assuming then that $k_a^{\text{H}}/k_d^{\text{H}} = k_a^{\text{D}}/k_d^{\text{D}} = 1.06$ according to Table 2 and using $K_{\text{eq}}^{\text{H}} = 0.44$ from Table 4 gives

$$k_a^{\text{H}} = 1.04 k_{\text{obs}}^{\text{H}}$$

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In fact, the correction factor $(k_a^{\text{H}}/k_d^{\text{H}} + K_{\text{eq}}^{\text{H}}) / (1 + K_{\text{eq}}^{\text{H}})$ is rather insensitive to the value of K_{eq}^{H} and the same value 1.04 is obtained for $K_{\text{eq}}^{\text{H}} = 0.34 - 0.65$.

The correction factor has thus been found to be rather small. It would, however, be of interest to know the corresponding factor in other systems of ketones and it would be possible to determine the factor in all systems where the isomerization takes place through a common enolate ion and where the two ketones are not just enantiomers. In the camphor system it has been estimated at "a few percent".¹² A similar investigation to the present one would make a precise determination possible. It would rest, however, on the assumption that $k_a^{\text{D}}/k_d^{\text{D}} = k_a^{\text{H}}/k_d^{\text{H}}$.

EXPERIMENTAL

(-)-Menthone and (+)-isomenthone were synthesized and separated according to Ref. 10.

The solvents of listed quality were obtained from the following manufacturers and used without further purification: *Methanol*, Anhydrous, $H_2O < 0.01\%$ w/w, May & Baker. *Dimethyl sulfoxide*, $H_2O < 0.01\%$, Riedel-de Haën AG. *Methanol-O-d*, > 99.5 atom % D, CIBA. *Dimethyl sulfoxide-d₆*, > 99 atom %, CIBA.

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

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 $\sim 140^\circ C$ for about 24 h.

The polarimeter cell was rinsed with anhydrous methanol (or methanol-O-d) and then flushed with a stream of nitrogen.

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 thermostated 10 cm polarimeter cell. The temperature was maintained by a Hetotherm Ultrathermostat 03 Pt 623 UO together with a Hetofrig cooling bath, type CB6. The temperature was read on a thermometer, which could be read to $0.01^\circ C$, mounted in the thermostat bath. The temperature could also be checked by a calibrated thermistor capable of measuring changes in temperature of less than $0.002^\circ C$ mounted just outside and after the cell in the circulating water from the thermostat. A CompuCorp 425 Scientist calculator interfaced on line with the polarimeter and a voltmeter, collected polarimeter data, temperatures and times. The data were then analyzed using the computer program PROGAEXP.¹³

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