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The Solvent Effect on the Rate Ratio of Esterifications of Enantiomeric Menthols with *l*-Menthoxyacetyl Chloride

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Esterifications of *l*- and *d, l*-menthols were undertaked in various solvents, such as chloroform, benzene, *n*-hexane, acetonitrile, methyl ethyl ketone, and liquid sulfur dioxide, in order to obtain some information on the solvent effect of the resolution of epimers by a kinetical method. The rate ratios, k_{dl}/k_{ll} (generally larger than unity except in the case of sulfur dioxide), are in the following order: chloroform, benzene, *n*-hexane, acetonitrile, methyl ethyl ketone, and liquid sulfur dioxide, indicating higher k_{dl}/k_{ll} ratios, in the less specific solvating solvents. The possibility of kinetical resolution in a non-specific solvating solvent is suggested, and the reason for it is discussed.

Among the various methods used for the resolution of a mixture of enantiomers, separation by the formation of diastereoisomers has been most comprehensively employed. For example, for the resolution of a racemic alcohol, the acylation by an acid or acyl chloride with a *d*- or *l*-structural moiety, followed by physical methods such as fractionation or crystallization, has been a convenient and well established method.[1] The esterification of *d, l*-menthol with mandelic acid, followed by separation of the resultant mixtures of esters, has been studied,[2] and the possibility of resolution by a kinetic method has been discussed. However, practically, difficulties may sometimes be encountered since the differences in the rates of the *d*- and *l*-menthol with mandelic acid are frequently small.

The solvent effect in the kinetical resolution has not yet been reported.

In a preceding paper,[3] Akiyama and Tokura have examined the solvent effect on the esterification of *l*-menthol by using polarimetry; their results have revealed a dramatic rate enhancement in liquid sulfur dioxide. In the present paper the authors wish to indicate the possibility of the kinetic separation of the optical enantiomers by the esterification method if a suitable solvent, preferably a non-polar one, has been selected. The optical configuration of the *d*- and *l*-menthols has already been established as enantiomers with mirror images of one other, despite the fact that there are three asymmetric carbon atoms in the structure of the menthol.[4]

The solvent effects on the rates and the rate ratios of the esterification of *d, l*-menthol by *l*-menthoxyacetyl chloride in various solvents, such as chloroform, acetonitrile, benzene, methyl ethyl ketone, *n*-hexane and liquid sulfur dioxide, will also be discussed. The rate ratios, k_{dl}/k_{ll}, in various solvents will be discussed in view of the possibility of the kinetic resolution of the alcohol.

Experimental

Materials. *l*-Menthol and *d, l*-menthol were used as received: *l*-menthol, mp 41.5—43.0°C, $[\alpha]^{25}_{D}$(benzene) $=47.6$, *d, l*-menthol, mp 37.0—38.0°C, $[\alpha]^{25}_{D}$(benzene) $=0$.

l-Menthoxyacetic acid was prepared[5] by the reaction of sodium menthoxide and monochloroacetic acid. *l*-Menthoxyacetyl chloride was prepared[5] by the chlorination of *l*-menthoxyacetic acid with thionyl chloride; bp 124°C/8 mmHg $[\alpha]^{25}_{D}$(chloroform) $= -109.4°$.

Chloroform was shaken with concentrated sulfuric acid, with a dilute sodium hydroxide solution, and then with water. It was then dried with potassium carbonate before distillation. Benzene was shaken with concentrated sulfuric acid, with a dilute sodium hydroxide solution, and then with water. It was dried over sodium and then distilled. *n*-Hexane was purified by the same procedure as was used for benzene. Methyl ethyl ketone was dried over phosphorus pentoxide and distilled. Acetonitrile was dried with potassium carbonate and distilled. Liquid sulfur dioxide was dried over phosphorus pentoxide and distilled.

Kinetic Procedure. The rate constants of the esterification of *l*- and *d*-menthols by *l*-menthoxyacetyl chloride, k_{ll} and k_{dl} respectively, were obtained by polarimetry using a method which has been described elsewhere.[3] *d*-Menthol can be obtained by the optical resolution of the *d, l*-menthol.[1] In this project, however,

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[1] "Organic Reactions Vol. II," John Wiley and Sons, Inc., New York (1944), p. 398.

[2] E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw Hill Co., New York (1962), p. 65.

[3] a) N. Tokura and F. Akiyama, This Bulletin, **37**, 1723 (1964); b) F. Akiyama and N. Tokura, *ibid.*, **39**, 131 (1966).

[4] J. Read and W. J. Grubb, *J. Chem. Soc.*, **1934**, 1779.

[5] M. T. Leffer and A. E. Calkins, "Organic Syntheses," Vol. 23, pp. 52, 55 (1943).

for purposes of simplification, k_{dl} was calculated from the esterification reactions of *l*-menthol and *d, l*-menthol with *l*-menthoxyacetyl chloride by a method elucidated below. The esterification of *l*-menthol by acetyl or propionyl chloride in liquid sulfur dioxide or in acetonitrile follows the mixed first- and second-order rate law;[3] however, the reaction of the menthols with *l*-menthoxy acetyl chloride obeys the second-order rate law throughout the measurements, the over-all yield of the reactions being nearly 100 percent.

The rate equation may be expressed as;

$$\text{Rate} = \mathrm{d}x/\mathrm{d}t = k(a-x)^2 \tag{1}$$

where k is the second-order rate contant; a is the initial concentration of both the menthol and of *l*-menthoxyacetyl chloride, and x is the concentration of the ester formed at time t. Equation (1) may be integrated to Eq. (2);

$$1/(a-x) - 1/a = k\cdot t \tag{2}$$

When *l*-menthol and *l*-menthoxyacetyl chloride were used in equimolar concentrations, as is indicated in Eqs. (1) and (2), we can assume, that

$$\text{at } t=0,\ \alpha_0 = l\cdot[\mathrm{R}]^0_{l\text{-Cl}}\cdot a + l\cdot[\mathrm{R}]^0_{l\text{-}al}\cdot a \tag{3}$$

and that at $t=t$ α_t (rotation of the reaction solution) $=l\cdot[\mathrm{R}]^0_{ll\text{-}es}\cdot x + l\cdot[\mathrm{R}]^0_{l\text{-Cl}}\cdot(a-x) + l\cdot[\mathrm{R}]^0_{l\text{-}al}\cdot(a-x)$, where l is the length of the cell of the polarimeter in dm; α_0 and α_t are the rotations at times 0 and t, and $[\mathrm{R}]^0_{l\text{-Cl}}$, $[\mathrm{R}]^0_{l\text{-}al}$, and $[\mathrm{R}]^0_{ll\text{-}es}$ are the molar rotations of *l*-menthoxyacetyl chloride, *l*-menthol, and *l*-menthyl *l*-menthoxyacetate respectively. The rotation after the completion of the reaction, α_∞ may be written approximately as:

$$\alpha_\infty = l\cdot[\mathrm{R}]^0_{ll\text{-}es}\cdot a \tag{4}$$

$$\alpha_\infty - \alpha_t = (a-x)\cdot l\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-Cl}} - [\mathrm{R}]^0_{l\text{-}al}\}$$

$$a-x = \frac{\alpha_\infty - \alpha_t}{l\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-Cl}} - [\mathrm{R}]^0_{l\text{-}al}\}} \tag{5}$$

$$a = \frac{\alpha_\infty - \alpha_0}{l\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-Cl}} - [\mathrm{R}]^0_{l\text{-}al}\}} \tag{6}$$

By substituting (4) and (5) in (2), we obtain:

$$\frac{1}{\alpha_\infty - \alpha_t} - \frac{1}{\alpha_\infty - \alpha_0} = \frac{k_{ll}\cdot t}{\{l[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-Cl}} - [\mathrm{R}]^0_{l\text{-}al}\}} \tag{7}$$

The second-order rate constant, k_{ll}, may be obtained from the slope of the linear plot of $1/(\alpha_\infty - \alpha_t)$ *vs.* t, as is shown in Fig. 1.

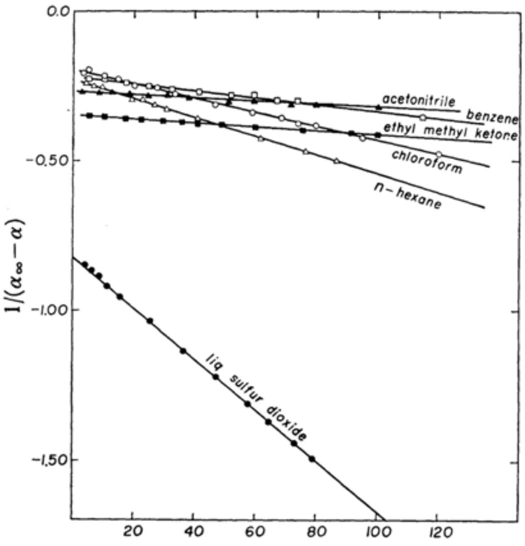


Fig. 1.

When $2a$ moles of *d, l*-menthol (or a moles each of *d*- and *l*-menthol) and a moles of *l*-menthoxyacetyl chloride were used, we can assume that:

$$\alpha_t' = l\cdot[\mathrm{R}]^0_{l\text{-}al}\cdot(a-y) + l\cdot[\mathrm{R}]^0_{d\text{-}al}\cdot(a-z) + l\cdot[\mathrm{R}]^0_{l\text{-Cl}}\cdot(a-x) + l\cdot[\mathrm{R}]^0_{ll\text{-}es}\cdot y + l\cdot[\mathrm{R}]^0_{dl\text{-}es}\cdot Z$$

where α_t' is the rotation of the reaction solution of *d, l*-menthol ($2a$ moles) with *l*-menthoxyacetyl chloride (a moles) at time t, and x, y, and z are the concentrations of the *l*-menthoxyacetyl chloride, *l*-menthol, and *d*-menthol consumed at time t respectively. $[\mathrm{R}]^0_{d\text{-}al}$, and $[\mathrm{R}]_{dl\text{-}es}$ are the molar rotations of *d*-menthol and *d*-menthyl *l*-menthoxyacetate at time t. The following relation may be assumed:

$$\left.\begin{matrix} l\text{-menthol; } (a-y) \\ d\text{-menthol; } (a-z) \end{matrix}\right\} + l\text{-menthoxyacetyl chloride; } (a-x)$$

$$\longrightarrow \left\{\begin{matrix} l\text{-menthoxyacetic ester of } l\text{-menthol; } (y) \\ l\text{-menthoxyacetic ester of } d\text{-menthol; } (z) \end{matrix}\right.$$

and $x=y+z$.

Differentiating with time, we obtain the relation:

$$\begin{aligned}\frac{\mathrm{d}\alpha_t'}{\mathrm{d}t} &= -l[\mathrm{R}]^0_{l\text{-}al}\cdot\frac{\mathrm{d}y}{\mathrm{d}t} - l[\mathrm{R}]^0_{d\text{-}al}\cdot\frac{\mathrm{d}z}{\mathrm{d}t} \\ &\quad - l[\mathrm{R}]^0_{l\text{-Cl}}\cdot\frac{\mathrm{d}x}{\mathrm{d}t} + l[\mathrm{R}]^0_{ll\text{-}es}\cdot\frac{\mathrm{d}y}{\mathrm{d}t} + l\cdot[\mathrm{R}]^0_{dl\text{-}es}\cdot\frac{\mathrm{d}z}{\mathrm{d}t} \\ &= l\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}\frac{\mathrm{d}z}{\mathrm{d}t} \\ &\quad + l\{[\mathrm{R}]^0_{dl\text{-}es} - [\mathrm{R}]^0_{d\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}\frac{\mathrm{d}z}{\mathrm{d}t}\end{aligned}$$

Since $\mathrm{d}y/\mathrm{d}t = k_{ll}(a-x)(a-y)$, $\mathrm{d}z/\mathrm{d}t = k_{dl}(a-x)(a-z)$,

$$\begin{aligned}\frac{\mathrm{d}\alpha_t'}{\mathrm{d}t} &= l\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}k_{ll}(a-x)(a-y) \\ &\quad + l\{[\mathrm{R}]^0_{dl\text{-}es} - [\mathrm{R}]^0_{d\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}k_{dl}(a-x)(a-z)\end{aligned}$$

at $t=0$, $X=Y=Z=0$,

$$\begin{aligned}\left(\frac{\mathrm{d}\alpha_t'}{\mathrm{d}t}\right)_{t=0} &= k_{ll}\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}l\cdot a^2 \\ &\quad + k_{dl}\{[\mathrm{R}]^0_{dl\text{-}es} - [\mathrm{R}]^0_{d\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}l\cdot a^2\end{aligned} \tag{8}$$

By the integration of Eq. (3), at $t=0$:

$$\left(\frac{\mathrm{d}\alpha_t}{\mathrm{d}t}\right)_{t=0} = k_{ll}\{[\mathrm{R}]^0_{ll\text{-}es} - [\mathrm{R}]^0_{l\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}l\cdot a^2 \tag{9}$$

Subtracting (9) from Eq. (8), we get:

$$\left(\frac{\mathrm{d}\alpha_t'}{\mathrm{d}t}\right)_{t=0} - \left(\frac{\mathrm{d}\alpha_t}{\mathrm{d}t}\right)_{t=0} = k_{dl}\{[\mathrm{R}]^0_{dl\text{-}es} - [\mathrm{R}]^0_{d\text{-}al} - [\mathrm{R}]^0_{l\text{-Cl}}\}l\cdot a^2 \tag{10}$$

$(\mathrm{d}\alpha_t'/\mathrm{d}t)_{t=0}$ and $(\mathrm{d}\alpha_t/\mathrm{d}t)_{t=0}$ can be obtained from the initial slopes of the α_t' *vs.* t and the α_t *vs.* t plots respectively.

Table 1. An typical example of calculation of esterification rate constant of d,l-menthol with l-menthoxyacetylchloride in chloroform

$ka^2{}_l$ mol² l^{-2}	degree⁻¹ sec⁻¹	k_{ll} l mol⁻¹ sec⁻¹	$\left(\frac{d\alpha'}{dt}\right)_{t=0}-\left(\frac{d\alpha}{dt}\right)_{t=0}$	$\left\{\left(\frac{d\alpha'}{dt}\right)_{t=0}-\left(\frac{d\alpha}{dt}\right)_{t=0}\right\}/a^2$	k_{dl} l mol⁻¹ sec⁻¹
0.53×10^{-2}	3.48×10^{-5}	5.19×10^{-4}	1.07×10^{-3}	2.01×10^{-1}	5.67×10^{-3}
3.53×10^{-2}	3.43×10^{-5}	5.02×10^{-4}	5.66×10^{-3}	1.89×10^{-1}	5.33×10^{-3}
8.06×10^{-2}	3.58×10^{-5}	5.23×10^{-4}	1.57×10^{-2}	1.94×10^{-1}	5.49×10^{-3}
12.53×10^{-2}	3.38×10^{-5}	4.96×10^{-4}	2.43×10^{-2}	1.94×10^{-1}	5.49×10^{-3}

Table 2. Specific rotation in various solvents at 25°C

	l-Menthol	l-Menthoxy-acetyl chloride	l-l Ester	d-l Ester
Chloroform	−7.00	−25.5	−39.0	−2.28
	−45.1	−109.5	−110.5	−6.5
Benzene	−7.50	−24.5	−39.5	−2.34
	−47.6	−105.0	−112.0	−6.6
n-Hexane	−7.81	−26.2	−39.5	−2.33
	−50.0	−112.5	−112.0	−6.6
Acetonitrile	−7.40	−24.4	−37.8	−2.30
	−50.7	−104.7	−107.0	−6.5
Methyl ethyl	−7.69	−23.9	−36.8	−2.25
ketone	−49.1	−104.2	−104.2	−6.4
Liquid sulfur	−7.58	−25.8	−39.7	−2.30
dioxide	−48.4	−110.7	−112.5	−6.5

The second-order rate constant of the reaction of d-menthol and l-menthoxyacetyl chloride, k_{dl}, may be obtained from the slope of the linear plot, $(d\alpha_t'/d_t)_{t=0}-(d\alpha_t/dt)_{t=0}$ *vs.* a^2. A typical example is shown in Fig. 2.

A typical run and calculations using Eqs. (7) and (10) are shown in Table 1. The specific rotations of alcohol, acyl chloride, and the ester in the various solvents are listed in Table 2.

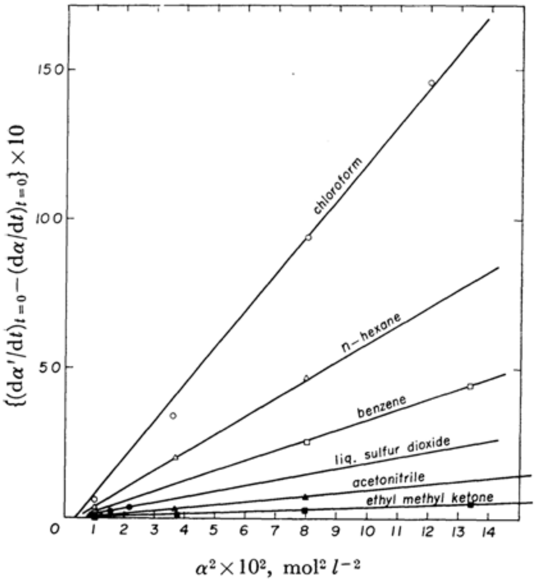


Fig. 2.

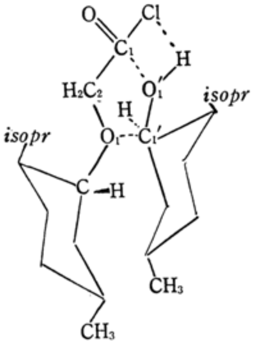
Results and Discussion

The rate constants of the esterifications of l- and d-menthols by l-menthoxyacetyl chloride, k_{ll} and k_{dl} respectively, as estimated by the method described above, are shown in Table 3, together with the ratios of the reaction rates, k_{dl}/k_{ll}, in several solvents. The rate ratios are in the following order: chloroform, benzene, n-hexane, acetonitrile, methyl ethyl ketone, liquid sulfur dioxide; the ratio is the smallest in liquid sulfur dioxide. Moreover, in the last solvent the rate ratio is reversed (less than unity). It may, therefore, reasonably be concluded that the kinetical resolution may be more favored in a non-specific solvating solvent than in a specific solvating solvent. Such a fact may be explained by the different solvation in the respective solvent. The rate ratios

Table 3. The rate constants k_{ll} and k_{dl} and the ratio of the rate constants k_{dl}/k_{ll}

	l mol⁻¹ sec⁻¹	l mol⁻¹ sec⁻¹	k_{dl}/k_{ll}
Chloroform	5.07×10^{-4}	5.49×10^{-3}	10.8
Benzene	3.28×10^{-4}	1.92×10^{-3}	5.8
n-Hexane	5.89×10^{-4}	2.89×10^{-3}	4.9
Acetonitrile	1.07×10^{-4}	4.58×10^{-4}	4.3
Methyl ethyl ketone	1.29×10^{-4}	1.34×10^{-4}	1.04
Liquid sulfur dioxide	1.83×10^{-3}	8.42×10^{-4}	0.46

are generally larger than unity; *viz.*, the production rate for the *d, l*-ester is larger than that for the *l, l*-ester except in liquid sulfur dioxide. This may be elucidated by the structure at the transition state of the *d, l*-ester formation. As is shown in Scheme 1, the approach of menthol to acyl chloride is favored by the interaction between the C_1' atom of menthol and the O_1 atom of the acyl chloride, together with the interaction betwen C_1 and O_1' atoms at the transition state. In the solvents used, k_{dl} is larger than k_{ll} since the approach of the C_1' to the O_1 atom is favored in the *l, d*(*l*-menthoxyacetyl chloride with *d*-menthol) reaction, as may be seen in Scheme 1, whereas the *l, l* reaction is hindered sterically. In the solvent which is not squeezed between two reactants, the transition state I is favored throughout the reaction. As the solvent increases in specific solvation, the solvent is squeezed between two reactants, therefore, steric hindrance is calmed. In such a solvent the rate ratio, k_{dl}/k_{ll}, gets smaller.



Scheme 1. *l*-Menthoxyacetyl chloride and *l*-menthol.

That which mitigates the difference in the rate of the two enantiomers will thus be the solvent solvation. If, for example, menthol is strongly solvated by a solvent, two paths of the esterification reactions may be considered, and the leveling of k_{dl} and k_{ll} will prevail: a) the rate-determining step may be the desolvation of the solvent, and the rate constants, k_{dl}, and k_{ll}, may be similar values, or b) the rate-determining step may be the reaction between the solvated menthol and acyl chloride, where no appreciable difference in rates is observed, since the reaction is very sluggish and so the conformational difference is negligible. The leveling effect by the polar solvents may be well elucidated by the solvation.

It is generally accepted that liquid sulfur dioxide solvates strongly with alcohol, and that even the hydrogen-bonding between alcohol molecules will be destroyed by sulfur dioxide.⁶⁾

In liquid sulfur dioxide, the ratio is reversed, k_{ll} becoming slightly larger than k_{dl}; this suggests that the solvation effect is not limited to the interaction of menthol with the solvent. However, an attempt to explain these phenomena will be reserved for a further study.

We gratefully acknowledge the donation of liquid sulfur dioxide by the Seitetsu Kagaku Co., Inc.

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6) H. Hayer, *Angew. Chem.*, **72**, 269 (1960).