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The Isokinetic Temperature of the Acylation of *l*-Menthol

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The acylations of *l*-menthol with *p*-substituted benzoyl- and substituted acetyl chlorides were carried out, and it was found that the electron-releasing substituents accelerate the reaction rate in chloroform even though the reaction is completely of the S_N2 type. This result is interpreted in relation to the low isokinetic temperature, the reaction itself being carried out above that temperature. Such a phenomenon is discussed in terms of the configurational and the solvent effects on the entropy of activation.

The mechanism of the solvolysis of the acyl halides has been studied comprehensively. The substituent effect of such a reaction has been discussed by Hudson *et al.*1) in relation to the mechanism of the solvolysis of the substituted benzoylchloride. In S_N1 solvolysis the acyl chloride which has an electron-releasing substituent reacts faster than the acyl chloride which has an electron-attracting substituent. However, the reverse trend has been observed in S_N2 solvolysis, where an electron-releasing substituent retards the reaction rate. These trends are quite generally accepted for nucleophilic substitutions.2)

The present authors have studied the acylation of *l*-menthol and observed a reverse substituent effect in the reaction despite the S_N2-character of this acylation. An abnormal change in the substituent effect is often explained as the result of a shift of the reaction mechanism from S_N1 to S_N2 or from S_N2 to S_N1.2) However, an alternative explanation, which may be reasonable in view of the present results, in that the reaction is carried out above the isokinetic temperature.3)

Such a phenomenon is usually accompanied with a low isokinetic temperature of the acylation. The configurational and the solvent effects are discussed with regard to the cause of the anomaly.

Experimental

Solvents. The solvents—chloroform, benzene, liquid sulfur dioxide, tetrahydrofuan and acetonitrile—were purified by the methods described in earlier papers.4,5)

Materials. Extra-pure-grade *l*-menthol was used without further purification. *p*-Substituted benzoyl chlorides were obtained by the chlorination of the corresponding *p*-substituted benzoic acids with thionyl chloride. Propionyl, monochloroacetyl, dichloroacetyl, and trichloroacetyl chlorides were commercial materials and were used after distillation.

The Identification of the Esters. The reaction mixture after the acylation was concentrated *in vacuo*, and the residual oil was fractionated. *l*-Menthyl monochloroacetate: bp 116°C/5 mmHg. Found: C, 61.89; H, 9.25%. Calcd for $C_{12}ClH_{21}O_2$: C, 61.92; H, 9.09%. *l*-Menthyl dichloroacetate: bp 128°C/5 mmHg. Found: C, 53.68; H, 7.64%. Calcd for $C_{12}Cl_2H_{20}O_2$: C, 53.94; G, 7.54%. *l*-Menthyl trichloroacetate: bp 113°C/3 mmHg. Found: C, 47.59; H, 6.50%. Calcd for $C_{12}Cl_3H_{19}O_2$: C, 47.78; H, 6.35%. *l*-Menthyl benzoate: bp 151°C/4 mmHg. Found: C, 77.73; H, 9.27%. Calcd for $C_{17}H_{24}O_2$: C, 78.41; H, 9.29%. *l*-Menthyl *p*-methylbenzoate: bp 170°C/2 mmHg. Found: C, 79.00: H, 9.93%. Calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.55%. *l*-Menthyl *p*-chlorobenzoate: bp 187°C/3 mmHg. Found: C, 69.41; H, 7.71%. Calcd for $C_{17}ClH_{23}O_2$: C, 69.25; H, 7.86%.

Kinetic Procedure. The polarimetric procedure was used for the measurement of the reaction rate. A graphic representation of the apparatus and the details of the kinetic procedure have been given in earlier papers.3,4) Equimolar concentrations of *l*-menthol and acyl chloride were used. The second-order reaction rate constant was given by the slope of the linear plot of:

$$\frac{1}{\alpha_\infty-\alpha} \text{ vs. the time } t,$$

since:

$$\frac{1}{\alpha_\infty-\alpha}-\frac{1}{\alpha_\infty-\alpha_0}=\frac{kt}{l\{[R]^\circ_E-[R]^\circ_A\}} \qquad (1)$$

where $[R]^\circ_A$ and $[R]^\circ_E$ are the specific optical rotations of *l*-menthol and of the ester, rotations which were measured beforehand and which are listed in Table 1, where l, α, α_0, and α_∞ are the length of the cell, dm, and the rotations of the solutions at time t, zero, and infinity, respectively. The second-order plots of typical runs are shown in Fig. 1.

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1) D. A. Brown and R. F. Hudson, *J. Chem. Soc.*, **1953**, 883.

2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, New York (1953), pp. 307—417.

3) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, New York (1963), p. 325.

4) N. Tokura and F. Akiyama, This Bulletin, **37**, 1723 (1964).

5) F. Akiyama and N. Tokura, *ibid.*, **39**, 131 (1966).

TABLE 1. THE SPECIFIC ROTATIONS OF *l*-MENTHOL AND *l*-MENTHYL ESTERS IN THE VARIOUS SOLVENTS

Substance		Solvent			
		Chloroform	Benzene	Liquid sulfur dioxide	Tetra-hydrofuran
l-Menthol	[α]*	45.0	47.6	53.5	45.8
	[R]	7.0	7.4	8.4	7.2
l-Menthyl Propionate	[α]	84.2	82.2	79.0	78.1
	[R]	17.9	17.4	16.8	16.6
l-Menthyl Monochloroacetate	[α]	82.0	74.2	88.7	76.6
	[R]	19.1	17.3	20.6	17.8
l-Menthyl Dichloroacetate	[α]	67.6	65.2	76.7	63.8
	[R]	18.0	17.4	20.5	17.0
l-Menthyl Trichloroacetate	[α]			72.1	61.7
	[R]			21.7	18.6
l-Menthyl Benzoate	[α]	87.2			
	[R]	22.7			
l-Menthyl *p*-Methoxy benzoate	[α]	78.8			
	[R]	22.9			
l-Menthyl *p*-Methyl benzoate	[α]	83.7			
	[R]	23.0			
l-Menthyl *p*-Chlorobenzoate	[α]	76.7			
	[R]	22.6			

* [α]: degree dm^{-1} cc g^{-1}
[R]: degree dm^{-1} mol^{-1} *l*

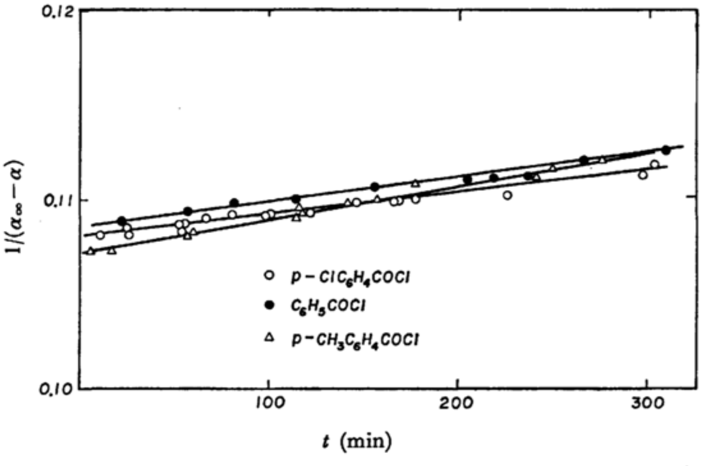

Fig. 1. The second-order rate plots of the reaction of *l*-menthol with *p*-substituted benzoyl chlorides in chloroform. (35°C)

Results

The reactions of *l*-menthol with *p*-substituted benzoyl chlorides were studied in chloroform at various temperatures. The same reactions in liquid sulfur dioxide and in acetonitrile were also performed with substituted benzoyl chlorides. However, the results were complicated and difficult to interpret, since in both solvents the S_N1 reaction was predominant under the same conditions. The second-order rate constants in chloroform are listed in Table 2, while the activation parameters of these reactions are listed in Table 3. An isokinetic relationship is observed in the linear plot of the activation enthalpy, $\Delta H^{\ddagger}$, *vs.* the activation entropy, $\Delta S^{\ddagger}$, as is shown in Fig. 2.

This result demonstrates the abnormal trend of the substituent effect and the extraordinarily low isokinetic temperature. The tendency of the rate constant in connection with the substituent is in the order:

$$p\text{-}CH_3O > p\text{-}CH_3 > H > p\text{-}Cl$$

which is the reverse of the ordinary order in an S_N2 reaction, whereas the activation enthalpy is characteristic of the S_N2 acylation, the values of $\Delta H^{\ddagger}$ being in the order:

Table 2. The second-order rate constants of the benzoylations of *l*-menthol with *p*-substituted benzoyl chlorides in chloroform ($l\ mol^{-1}\ sec^{-1}$)

	25°C	35°C	42°C	45°C	49°C
p-CH_3O	8.49×10^{-6}	2.34×10^{-5}		5.75×10^{-5}	
p-CH_3		9.26×10^{-6}	1.60×10^{-5}		2.57×10^{-5}
H		7.22×10^{-6}	1.09×10^{-5}		1.90×10^{-5}
p-Cl		5.93×10^{-6}	8.03×10^{-6}		1.10×10^{-5}

Table 3. The activation parameters of the benzoylation of *l*-menthol in chloroform at 35°C

Substituted benzoyl chloride	*E* (kal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (e.u.)
p-CH_3O	20.1	19.50	−15.0
p-CH_3	14.6	14.0	−34.9
H	13.7	13.1	−38.7
p-Cl	11.9	11.3	−45.1

Table 4. The second-order rate constants of the acetylations of *l*-menthol in chloroform ($l\ mol^{-1}\ sec^{-1}$)

	15°C	25°C	35°C	45°C
Propionylation	8.99×10^{-4}	1.35×10^{-3}	2.17×10^{-3}	
Monochloroacetylation		1.05×10^{-3}	1.23×10^{-3}	1.40×10^{-3}
Dichloroacetylation		1.00×10^{-3}	1.14×10^{-3}	1.20×10^{-3}

Table 5. The second-order rate constants of the acetylations of *l*-menthol in benzene ($l\ mol^{-1}\ sec^{-1}$)

	15°C	25°C	30°C	35°C	45°C
Propionylation	2.39×10^{-4}	4.40×10^{-4}	5.70×10^{-4}		
Monochloroacetylation		1.29×10^{-3}		1.43×10^{-3}	1.61×10^{-3}
Dichloroacetylation		1.39×10^{-3}		1.52×10^{-3}	1.68×10^{-3}

Table 6. The second-order rate constants of the acetylations of *l*-menthol in liquid sulfur dioxide ($l\ mol^{-1}\ sec^{-1}$)

	25°C	35°C	42°C
Monochloroacetylation	4.27×10^{-4}	6.81×10^{-4}	9.95×10^{-4}
Dichloroacetylation	5.52×10^{-4}	8.00×10^{-4}	1.06×10^{-3}
Trichloroacetylation	1.16×10^{-3}	1.63×10^{-3}	2.04×10^{-3}

Table 7. The second-order rate constants of the acetylations of *l*-menthol in tetrahydrofuran ($l\ mol^{-1}\ sec^{-1}$)

	15°C	25°C	35°C	42°C	45°C
Propionylation	3.17×10^{-5}	5.96×10^{-5}	1.06×10^{-4}		
Monochloroacetylation		9.93×10^{-4}	1.61×10^{-3}		2.87×10^{-3}
Dichloroacetylation		3.12×10^{-3}	4.48×10^{-3}		6.40×10^{-3}
Trichloroacetylation		7.76×10^{-3}	9.14×10^{-4}	1.04×10^{-2}	

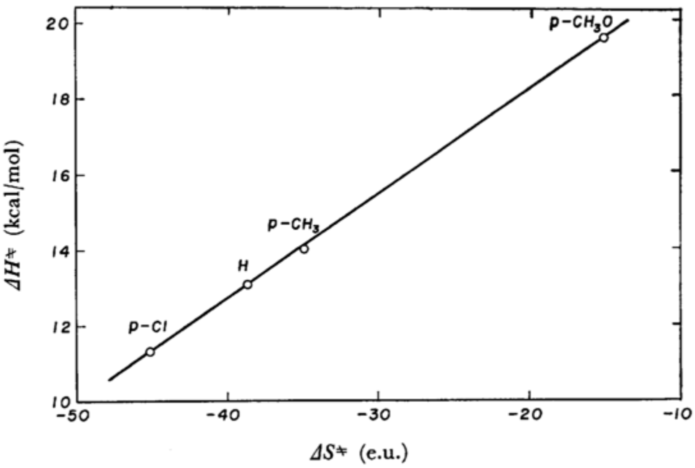

Fig. 2. The isokinetic relation of the reaction of *l*-menthol with *p*-substituted benzoyl chlorides in chloroform.

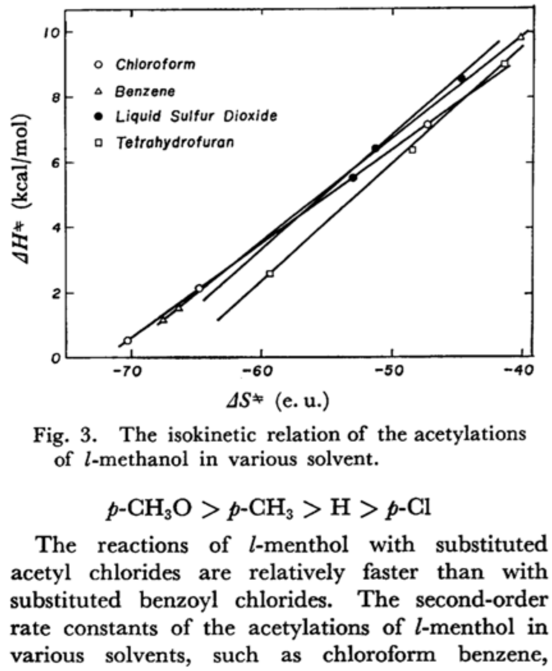

Fig. 3. The isokinetic relation of the acetylations of *l*-methanol in various solvent.

$$p\text{-CH}_3\text{O} > p\text{-CH}_3 > \text{H} > p\text{-Cl}$$

The reactions of *l*-menthol with substituted acetyl chlorides are relatively faster than with substituted benzoyl chlorides. The second-order rate constants of the acetylations of *l*-menthol in various solvents, such as chloroform benzene, liquid sulfur dioxide, and tetrahydrofuran, are listed in Tables 4, 5, 6, and 7. The isokinetic relationships obtained in these solvents are visualised in Fig. 3. From this figure the isokinetic temperatures can be estimated to be as listed in Table 9.

The trend of the activation enthalpies is also characteristic of an S_N2 reaction. However the rate in chloroform is in an anomalous order:

propionyl > monochloracetyl > dichloroacetyl

whereas in benzene, liquid sulfur dioxide, and tetrahydrofuran the order is:

trichloroacetyl > dichloroacetyl >
monochloroacetyl > propionyl

Discussion

According to the absolute reaction rate theory, the reaction rate constant, k, is expressed as a function of the activation enthalpy, $\Delta H^{\neq}$, and of the activation entropy, $\Delta S^{\neq}$:[6] Since $\Delta F^{\neq}=\Delta H^{\neq}-T\Delta S^{\neq}$ (2):

$$k = \frac{\boldsymbol{k}T}{\boldsymbol{h}}\,\mathrm{e}^{-\Delta F^{\neq}/RT} = \frac{\boldsymbol{k}T}{\boldsymbol{h}}\,\mathrm{e}^{\Delta S^{\neq}/R}\cdot\mathrm{e}^{-\Delta H^{\neq}RT} \quad (3)$$

where $\boldsymbol{k}$ and $\boldsymbol{h}$ are the Boltzmann and the Planck constants respectively. Empirically, the isokinetic relation holds:[3,7]

$$\Delta H^{\neq} = \Delta H_0^{\neq} + \beta\Delta S^{\neq} \quad (4)$$

where β is an isokinetic temperature and $\Delta H^{\neq}$ is the activation enthalpy at the standard state. As a result, k is expressed as a function of β, $\Delta H^{\neq}$, and $\Delta S^{\neq}$.

From Eqs. (2) and (3), as has been derived by Leffler:[3]

$$\begin{aligned}\Delta F^{\neq} &= \Delta H^{\neq} + (\beta-T)\Delta S^{\neq}\\ &= \frac{T}{\beta}\Delta H_0^{\neq} + \frac{(\beta-T)}{\beta}\Delta H^{\neq} \quad (5)\end{aligned}$$

$$k = \frac{\boldsymbol{k}T}{\boldsymbol{h}}\exp-\left\{\frac{T}{\beta}\Delta H_0^{\neq} + \frac{(\beta-T)}{\beta}\Delta H^{\neq}\right\}\Big/\boldsymbol{R}\boldsymbol{T} \quad (6)$$

Therefore, provided

$$\beta > T$$

then:

$$\Delta F^{\neq} \propto \Delta H^{\neq}$$

and if,

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[6] S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Process," McGraw Hill Co., New York (1941).

[7] J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

$$\beta < T$$

the situation is reversed:

$$\Delta F^{\neq} \propto -\Delta H^{\neq}$$

Thus, the above discussion allows one to understand that the reaction will be accelerated (or suppressed) below the isokinetic temperature and suppressed (or accelerated) above the isokinetic temperature, as long as the isokinetic relationship is sustained.

The reaction temperatures adopted here are in the range between 15 and 49°C; actually the reactions were undertaken near the isokinetic temperatures. As may be seen in Figs. 2 and 3 and in Table 9, the isokinetic temperatures of the acylation of *l*-menthol are low, being 285° in chloroform, 315° in benzene, 344° in liquid sulfur dioxide, *and 357°K in tetrahydrofuran. In general, the* isokinetic temperatures of the solvolyses of substituted benzoyl chlorides are as high as 450°K(8) in ether-ethanol and over 600°K in aceton-water,(1) as Fig. 4 shows.

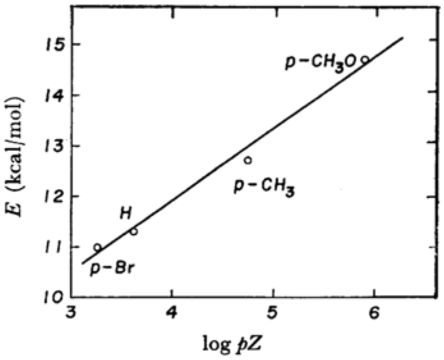

Fig. 4. The isokinetic relation of the hydrolysis of the *p*-substituted benzoylchloride in 95% acetone-5% water.(1) $\beta=652$°K

The present results indicate that the substituent effect in this reaction is contrary to the expected order in the S_N2 acylation, and that the rate decreases in the order:

$$p\text{-CH}_3\text{O} > p\text{-CH}_3 > \text{H} > p\text{-Cl}$$

Such a reversal may adequately be explained by the fact that the reaction was undertaken above isokinetic temperature, the large entropy-controlled reaction operating throughout the acylation (*vide infra*).

Such a phenomenon, encountered for the first time in acylations by the present authors, will be discussed further below.

By the definition of Eq. (3), as long as the isokinetic relation is sustained, the value of β can be rewritten as:

$$\beta \frac{\Delta\Delta H^{\neq}}{\Delta\Delta S^{\neq}} \tag{7}$$

where $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ are the differentials of the activation enthalpies and entropies. As the $\Delta\Delta S^{\neq}$ becomes larger, or as the reaction becomes more entropy-controlled, the isokinetic temperature, β, will become smaller, whereas a larger value of β will be obtained when the $\Delta\Delta H^{\neq}$ becomes larger or when the reaction is enthalpy-controlled. Thus, the small value of β is attributable to the entropy-controlled reaction.

Two factors which may have a predominant influence on the low isokinetic temperature are the steric configuration of the activated complex in the reaction medium and the nature of the solvent applied.

The term $\Delta\Delta S^{\neq}$ may be divided into two parts, the change in the activation entropy of the reactant molecules, $\Delta\Delta S_R^{\neq}$, which is characteristic of the reactants, and the change in the activation entropy of the solvent molecules, $\Delta\Delta S_S^{\neq}$, which is the solvent effect. Assuming the additivity of the entropies, $\Delta\Delta S^{\neq}$ may be expressed as:

$$\Delta\Delta S^{\neq} = \Delta\Delta S_R^{\neq} + \Delta\Delta S_S^{\neq} \tag{8}$$

The difference between the acylations of *l*-menthol and ordinary alcohols may be largely due to the difference in the transition states of the acylation, which is illustrated in Fig. 5, the value of $\Delta\Delta S_R^{\neq}$ in the acylation of *l*-menthol being much larger by steric reasons.

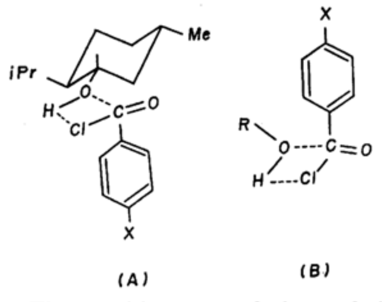

Fig. 5. The transition state of the acylation of *l*-menthol (A) and the ordinary alcohol (B).

At a lower energy state, the internal motion in the transition state of the acylation of *l*-menthol is inhibited. However, at a higher energy state the internal rotation comes into action against the steric restriction. In the acylation of ordinary alcohols, the steric inhibition to the internal motion is not as large as in the menthol. Consequently, the $\Delta\Delta S_R^{\neq}$ in the acylation of menthol may be larger than that of ordinary alcohol.

The dependency of the isokinetic temperature on the solvent is indicated in Table 9. The relative rate of the acylation of *l*-menthol with substituted acetyl chlorides at 35°C undergoes an almost complete reversal in order as the solvent is changed from chloroform to benzene, liquid sulfur dioxide, or tetrahydrofuran.

Suppose two circumstances, 1 and 2, where the

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8) G. E. Branch and A. C. Nixon, *J. Am. Chem. Soc.*, **58**, 2499 (1936).

TABLE 8. THE ACTIVATION PARAMETERS OF THE ACETYLATIONS OF *l*-MENTHOL AT 35°C

Solvent	Reaction	E (kcal/mol)	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (e.u.)
Chloroform	Propionylation	7.7	7.1	−47.3
	Monochloroacetylation	2.7	2.1	−64.8
	Dichloroacetylation	1.1	0.5	−70.3
Benzene	Propionylation	10.4	9.8	−40.1
	Monochloroacetylation	2.1	1.5	−66.5
	Dichloroacetylation	2.1	1.5	−67.5
Liquid sulfur dioxide	Monochloroacetylation	9.1	8.5	−44.7
	Dichloroacetylation	7.0	6.4	−51.3
	Trichloroacetylation	6.1	5.5	−53.0
Tetrahydrofuran	Propionylation	10.6	10.0	−43.8
	Monochloroacetylation	9.6	9.0	−4.15
	Dichloroacetylation	6.9	6.3	−48.5
	Trichloroacetylation	3.2	2.6	−59.4

TABLE 9. THE ISOKINETIC TEMPERATURE OF THE ACETYLATIONS IN VARIOUS SOLVENTS

Solvent	β°K
Chloroform	285°K
Benzene	315°K
Liquid sulfur dioxide	344°K
Tetrahydrofuran	357°K

activation enthalpies and entropies are indicated as $\Delta H_1^{\neq}$, $\Delta H_2^{\neq}$, $\Delta S_1^{\neq}$ and $\Delta S_2^{\neq}$, respectively. The suffixes 1 and 2 indicate the respective cases of 1 and 2. The entropy differences, $\Delta S_1^{\neq}$ and $\Delta S_2^{\neq}$, can then be expressed as:

$$\begin{aligned}\Delta S_1^{\neq} &= \{l-(m+n)\}(S_{AB}^{\neq}-S_S) + m(S_{AB}^{\neq}-S_A) \\ &\quad + n(S_{AB}^{\neq}-S_B) \\ &= l(S_{AB}^{\neq}-S_S) - m(S_A-S_S) - n(S_B-S_S)\end{aligned} \tag{9}$$

$$\begin{aligned}\Delta S_2^{\neq} &= \{l'-(m'+n')\}(S'_{AB}{}^{\neq}-S_S) \\ &\quad + m'(S'_{AB}{}^{\neq}-S'_A) + n'(S'_{AB}{}^{\neq}S'_B) \\ &= l'(S'_{AB}{}^{\neq}-S_S) - m'(S'_A-S_S) \\ &\quad -n'(S'_B-S_S)\end{aligned} \tag{10}$$

The l, m, and n symbols are the solvation numbers of the solvents to the transition state $AB^{\neq}$, the reactants being A and B in case 1. S_A, S_B, and $S_{AB}^{\neq}$ are the entropies of the solvent molecules which solvate to A, B, and AB in case 1. All the symbols with dashes correspond to case 2. S_S is the entropy of the unsolvated solvent.[9] Since $\Delta\Delta S_R^{\neq}$ is a constant in both cases:

$$\begin{aligned}\Delta\Delta S_S^{\neq} &= \Delta S_2^{\neq} - \Delta S_1^{\neq} = l(S'_{AB}{}^{\neq}-S_{AB}^{\neq}) \\ &\quad - m(S'_A-S_A) - n(S'_B-S_B) \\ &\quad - (l-l')(S'_{AB}{}^{\neq}-S_S) - (m-m')(S'_A-S_S) \\ &\quad - (n-n')(S'_B-S_S)\end{aligned} \tag{11}$$

Equation (11) may then be rewritten as:

$$\Delta\Delta S_S^{\neq} = \Delta\Delta S_C^{\neq} + \Delta\Delta S_P^{\neq}$$

where:

$$\begin{aligned}\Delta\Delta S_C^{\neq} &= l(S'_{AB}{}^{\neq}-S_{AB}^{\neq}) - m(S'_A-S_A) \\ &\quad - n(S'_B-S_B)\end{aligned} \tag{12}$$

$$\begin{aligned}-\Delta\Delta S_P^{\neq} &= (l-l')(S'_{AB}{}^{\neq}-S^{\neq}) \\ &\quad + (m-m')(S'_A-S_S) + (n-n')(S_B'-S_S)\end{aligned} \tag{13}$$

Equation (11) indicates that $\Delta\Delta S_S^{\neq}$ consists of two components, the *solvent coordinate* and the *solvent polarity factors*, $\Delta\Delta S_C^{\neq}$ and $\Delta\Delta S_P^{\neq}$.

The $(S'_{AB}{}^{\neq}-S_{AB}^{\neq})$, (S'_A-S_A), and (S'_B-S_B) terms mean the change in the entropy of the solvent molecules with the changes in the energy state of the activated complex and the reactant molecules respectively, and may be defines as the *solvent coordinate factor*, $\Delta\Delta S_C^{\neq}$. The $(S'_{AB}{}^{\neq}-S_S)$, (S'_A-S_S), and (S'_B-S_S) terms indicate the change in the entropy of the solvent molecules with the transfer of the solvent molecules from the solvent layer to the solvation shell. These terms may be called the *solvent polarity factor*, $\Delta\Delta S_P^{\neq}$. The *solvent coordinate factor* is related to the solvent effect on the activation entropy within the solvation shell, while the *solvent polarity factor* correlates with that of the solvation of the solvent molecules.

As the non-polar solvents associate with each other more loosely than as the polar solvents in the solvent layer, the *solvent polarity factor* is larger in a non-polar solvent than in a polar solvent. Therefore, the $\Delta\Delta S^{\neq}$ value is larger in a non-polar solvent than in a polar solvent.

As a result, if the $\Delta\Delta H^{\neq} = \Delta H_2^{\neq} - \Delta H_1^{\neq}$ change is not as pronounced as the $\Delta\Delta S^{\neq}$ change, the isokinetic temperature is lower in the case of benzene and chloroform than in tetrahydrofuran and liquid sulfur dioxide.

The high isokinetic temperature in tetrahydrofuran may be due to the *solvent coordinate factor*. The change in the entropy with the change in the energy state is larger in the liquid sulfur dioxide than in tetrahydrofuran. While tetrahydrofuran is a cyclic molecule with only one solvation center, liquid sulfur dioxide has three centers, one sulfur and two oxygen atoms.

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[9] S_S is assumed to be constant under any circumstances.