

The Iselective Relationship[†]

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The rate constants of chemical reactions generally vary with temperature, and the variation is often treated in terms of the Eyring equation:

$$k = (kT/h)e^{-\Delta H^*/RT}e^{\Delta S^*/R} \quad (1)$$

ΔH^* and ΔS^* are, respectively, the enthalpy and entropy of activation. To a first approximation they are independent of temperature. For many purposes it is more satisfying to discuss reactivity in terms of ΔH^* and ΔS^* rather than with respect to the temperature-dependent rate constant.

The Isokinetic Relationship

One is often interested in the variation of rate within a reaction series. A reaction series may comprise, for example, the reactions of a series of molecules (X_i), with the same functional group but different substituent groups, with a common reagent (Y). About 30 years ago Leffler et al.¹ recognized that for many reaction series a linear relationship exists between the ΔH^*_i and the ΔS^*_i . He expressed it as eq 2, in which the operator δ denotes the effect of variation in the molecules X_i (on ΔH^* or on ΔS^*) and β is the isokinetic temperature.

$$\delta\Delta H^*_i = \beta\delta\Delta S^*_i \quad (2)$$

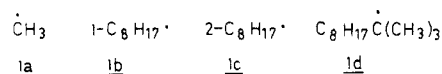
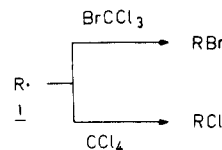
If the linear correlation according to eq 2 is perfect, the slope (β) is the temperature at which all the reactions in the series occur at identical rate. Above and below β , reactions in the series differ in rate, but whatever trend is observed below β is inverted above β . Thus, if the reaction series concerns the effects of meta and para substituents on rate and the Hammett ρ is positive below β , it must be negative above β .

Let us now consider a series of compounds X_i reacting, in competition experiments, with two reagents Y_1 and Y_2 . From properly designed experiments, one can reckon from product compositions the relative rate constants, k_1/k_2 , for reaction of each X_i with Y_1 and Y_2 . If one plots $\log(k_1/k_2)$ against $1/T$ for each X_i , a straight line results. Moreover, it turns out that the lines for the several compounds in the series often cross at a single value of $1/T$. The temperature so identified is called the isoselective temperature.

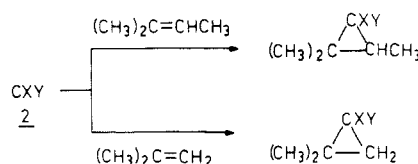
An example is presented as Figure 1: several alkyl radicals react competitively with BrCCl_3 (abstracting Br) and with CCl_4 (abstracting Cl), and the plots of $\log(k_{\text{Br}}/k_{\text{Cl}})$ vs $1/T$ coincide at $70^\circ \pm 10^\circ \text{C}$.⁴

Below and above this narrow temperature range the selectivity order of the radicals is completely reversed. At 0°C the methyl radical is less selective than the

primary, secondary, and tertiary alkyl radicals 1. Between 60 and 80°C the order reverses and at 130°C the methyl radical is the most selective alkyl radical in halogen abstraction reactions from BrCCl_3 and CCl_4 .⁴



The cycloaddition reactions of dihalocarbenes 2 provide a further example in which an inverse of the selectivity order can be observed (Figure 2).⁵ Measurements between -20 and 150°C show that the selectivities of CF_2 , CFCl , CCl_2 , CClBr and CBr_2 in a $(\text{CH}_3)_2\text{C}=\text{CH}(\text{CH}_3)/(\text{CH}_3)_2\text{C}=\text{CH}_2$ competition system coincide at $90 \pm 10^\circ \text{C}$. Below this temperature CF_2 is the most selective and above it CBr_2 is the most selective dihalocarbene.⁵



Equation 3 describes the temperature influence on the selectivity of molecules X_i in the competing reactions with Y_1 and Y_2 . If there is a temperature T_{is} at which variation of the reactants has no effect on their selectivities, eq 4 and 5 hold.

$$\log \frac{k_{i,1}}{k_{i,2}} = \frac{\Delta H^*_{i,2} - \Delta H^*_{i,1}}{2.3RT} - \frac{\Delta S^*_{i,2} - \Delta S^*_{i,1}}{2.3R} \quad (3)$$

[†] Other reviews in the last five years: "Formation of CC Bonds by Addition of Free Radicals to Alkenes" *Angew. Chem., Int. Ed. Engl.* 1983, 22, 753.

(1) (a) Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963. (b) Exner, O. *Prog. Phys. Org. Chem.* 1973, 10, 411.

(2) For example, see: Lamaty, G.; Sivade, A. *Bull. Soc. Chim. Fr.* 1974, 2149. Pivovarov, S. A.; Selivanov, V. F.; Gidasov, B. V. *Org. React.* 1975, 12, 305. Hall, J. H.; Dolan, F. W. *J. Org. Chem.* 1978, 43, 4608. Nishimura, N.; Sueishi, Y.; Amamoto, S. *Chem. Lett.* 1979, 429.

(3) Exner, O. *Coll. Czech. Chem. Commun.* 1975, 40, 2763. Krug, R. *R. Ind. Eng. Chem. Fundam.* 1980, 19, 50. Linert, W.; Kudrjartsev, A. B.; Schmidt, R. *Aust. J. Chem.* 1983, 36, 1903.

(4) Giese, B. *Angew. Chem.* 1976, 88, 159; *Angew. Chem., Int. Ed. Engl.* 1976, 15, 173. Giese, B.; Keller, K. *Chem. Ber.* 1979, 112, 1743.

(5) Giese, B.; Meister, J. *Angew. Chem.* 1978, 90, 636; *Angew. Chem., Int. Ed. Engl.* 1978, 17, 595. Giese, B.; Lee, W. B.; Meister, J. *Liebigs Ann. Chem.* 1980, 725.

Bernd Giese was born in Hamburg, Germany. He studied in Heidelberg, Hamburg, and Munich where he received his Dr. rer. nat. (1969) working in the group of R. Huisgen. After 2 years at the BASF/Ludwigshafen he joined the group of C. Rüchardt in Münster and Freiburg i. Br. (habilitation 1976). Since 1978 he has been Professor of Organic Chemistry at the TH Darmstadt. Besides the selectivities of intermediates, he is primarily interested in mechanisms and synthetic applications of radical reactions.

$$\delta \log \frac{k_{i,1}}{k_{i,2}} = 0 = \frac{\delta(\Delta H^*_{i,2} - \Delta H^*_{i,1})}{2.3 RT_{is}} - \frac{\delta(\Delta S^*_{i,2} - \Delta S^*_{i,1})}{2.3R} \quad (4)$$

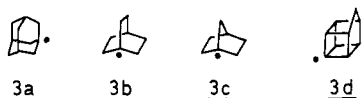
$$\delta(\Delta H^*_{i,2} - \Delta H^*_{i,1}) = T_{is} \delta(\Delta S^*_{i,2} - \Delta S^*_{i,1}) \quad (5)$$

In analogy to the isokinetic relationship we call eq 5 the isoselective relationship; T_{is} is the isoselective temperature and the operator δ denotes the variation of the reacting educts X_i .⁶ From the theoretical point of view, an isoselective relationship is built up by two isokinetic reaction series.^{6,7} Therefore, the observation of eq 5 proves the existence of eq 2. But two isokinetic relationships yield an isoselective relationship only if the reactions of X_i with the molecules Y_1 and Y_2 are so similar that the activation enthalpies $\Delta H^*_{i,1}$ and $\Delta H^*_{i,2}$ are linearly related with each other.^{6,7}

The Significance of Isoselective Relationships for Linear Free Energy Relationships

Leffler et al.^{1a} and Exner^{1b,8} have shown that the existence of an isokinetic relationship (eq 2) is a necessary condition for a linear correlation between reactivities of molecules X_i and their substituent parameters (e.g., Hammett σ or Taft E_s values). For a linear correlation between the reactivities $\log k_{i,1}$ and $\log k_{i,2}$ of two reaction series ($X_i + Y_1$ and $X_i + Y_2$), an isoselective relationship (eq 5) is prerequisite because both reactivities $\log k_{i,1}$ and $\log k_{i,2}$ depend upon the temperature, whereas reaction parameters σ , E_s , etc. are constants. Therefore, the scope of linear free energy relationships can be scrutinized by looking for an isoselective relationship.⁹

Selectivity measurements in a $\text{BrCCl}_3/\text{CCl}_4$ competition system show that flexible alkyl radicals 1 and rigid bridgedhead radicals 3 follow different isoselective relationships (Figure 3),¹⁰ and so a linear correlation that covers both radicals 1 and 3 cannot exist. The isoselective temperatures are 70 and -60°C for radicals 1 and 3, respectively. At 70°C a variation of the alkyl radicals 1 exerts the same effect on the reactivity of the bromine abstraction from BrCCl_3 and the chlorine abstraction from CCl_4 . The slope of the linear free energy relationship between the reactions of radicals 1 with BrCCl_3 and with CCl_4 is 1.0. Bridgehead radicals 3, which show quite different effects on the rates of the halogen abstractions at 70°C , give a slope that deviates from 1.0. Although the selectivities of radicals 1 and 3 depend on steric parameters, a common linear free energy relationship that covers these radicals does not exist and two different linear correlations result.¹¹



(6) Giese, B. *Angew. Chem.* 1976, 88, 161; *Angew. Chem., Int. Ed. Engl.* 1976, 15, 174.

(7) Exner, O.; Giese, B. *Angew. Chem.* 1978, 90, 816; *Angew. Chem., Int. Ed. Engl.* 1978, 17, 775.

(8) Exner, O. *Coll. Czech. Chem. Commun.* 1974, 39, 515.

(9) Giese, B.; Stellmach, J.; Exner, O. *Tetrahedron Lett.* 1979, 25, 2343.

(10) Giese, B.; Stellmach, J. *Chem. Ber.* 1980, 113, 3294.

(11) Giese, B.; Beckhaus, H. D. *Angew. Chem.* 1978, 90, 635; *Angew. Chem., Int. Ed. Engl.* 1978, 17, 594.

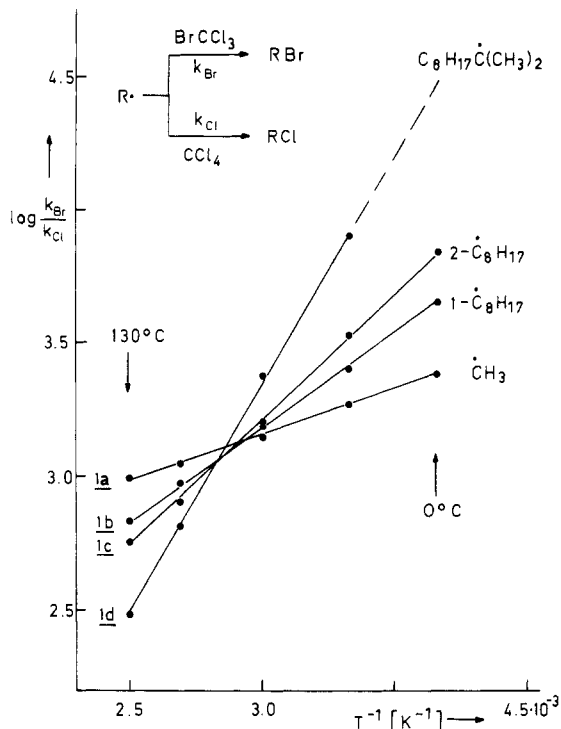


Figure 1. Temperature dependence of the selectivity of alkyl radicals 1 in the competition system $\text{BrCCl}_3/\text{CCl}_4$.

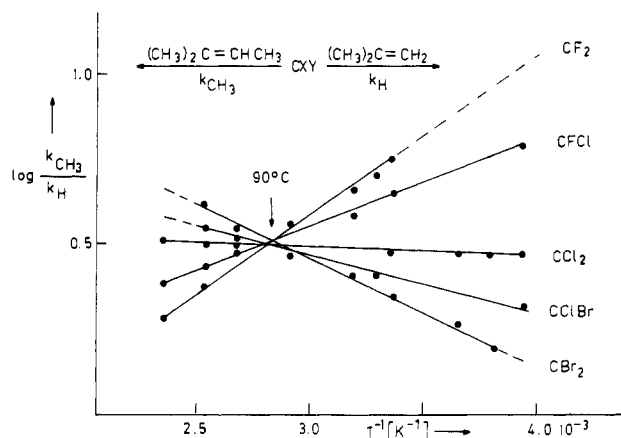
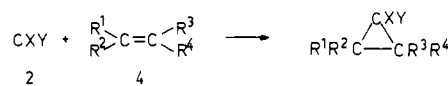


Figure 2. Temperature dependence of the selectivity of dihalocarbenes 2 in the competition system 2-methyl-2-butene/2-methylpropene.

Isoselective relationships can also help to analyze reactions of X_i with more than two different molecules Y_j . Cycloadditions of dihalocarbenes 2 with several methylated alkenes 4 clearly demonstrate that the constancy of isoselective temperatures is a necessary condition for a general correlation between the reactivities or selectivities of educts X_i in reactions with molecules Y_j . Methyl substituents in alkenes 4 increase



	R ¹	R ²	R ³	R ⁴
4a	CH ₃	CH ₃	CH ₃	CH ₃
4b	CH ₃	CH ₃	CH ₃	H
4c	CH ₃	CH ₃	H	H
4d	CH ₃	H	H	CH ₃

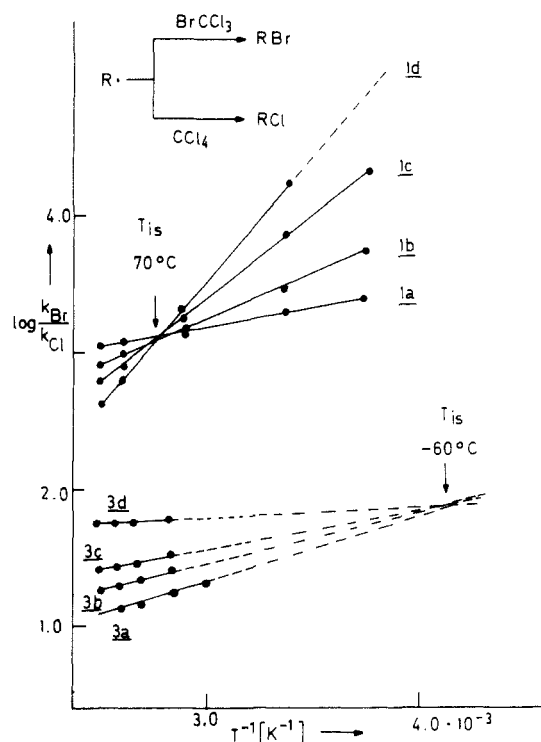


Figure 3. Isoselective relationships of flexible alkyl radicals 1 and rigid bridgehead radicals 3 in reactions with the $\text{BrCCl}_3/\text{CCl}_4$ competition system.

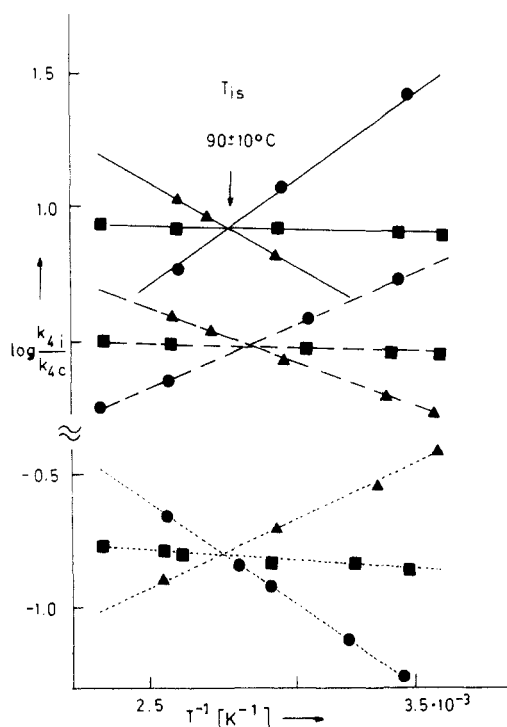


Figure 4. Isoselective relationships of CF_2 (●), CCl_2 (■), and CBr_2 (▲) in cycloadditions with alkene pairs $4a/4c$ (solid lines), $4b/4c$ (dashed lines), and $4d/4c$ (dotted lines).

the rates in cycloaddition reactions with dihalocarbenes 2.¹² Therefore, different isoselective relationships exist for different alkene pairs, but their isoselective temperatures are the same (Figure 4).¹³ The linear free

(12) Moss, R. A. In "Carbenes"; Jones, M., Moss, R. A., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 2.

(13) Giese, B.; Lee, W. B. *Angew. Chem.* 1980, 92, 864; *Angew. Chem., Int. Ed. Engl.* 1980, 19, 835.

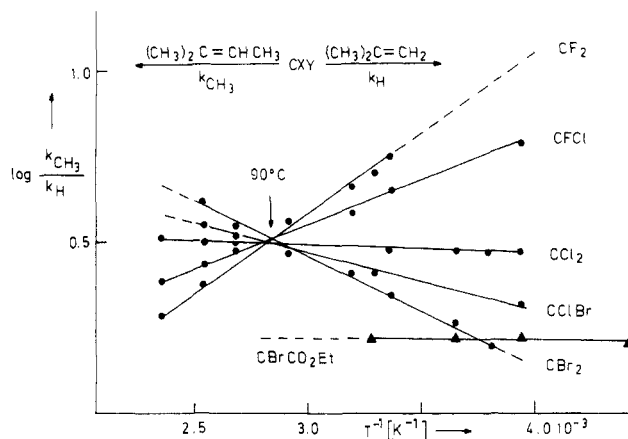


Figure 5. Temperature dependence of the selectivity of dihalocarbenes and of CBrCO_2Et in the competition system 2-methyl-2-butene/2-methylpropene.

energy relationship that describes the reactions between carbenes 2 and alkenes 4 is the Moss relationship (eq 6).¹⁴

$$m_{\text{CXY}} = -1.10 \sum_{\text{XY}} \sigma_{\text{R}}^+ + 0.53 \sum_{\text{XY}} \sigma_{\text{I}} - 0.31 \quad (6)$$

In the Moss relationship, which is valid only at 25 °C, m_{CXY} is the slope for carbene CXY in a $\log k_{\text{CXY}}/\log k_{\text{CCl}_2}$ diagram, and σ_{R}^+ and σ_{I} are parameters of the carbene substituents X and Y. For carbene cycloaddition reactions at different temperatures, general eq 7 with temperature-dependent factors a , b , and c must be employed.¹⁵ But the general eq 7 holds only if

$$m_{\text{CXY}} = a \sum_{\text{XY}} \sigma_{\text{R}}^+ + b \sum_{\text{XY}} \sigma_{\text{I}} + c \quad (7)$$

carbenes CXY show the same isoselective temperatures with all alkenes 4. At the isoselective temperature in a given alkene competition system all carbenes 2 exert the same rate effects on the alkenes and the slope in a $\log k_{\text{CXY}}/\log k_{\text{CCl}_2}$ diagram is 1.0. Therefore, only alkenes and carbenes with the same isoselective temperature can be described by a common linear free energy relationship.

With dihalocarbenes 2 and methylated alkenes 4, this isoselective temperature is 90 °C. But $\text{CBrCO}_2\text{C}_2\text{H}_5$ does not cross the selectivities of dihalocarbenes at this temperature (Figure 5).¹⁶ The carbene $\text{CBrCO}_2\text{C}_2\text{H}_5$ cannot be described by general eq 7 and the fit with the Moss correlation (eq 6) is only fortuitous. The reason for the different behavior of $\text{CBrCO}_2\text{C}_2\text{H}_5$ is not a change from the singlet to a triplet carbene, because both dihalocarbenes¹² and $\text{CBrCO}_2\text{C}_2\text{H}_5$ ¹⁷ react with *cis*-butene with retention of the stereochemistry. Presumably, $\text{CBrCO}_2\text{C}_2\text{H}_5$ reacts with a diffusion-controlled rate¹⁸ and, therefore, an equation which describes the substituent influence on the selectivity cannot be applied.¹⁹

(14) Moss, R. A. *Acc. Chem. Res.* 1980, 13, 58.

(15) Giese, B.; Lee, W. B. *Chem. Ber.* 1981, 114, 3306.

(16) Giese, B.; Mehl, W. H. *Tetrahedron*, in press.

(17) Schöllkopf, U.; Reetz, M. *Tetrahedron Lett.* 1969, 20, 1541.

(18) Diffusion-controlled rates have been measured for arylchlorocarbenes: Turro, N. J.; Lehr, G. F.; Butcher, J. A.; Moss, R. A.; Guo, W. *J. Am. Chem. Soc.* 1982, 104, 1754. Moss, R. A.; Perez, L. A.; Turro, N. J.; Gould, J. R.; Hacker, N. P. *Tetrahedron Lett.* 1983, 24, 685.

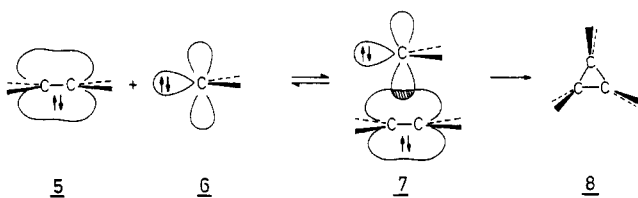
Table I
Influence of Varying the Substituents in 2-Methylpropene ($R = CH_3$) on the Activation Enthalpies ($\text{kJ}\cdot\text{mol}^{-1}$) and Activation Entropies ($\text{J}\cdot\text{mol}^{-1}\cdot\text{s}^{-1}$) of Cycloadditions with CBr_2 and CCl_2

alkene	CBr_2		CCl_2	
	$\Delta\Delta H^\ddagger$	$\Delta\Delta S^\ddagger$	$\Delta\Delta H^\ddagger$	$\Delta\Delta S^\ddagger$
$\text{CH}_3\text{CR}=\text{CH}_2$	$\equiv 0.0$	$\equiv 0.0$	$\equiv 0.0$	$\equiv 0.0$
$\text{CH}_3\text{OCR}=\text{CH}_2$	2.5	17	2.0	16
$\text{C}_6\text{H}_5\text{CR}=\text{CH}_2$	3.4	14	2.6	13
$\text{CH}_3\text{CR}=\text{CHCH}_3$	5.8	26	0.3	11
$\text{CH}_3\text{CR}=\text{C}(\text{CH}_3)_2$	10	47	1.2	22
$\text{C}_2\text{H}_5\text{CR}=\text{CH}_2$	0.0	-0.4	0.0	-1.0
$i\text{-C}_3\text{H}_7\text{CR}=\text{CH}_2$	0.2	-9.2	3.3	-0.5

Consequences for the Mechanism of Carbene Cycloadditions

The crossing of the selectivity lines at one temperature proves that in cycloaddition reactions of dihalocarbenes **2** with alkenes **4** a common linear free energy relationship exists. The slopes of the selectivity lines offer a deeper insight into the mechanism of carbene cycloadditions. An increase in temperature increases the selectivity of CBr_2 and CBrCl (Figures 2 and 5). This surprising dependence and the vanishing temperature effect on CCl_2 selectivities, which were first observed by Skell,²⁰ show that cycloaddition reactions of highly reactive carbenes like CBr_2 or CCl_2 are "entropy controlled".^{20,21} Methyl, methoxy, and phenyl groups increase the reactivity of alkenes because the relative activation entropies become more positive (Table I); therefore, the electrophilicity of CBr_2 and CCl_2 is an entropy effect. On the other hand, by activation enthalpies, CBr_2 exhibits nucleophilic behavior (Table I) because methyl and methoxy substituents at alkene **4** increase the activation enthalpies.²¹

These substituent effects and the negative activation enthalpies of highly reactive carbenes, measured by Turro and Moss,¹⁸ could be explained by a stepwise cycloaddition reaction.^{21,22} In the first step the empty p orbital of the singlet carbene **6** overlaps with the π -bond of alkene **5** to form the loose complex **7**. The enthalpy change during this adduct formation should be small. Therefore, this electrophilic carbene attack is governed by entropy effects. The intermediate **7** either reacts backwards to the starting material or to the cyclopropane **8**. In this step the nonbonded electron pair of the carbene comes into play and the carbene behaves more like a nucleophile. The entropy change should be so small that the enthalpy can be more important now.



(19) A diffusion-controlled rate could also explain the deviation of the selectivity of CClCF_3 from the Moss equation: Moss, R. A.; Guo, W.; Denney, D. Z.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1981**, *103*, 6164.

(20) Skell, P. S.; Cholod, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 7131.

(21) Giese, B.; Lee, W. B.; Neumann, C. *Angew. Chem.* **1982**, *94*, 320; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 310.

(22) Moss, R. A.; Perez, L. A.; Turro, N. J.; Gould, I. R.; Hacker, N. P. *Tetrahedron Lett.* **1983**, *24*, 685. Platz, M. S. *Tetrahedron Lett.* **1983**, *24*, 4763.

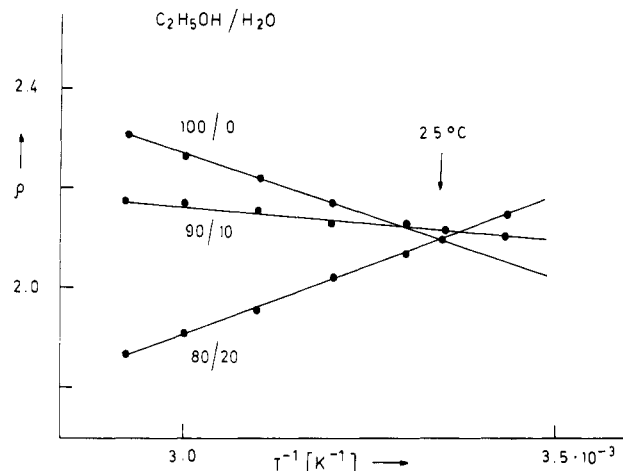
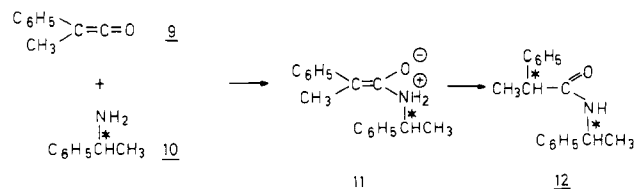


Figure 6. Temperature influence on the ρ values of the solvolysis of p -chlorotrityl benzoates **13** in ethanol-water mixtures.

Recently, Houk et al.²³ have offered a different interpretation. From ab initio calculations they concluded that the entropy control and the negative activation enthalpies can be explained even without postulating an intermediate: In the reaction of a highly reactive singlet carbene with a methylated alkene there should be always an enthalpy gain along the reaction coordinate, but there is an activation free energy ΔG^\ddagger because the loss of entropy in the reaction between the two molecules plays the major role. The "later" the transition state, the more enthalpy is gained; therefore, in slower reactions the activation enthalpy ΔH^\ddagger is more negative. This could explain the data of Table I in which the slower reaction has the smaller activation enthalpy. The isoselective temperature is calculated by Houk et al.²³ to be 105 ± 20 °C, which is in good accord with the experimental value of 90 ± 10 °C.

Solvent Effects

It is well documented that activation entropies of ionic reactions depend dramatically on the solvent.^{24,25} Therefore, low isoselective temperatures could be expected if competition reactions were carried out in different solvents. Pracejus²⁶ has observed the first example of this kind in addition reactions of the chiral amine **10** to methylphenylketene **9**. At 60 °C the diastereoselectivity increases if the solvent is varied from diisopropyl ether via ethyl acetate to tetrahydrofuran, whereas below -30 °C the selectivity order is completely reversed. The diastereoselective step in which the solvent plays a major role is presumably the protonation of the zwitterion **11** leading to the diastereomers of **12**.^{26,27}



(23) Houk, K. N.; Rondan, N. G.; Mareda, J. *J. Am. Chem. Soc.* **1984**, *106*, 4291. Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 4293.

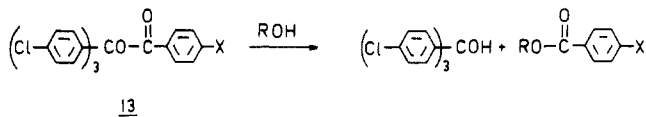
(24) Schaleger, L. L.; Long, R. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1.

(25) Blandamer, M. J. *Adv. Phys. Org. Chem.* **1977**, *14*, 203.

(26) Pracejus, H.; Tille, A. *Chem. Ber.* **1963**, *96*, 854.

(27) Jähme, J.; Rüchardt, C. *Angew. Chem.* **1981**, *93*, 919; *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 885.

In a similar way the variation of a water-ethanol mixture influences the ρ values of the solvolysis of *p*-chlorotrityl benzoates **13**.²⁸ An increasing amount of water increases the substituent effect on the solvolysis of **13** at 0 °C, but it decreases the ρ values above 40 °C. The isoselective temperature at which the ρ values are independent of the water-ethanol mixture is 25 °C (Figure 6).



Concluding Remarks

The temperature dependence of selectivities has long been neglected. Since activation enthalpies sometimes differ by only a small amount, the differences in the activation entropies become dominant. If this is the

case, the interpretation of selectivities (e.g., the substituent effect on the reactivity) has to take reaction entropies into consideration.

According to the isoselective relationship (eq 5), the isoselective temperature T_{is} is low if substituents influence $\Delta\Delta S^\ddagger$ more than $\Delta\Delta H^\ddagger$. This could often be the case in reactions with "early" transition states in which bond formation and bond cleavage are not far advanced and the enthalpy difference between the educts and the transition state is small. Substituents can influence the "looseness" of this transition state without changing the activation enthalpies very much. On the other hand, even in early transition states the molecules that react with each other have lost a considerable amount of translational entropy and the activation entropy depends very much on the "looseness" of the transition state.²⁴ Therefore, in bimolecular reactions of reactive intermediates one should be aware of the possibility that low isoselective temperatures might exist. An interpretation of selectivity data without knowledge of the temperature effect might then lead to an incorrect conclusion.

(28) Karavan, V. S.; Lukaashina, L. A. *Zh. Org. Khim.* 1978, 14, 2106.
 Karavan, V. S.; Eliseeva, E. E. *Zh. Org. Khim.* 1982, 19, 746.