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Author's Review

A Kinetic Approach to the Mechanism of Cationic Polyolefinic Cyclization. Simple and Extended π–Participation

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This review deals with the mechanism of the biomimetic olefinic cationic polycyclizations considering relative rate effects, activation parameters, substituent rate effects, σ, ρ correlation and secondary deuterium kinetic isotope effects (KIE) in solvolysis, obtained with tertiary and benzylic substrates comprising one, two or more double bonds, respectively, sited at the same positions as in the natural precursor (C-5, C-9, C-13). Kinetic behaviour of substrates with one double bond at position 5 (models for monocyclization) which are structurally related to structures **16U** and **22U** suggests that the formation of the first cyclohexane ring is a concerted process with some exceptions (**16U** with *p*-OCH_3). In solvolysis of chlorides with double bonds at positions 5 and 9 (**28** and **29U**) extended π-parcipation occurs, *i.e.* both double bonds of the aliphatic chain are involved in the rate determining step. Substrastes with more then two double bonds (**30U** and **31U**) solvolyze by way of extended π-participation. It remains unclear if two or three double bonds are involved. The paper also shows clear evidence that the magnitude of β-deuterium secondary KIE are the most sensitive probe for neighboring group participation.

INTRODUCTION

It has been established that the biological precursor of all steroids and polycyclic triterpenes is squalene[1], which is an aliphatic (acyclic) and achiral pentaene (isoprenoid) found in the liver of some sharks. The first step in the biogenesis of polycyclic compounds is the terminal epoxidation of squalene to 2,3-epoxysqualene **1**. Subsequent acid catalyzed epoxy-ring opening initiates cyclization in a carbocationic type of reaction.

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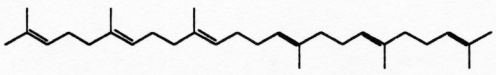
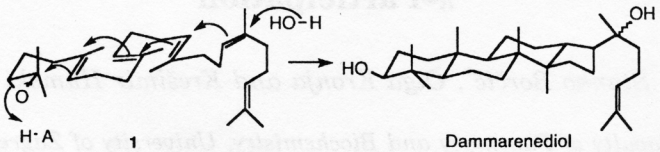


Squalene

The polycyclization is stereospecific. Possibly the simplest example of the latter reaction is the biogenesis of dammarenediol from **1**, a triterpene found in some plants.[2]



1 Dammarenediol

Even though the product contains nine asymmetric carbons, only two enantiomers (epimeric at C-20) of possible 512 stereoisomers are formed with all rings *trans*-fused. In a similar manner (involving some rearrangements), lanosterol, and from it cholesterol, are formed in the human body.

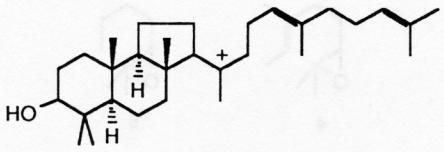
When the latter facts were recognized, obvious questions arouse. Is it possible to imitate nature? Is it possible to get (poly)cyclic products from acyclic (or partially cyclized) starting material in carbocationic reactions? Are these reactions controlled only by enzymes in living organisms and to what extent is it possible to reproduce nature in the laboratory without the help of enzymes by using carefully chosen substrates and reaction conditions? These questions lead to a fascinating field of research which may be called *biomimetic olefinic cyclizations*.

The most important contributors in these investigations are W. S. Johnson[3] and E. E. van Tamelen[4], both from Stanford University. They (and other authors[5]) have prepared tens, possibly hundreds of (poly)cyclic compounds in carbocationic reactions using acyclic or partially cyclized starting materials.

The outstanding features of these reactions, as we see it, are the following:

1. It is possible to imitate nature to some extent. (Poly)cyclizations do occur from acyclic and partially cyclized starting compounds that have an appropriate leaving group, and under reaction conditions which can be expected to produce carbocations. The products are not always the same as those produced in nature. As an example, the acid catalyzed epoxyde-ring opening with **1** yields products derived from the tricyclic carbenium ion **2**.[6] No tetracyclic products are formed. Such a result is understandable on the basis of the organic chemist's intuition. Ion **2** is tertiary and therefore, more stable than the secondary one (cyclohexyl cation) that could lead to tetracyclic products.

2. Biomimetic cyclizations are often stereospecific or highly stereoselective. For example the dienyl derivative **3** (*E*-configuration) yields, upon solvolysis exclusively *trans*-fused bicyclic products while its *Z*-stereoisomer yields only the corresponding *cis*-decaline derivatives.[7]



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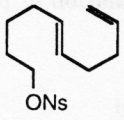


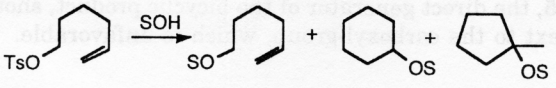
3

3. In polycyclizations, in most cases, partially cyclized intermediates are either not found in any significant amount and/or they do not show any further cyclization under relevant reaction conditions.

The outstanding problem is whether cyclizations occur in a *stepwise* or *concerted* manner, upon or during the formation of the carbocationic intermediate. Before describing our work, we give some selected examples from the literature on cationic olefinic cyclizations which seem to proceed either in a concerted or, alternatively in a non concerted manner.

Potentially concerted reactions

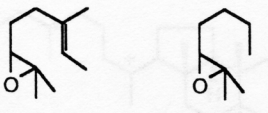
Bartlett[8] and Trahanovsky[9] have investigated the solvolysis of 5-hexenyl tosylates. These reactions show a small rate increase relative to the saturated analogues and yield some cyclohexyl and methylcyclopentyl products:



Formation of the cyclic products is best explained assuming a direct displacement of the leaving group by the double bond, leading to a carbocationic intermediate, which then reacts with the solvent.

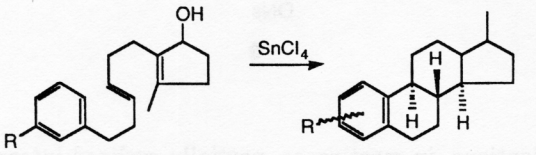
Van Tamelen[10] has investigated the acid catalyzed epoxy-ring opening of **4** and **5**. It was found that the former reaction is much faster than the latter and that it yields cyclic products.

Johnson *et al.*[11] looked at the rate of cyclization of **6** yielding **7**. They found that the reaction rate depended upon the nature of the phenyl substituent R. The rate



4 **5**

effects are rather small. Moreover, a kinetic analysis of the results is complicated by an equilibrium preceding the formation of products.

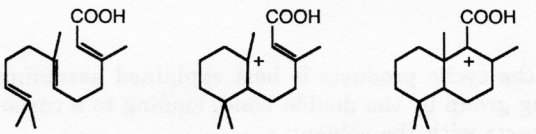


6 **7**

Concerted cationic polycyclizations inevitably involve either *simple* (one double bond) or *extended* (two or several double bonds) neighboring group participation. Bly *et al.*[12] have shown that the latter is effectively operative only in cases when the former gives small rate effects.

Potentially stepwise reactions

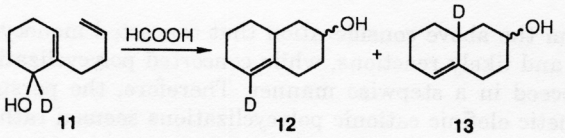
The whole field of biomimetic cationic polycyclizations started with the works of Eschenmoser[13] and Stork.[14] Stork proposed that the acid-catalyzed bicyclization of farnesyl acid **8** proceeded through the imtermediate ion **9**. Monocyclic products were isolated but, typically, did not react to form bicyclic products under the same reaction conditions. Bicyclic products derived from **10** were obtained from monocyclic products under more drastic conditions. This is understandable, since the transition state cognate to **15**, the direct generator of the bicyclic product, should have a partial positive charge next to the carboxyl-group, which is unfavorable.



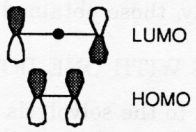
8 **9** **10**

Sunko *et al.*[15] showed that in acid catalyzed cyclization of deuterated allyl alcohol **11**, two products **12** and **13** were formed in equal amounts. This result might be

explained by the formation of an allylic cation in the rate determining step which is then attacked by the internal double bond indiscriminately at both ends. The cyclization cannot be concerted since in that case at least a predominance of **12** would be expected.



However, we would like to point out that allylic substrates might not always be good substrates for effecting concerted cyclizations. If the geometry approach of the two interacting groups are as depicted below, then the opposite symmetries between HOMO and LUMO preclude this interaction.

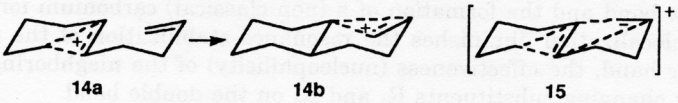


Japanese authors[16] have demonstrated that a polycyclization reaction occurs in a stepwise manner. However, their method of formation of carbocations is unusual in that the leaving group is a mercury compound that reacts without a formation of ion pairs.

Theoretical considerations

Van Tamelen[17] has pointed out that the sequence of conformationally rigid (*quasi*)monocyclic carbonium ions **14** could account for the stereochemical control of biomimetic polycyclizations. Thus, the existence of ions with extensively delocalized charge (**15**) is not a necessary requirement. It follows that even though concertedness results in stereospecificity, the converse is not necessarilly true.

Dewar,[18] using π-complex rather than carbonium ion formalism, has calculated that species like **14a** are more stable than the corresponding acyclic carbenium ions. Hence, concerted monocyclizations are a distinct possibility. Moreover, the direct oc-



14a 14b 15

currence of concerted bicyclization by way of species like **15** turns out to be improbable since this reaction would require an energy of activation 92–96 kJ/mol higher than the stepwise process (MINDO/3).

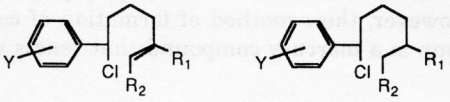
According to the terminology of Goldstein and Hoffmann[19] (laticyclic interactions) transition states involving the interactions of one empty p-orbital (**14**) with an ethylenic double bond are stabilized while those involving another double bond (**15**) are not.

It follows from the above consideration that concerted monocyclizations are indeed predictable and likely reactions, while concerted polycyclizations are not. The latter should proceed in a stepwise manner. Therefore, the perspective of finding concerted biomimetic olefinic cationic polycyclizations seemed rather bleak.

The present paper deals with the *mechanism* of olefinic cationic polycyclizations. Although many compounds have been prepared in this elegant manner, the pathways by which they are formed are largely unknown. Especially, *kinetic* data are, at best, scarce in the literature. We have used most of the arsenal of physical-organic chemistry to elucidate this question, *i.e.* relative rate effects, activation parameters, substituent rate effects, σ, ρ correlations and secondary deuterium kinetic isotope effects (KIE). In further text, we shall present many *kinetic* data which pertain to the mechanism of cationic biomimetic (poly)cyclization. We shall first discuss the results obtained in solvolysis of substrates with one CC double bond, then those obtained with two double bonds and, finally, those obtained with several CC double bonds.

SUBSTRATES WITH ONE DOUBLE BOND

We first focused our attention to the solvolysis of chlorides **16U**.[20] This is a flexible system and offers many experimental possibilities.

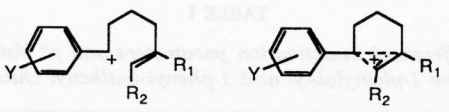


16U **16S**

a $R_1 = CH_3$, $R_2 = H$;
b $R_1 = H$, $R_2 = CH_3$;
c $R_1 = R_2 = CH_3$

Y = *p*-OCH_3, *p*-CH_3, *p*-Br and *m*-Br

The rate determining unassisted process (k_c) proceeds by way of a secondary benzylic carbenium ion (**17**) whose resonance stabilization can be varied by changing the phenyl substituent Y. Neighboring group participation (k_Δ process) involves delocalization of the incipient positive charge away from the reaction center to carbons of the double bond and the formation of a (non classical) carbonium ion (**18**). However, this delocalization diminishes the resonance stabilization of the carbocation. On the other hand, the effectiveness (nucleophilicity) of the nieghboring group can be varied by changing substituents R_1 and R_2 on the double bond.



17 **18**

Thus, it is possible to influence the competition between k_c and k_Δ processes. Moreover, substrates can be deuterated either in β position relative to the leaving group or at the double bond and the secondary deuterium KIE measured. The magnitude of these effects (k_H/k_D) is quite sensitive to participation.

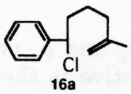
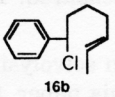
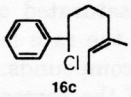
As reference substrates for estimating the importance of k_c in solvolysis of **16U** corresponding saturated chlorides **16S** were used. Throughout this paper, the symbols **S** and **U** are used for substrates with saturated and unsaturated aliphatic chains, respectively. It is expected that, if participation occurs, the rate for the **U** compounds should be larger than that of the corresponding **S** compounds. At this point, it should be emphasized that using the rate constant of the corresponding saturated analogues (k_S) for estimating k_c for compounds of the **U** series is only an approximation, since the rate constant for the unassisted route (k_c) is not necessarily identical for **S** and **U** series.

Titrimetric rate constants (pH-stat, 95 and 80% v/v aq. ethanol, 97 wt./wt. 2,2,2-trifluorethanol; 95E, 80E and 97 TFE, resp.) were measured in solvolysis of both **16U** (k_U) and **16S** (k_S) in several solvents and at several temperatures. Some results are shown in Table I.[21] It is observed that k_U/k_S values are small. Only large rate acceleration ($k_U/k_S >> 1$) can be taken as a valid proof of participation. Small rate effects are ambiguous but *do not prove* lack of participation. When k_c and k_Δ are of similar magnitude, the approximation mentioned earlier can obscure even an important contribution of k_Δ to the overall rate constant. It should be mentioned that k_U/k_S is practically unity in all cases when Y = *p*-OCH_3. Since other results (discussed below) also show that the latter chlorides solvolyze exclusively by way of k_c, this indicates that the approximation discussed above is valid in the particular case and that small rate accelerations observed with other chlorides of the **16U** series are in fact due to a contribution of k_Δ.

Linear free energy relationships are often used in elucidating the reaction mechanism.[22] We have used Shiner's[23] data published for the solvolysis of 1-arylethyl chlorides and obtained an excellent $\rho^+\sigma^+$ correlation (ρ^+ –6.09, 8 points; r = 0.998).[21] This is rather remarkable since the data were extrapolated from measurements in six different solvents (rate range 10^{10}) in spite of the fact that ρ^+ values are generally solvent dependent.[22] Our compounds of the **S** series behave in the same way. ρ^+ values are –6.24, –6.40 and –6.31 for **16S-a**, **-b** and **-c** resp., with $r > 0.99$ in all cases. The fit is as good in the **U** series but the ρ^+ values are significantly less negative (Table I). Moreover, for the **U** chlorides, the points with Y = *p*-OCH_3 deviate from the correlation line in all three series, indicating a change in the mechanism (Figure 1). We interpret these observations as a result of delocalization of π-electrons from the aliphatic double bond into the incipient empty p-orbital at the reaction center in the solvolysis transition state. This makes the orbital vacancy at the benzylic carbon less pronounced and diminishes the necessity for resonance stabilization. Hence, the influence of the phenyl substituents Y diminishes and the ρ^+ values are less negative.

TABLE I

Relative rates, differences in activation parameters and ρ^+ Values in solvolysis of some 1-phenylalkyl and 1-phenyl-5-alkenyl chlorides

Compound	k_U/k_S[a]	$\Delta\Delta H^{\#}$ [b] / kJmol^{-1}	$\Delta\Delta S^{\#}$ [c] / JK^{-1}mol^{-1}	$\Delta\rho+$[d]
 **16a**	2.6	29.2	29.2	–1.41
 **16b**	5.9	15.9	38.4	–1.73
 **16c**	16.1	15.0	89.0	–2.37

[a] at 25 °C; k_U is the rate of the 5-alkenyl chloride, k_s is the rate of the corresponding alkyl chloride. [b] difference between the enthalpies of activation of saturated and the corresponding unsaturated chlorides ($\Delta\Delta H^{\#} = \Delta H_S^{\#} - \Delta H_U^{\#}$); data obtained from rate constants at three different temperatures. [c] difference between the entropy of activation of saturated and the corresponding unsaturated chlorides ($\Delta\Delta S^{\#} = \Delta S_S^{\#} - \Delta S_U^{\#}$); data obtained from rate constants at three different temperatures. [d] difference between ρ^+ values of saturated and the corresponding unsaturated series ($\Delta\rho^+ = \rho_S^+ - \rho_U^+$); ρ_U^+ values were obtained using the whole series of Y substituents (Y = *p* – OCH_3, *p*-CH_3, H, *p*-Br and *m*-Br), except for where the point Y = *p*-OCH_3 was omitted.

The resonance stabilization is, however, so exalted by the large electron donating power of the *p*-OCH_3 substituent that the neighboring group participation becomes

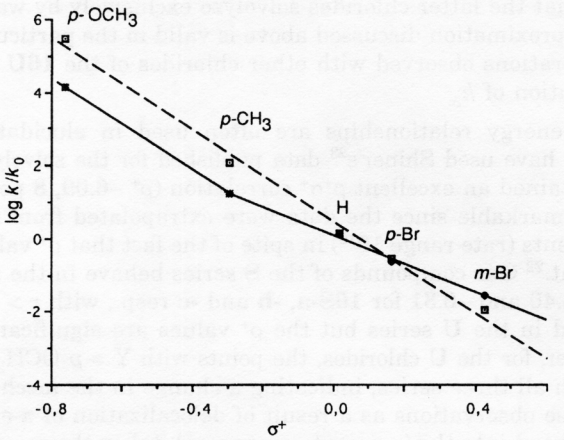
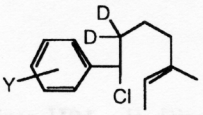


Figure 1. ρ^+ σ^+ plot for trifluoroethanolysis at 25 °C of 1-aryl-5-methyl-5-heptenyl chlorides **16U-c** (—) and 1-aryl-5-methylheptyl chlorides **16S-c** (---).

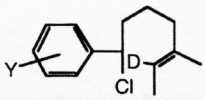
unimportant. In other words, k_Δ makes a significant contribution to the overall rate, except when Y = *p*-OCH_3. The latter chlorides react by way of k_c.

Activation parameters are consistent with the above conclusion. In all cases (except when Y = *p*-OCH_3) $\Delta H^\#$ for the **U** series are smaller than in the **S** series while $\Delta S^\#$ are more negative (Table II). It is well known that the neighboring group participation lowers $\Delta H^\#$. On the other hand, the k_Δ process involves loss od some degrees of rotational freedom of the alkenyl chain in the transition state, resulting in a more negative $\Delta S^\#$.[24] Typically, there is no difference in activation parameters between the **U** and **S** series with *p*-anisyl derivatives.

Secondary β-deuterium KIE are due to the hyperconjugative electron release from the C-D(H) bonding orbitals into the orbital vacancy at the reaction center occurring in S_N1 solvolyses.[25] This effect is known to be very sensitive to the neighboring group participation which reduces its magnitude.[26] Indeed, the whole series **16U-c**-2,2-d_2 solvolyzes with greatly reduced k_H/k_D except with the *p*-anisyl derivative,[27] for which this value is practically identical to that of 1-phenylhexyl-2,2-d_2 chloride (1.15)



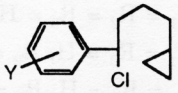
16U-c-2,2-d_2



16U-c-6-d_1

Deuteration at the aliphatic double bond as in **16U-c**-6-d_1 results in inverse isotope effects (Table II). These effects are the converse of secondary α-deuterium KIE and are thought to be due to the sp^2 to sp^3 rehybridization at carbon 6. Involvement of the double bond in the rate determining step is thus demonstrated. Again, the exception is the *p*-anisyl derivative, for which k_H/k_D is unity.

There are no rate effects in the whole series **16U** if R_1=R_2=H. Thus it appears, at least by this criterion (which is uncertain), that in this case the double bond is not nucleophylic enough to act as a neighboring group. Neither are any rate accelerations observed with the series **19**.[28]



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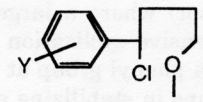
Finally, we measured the solvolysis rates of series **20**,[29] which are thought by analogy[30] to react, at least in part, by way of methoxyl participation through formation of the oxonium ion **21**.



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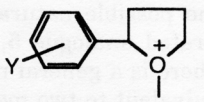

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TABLE II

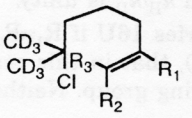
*Secondary deuterium kinetic isotope effects in solvolysis of some 1-aryl-5-hexenyl chlorides (**16U-c**) at 50 °C*

Phenyl Substituent Y	Solvent[b]	k_H/k_D[a]	
		16U-c-2,2-d_2 (β-KIE)	**16U-c**-6-d_1 (ω-KIE)
p-OCH_3	95 E	1.13 (1)[c]	1.01 (1)
p-CH_3	95 E	1.06 (2)	0.96 (2)
H	80 E	1.04 (2)	0.90 (2)
p-Br	97 T	0.99 (1)	0.93 (1)
m-Br	97 T	1.03 (2)	0.93 (1)

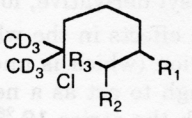
[a] The uncertainty of the last reported figure (standard deviation of the mean) is shown in parentheses.
[b] 95 E, 80 E and 97 TFE are 96%, 80% aq. v/v ethanol and 97% aq. wt./wt. 2,2,2-trifluoroethanol, respectively.
[c] The corresponding k_H/k_D for 1-phenylhexyl-2,2-d_2 chloride is estimated to be 1.15[25]

The results are similar to those obtained with the **16U** series. The rate accelerations are generally somewhat larger than those with **16U** but still quite small. The ρ^+ value of –3.8 is practically the same as with **16U** and the points for the *p*-anisyl derivatives deviate from the correlation line.

We turned our attention next to the solvolyses of tertiary chlorides **22U** and **22S** and their protio analogues[31]



22U



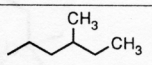
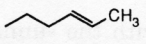
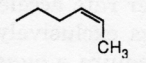
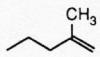
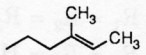
22S

a $R_1 = R_2 = R_3 = H$;
b $R_1 = R_3 = H$, $R_2 = CH_3$;
c $R_1 = R_2 = H$, $R_3 = CH_3$;
d $R_1 = CH_3$, $R_2 = R_3 = H$;
e $R_1 = R_2 = CH_3$, $R_3 = H$;

These compounds were chosen because the carbocation intermediate with **22U-e** should be similar to that produced in the acid-catalyzed epoxy ring opening with **4** (and therefore to the possible natural precursor) where a large rate acceleration, relative to the saturated analogue **5**, and extensive cyclization have been demonstrated. Moreover, there is a general rule that a phenyl group at the reaction center is approximately equivalent to two methyl groups in stabilizing a carbenium ion. In this respect, **22U** and **22S** are similar to **16U** and **16S**, respectively.

TABLE III

Relative solvolysis rates and β-deuterium kinetic isotope effects of some 1,1-dimethyl-5-alkenyl chlorides in 80% v/v aqueous ethanol

Compound	$(CD_3)_2C(Cl)R$ R	k_U/k_S [a]	k_H/k_D [b]
22S-e		–	1.80 (3)[c]
22U-a		0.78	1.57 (2)
22U-b		1.25	1.38 (1)
22U-c		0.75	1.72 (4)
22U-d		1.63	1.22 (3)
22U-e		18.9	1.37 (3)

[a] at 25 °C; k_u is the rate of 5-alkenyl chloride, k_s is the rate of the corresponding alkyl chloride; ratios are for protio compounds. [b] at 50 °C; the uncertainty of the last reported figure (standard deviation of the mean) is shown in parentheses. [c] This value for 1-phenylethyl-2-2-2-d_3 was measured to be 1.79 (3) at 25 °C.[30]

The results of this investigation are ashown in Table III. Only the substrate with two methyl groups on the double bond (**22U-e**) shows a moderate rate enhacement relative to the saturated analogue (**22S-e**) . In all other cases, the rate effects are small or even inverse. Activation parameters vary in an erratic manner without a perceivable trend. The *only* indication of the neighboring group participation is found in the magnitude of the secondary β-deuterium KIE. While k_H/k_D for **22S** is 1.80 (practically the same as with 1-phenylethyl chloride[32]), all other KIE are significantly smaller (except with **22U-c**, see later).

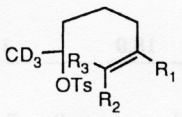
It is interesting that even **22U-a**, the chloride without methyl groups on the aliphatic double bond, shows a reduced KIE. This can only be interpreted by the fact that **22U-a** reacts in part by way of k_Δ. Moreover, it demonstrates that the rate effects, as measured against even a carefully chosen reference substrate, can be misleading, as pointed out earlier (in the particular case this effect is slightly inverse). By analogy, it is possible that the corresponding aryl-substituted derivatives **16U** where R_1=R_2=H also solvolyze, at least in part, by way of k_Δ although no rate effects were observed, *i.e.* $k_U/k_S \approx 1$. In any case, this result confirms our contention that small rate effects conventionally measured, are an ambiguous criterion for *discarding* the neighboring group participation.

Another point of interest is that the chloride with a methyl-group at position 5 (**22U-d**) reacts with a smaller KIE than the doubly methyl substituted compound

22S-e. Our interpretation is that the transition state of the slower reacting **22U-d** occurs later along the reaction coordinate than that of **22U-e** and resembles more the cyclohexyl cation **23** while in the latter the positive charge is more evenly distributed, as shown in **24**.

23 **24**

An exception to the rule is **22U-c** with the »unnatural« *cis*-configuration of the double bond which reacts without neither rate acceleration nor reduced KIE. Thus, by all criteria, this compound solvolyzes exclusively by way of k_c. This is understandable since the k_Δ process would require a *quasi*-axial position of two methyl groups, which is unfavorable.

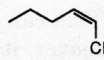
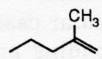
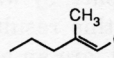


25U

a $R_1 = R_2 = R_3 = H$;
b $R_1 = R_2 = H$, $R_3 = CH_3$;
c $R_1 = CH_3$, $R_2 = R_3 = H$;
d $R_1 = R_2 = CH_3$, $R_3 = H$;

TABLE IV

Relative solvolysis rates and β-deuterium kinetic isotope effects of some 1-methyl-5-alkenyl tosylates in 97% wt. trifluoroethanol

	$CD_3CH(OTs)R$	k_U/k_S [a]	k_H/k_D [b]
Compound	R		
26		–	1.37 (6)
25U-a		1.34	–
25U-b		1.37	–
25U-c		1.17	1.20 (5)
25U-d		10.1	1.16 (2)

[a] at 25 °C; k_u is the rate of 5-alkenyl chloride, k_s is the rate of corresponding alkyl chloride; ratios are for protio compounds. [b] at 50 °C; the uncertainty of the last reported figure (standard deviation of the mean) is shown in parentheses.

Kinetic measurement were also carried out in solvolysis of the corresponding secondary tosylates **25**. The most significant results are presented in Table IV.

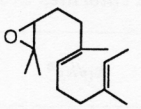
At first sight the trend in the solvolytic behaviour of the secondary substrates seems to be parallel with those of the tertiary ones. Again, there are no considerable rate effects (except possibly for substrate **25U-d**) and the magnitudes of the isotope effects are significantly lower than those of the saturated analogues. However, the isotope effects obtained for the referent substrate **26** (2-heptyl tosylate) correspond to the maximum excepted for rate determining ion-pair separation. The smaller β-d_3 effect for **25U-c** are consistent with a mechanism that involves rate-determining ionization or rate determining capture by the π-bond electrons after reversible ionization. Compound **25U-d** which shows a relative small β-d_3 isotope effect along with some rate acceleration apparently ionizes with participation.

We conclude that the magnitude of the β-deuterium secondary KIE are the most sensitive test of the neighboring group participation and details of reaction mechanism.

The final conclusion is that in monocyclization with compounds structurally related to **16U** and **22U** the formation of the (first) cyclohexane ring is indeed concerted with the formation of the carbocation (with the above mentioned exceptions).

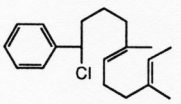
SUBSTRATES WITH TWO DOUBLE BONDS

There are several examples in the literature where 5,9-dienyl substrates show extensive bicyclization (two cyclohexane rings) in carbocationic reactions.[3,4] Thus, *e.g.* epoxide **27** in an ionogenic reaction gives bicyclic but no monocyclic products.[9]

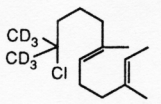


27

In a logical extension of our work, we investigated the kinetic behavior in solvolysis of **28**[33] and **29** (and its protio analogue).[34]



28



29

It should be pointed out that **28** reacts about 160 times faster than its saturated analogue.[35] The outstanding feature in solvolysis of **28** are the activation parameters. The moderate rate increase is due to a very low $\Delta H^{\#}$, which overcompensates a very negative $\Delta S^{\#}$. In fact, we do not know of a solvolysis reaction with such a low

$\Delta H^{\#}$ whose rate can be followed using conventional methods at conventional temperatures (Table V). Although activation parameters are not generally used as a criterion of the neighboring group participation, they are, in our opinion, significant in this particular case. Extended π-participation (involvement of both double bonds in the rate determining step) *i.e.* extended π-electron delocalization, should involve a lowering of $\Delta H^{\#}$. On the other hand, the presumed bicyclization requires a particular conformation of the ground state, which requires a relatively high degree of order and, therefore, a very negative $\Delta S^{\#}$. Confirmation of the extended π-participation in solvolysis of **28** has been obtained by the Noble *et al.*[36] by a different method.

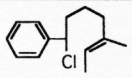
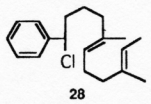
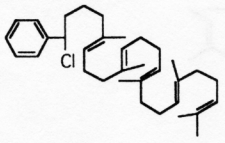
The solvolysis of **29** (protio analogue) should proceed by way of a carbocation similar to that in the reaction mentioned for **27** and **28**. No rate increase is observed relative to the saturated analogue. Again, however, activation parameters point to the possibility of extended π-participation (compare with **28**, Table V and VI). Secondary β-deuterium KIE are in agreement with this contention. While saturated reference compounds with two CD_3-groups at the reaction center react with a KIE of 1.80, the chloride with one double bond with KIE of 1.37, this value is unity for the substrate **29** with two double bonds! (Table VI). According to the above criteria, extended π-participation (two double bonds) seems a distinct possibility.

COMPOUNDS WITH SEVERAL DOUBLE BONDS

It has been mentioned that 1,2-epoxysqualene **1** in an ionogenic reaction yields tricyclic products (**1**→**2**). We have investigated the solvolysis kinetics of related com-

TABLE V

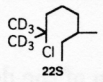
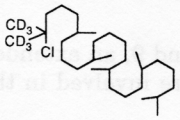
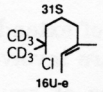
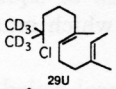
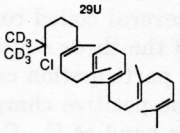
Relative solvolysis rates and activation parameters of some 1-phenyl-5-alkenyl chlorides in 80% (v/v) ethanol at 50 °C

Compound	k_U/k_S [a]	$\Delta H^{\#}$ [b] / kJmol^{-1}	$\Delta S^{\#}$ [b] / JK^{-1}mol^{-1}
 **16Uc**	16	72.3	–99.0
 **28**	166	36	–194. (12)
 **30**	16	65	–119 (21)

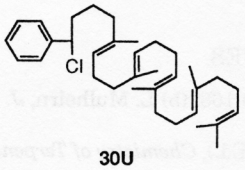
[a] k_U is the rate constant of the alkenyl chloride, k_s is the rate constant of the corresponding alkyl chloride.[34]
[b] values obtained from rate constants at three different temperatures.

TABLE VI

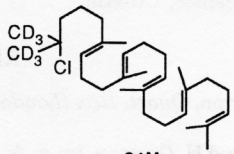
Relative solvolysis rates, secondary β-deuterium kinetic isotope effects, and activation parameters of some tertiary chlorides in 80% (v/v) ethanol

Compound	k_U/k_S [a]	k_H/k_D [b]	$\Delta H^{\#}$ [c] / kJmol^{-1}	$\Delta S^{\#}$ [c] / JK^{-1}mol^{-1}
 22S	–	1.80 (3)	88.9 (1.9)	–39.5 (6.3)
 31S	–	1.82 (4)	93.3 (2.10)	–30.5 (6.3)
 16U-e	16	1.37 (3)	77.6	–73.8
 29U	1.1	1.01 (4)	51.4	–117.5
 31U	0.75 1.6[d]	1.02 (1) 1.10 (3)d	97.9 (2.1) 83.7 (2.5)d	–17.6 (6.7) –33.9 (8.8)d

[a] k_U is the rate of unsaturated chloride, k_s *is the rate constant of the corresponding alkyl chloride; ratios are for protio compounds; at 25 °C;* [b] *at 50 °C; the uncertainty of the last reported figure (standard deviation of the mean) is shown in patentheses;* [c] *values obtained from rate constants at three different temperatures for protio compounds; uncertainties are standard deviations of the mean;* [d] *data obtained in TFE;*



30U



31U

pounds, *i.e.* **30**[37], the phenyl substituted analogues of squalene and its dimethyl substituted analogue **31U**.[38]

Chloride **30** reacts with a small rate acceleration similar to that of the chloride with one double bond (**16U**). Activation parameters do not allow any conclusion due to large experimental errors (**16U-c**, Table V). Nevertheless, by analogy, the solvolysis of **30** in this respect seems to be more similar to that of chloride **28** than that of chloride **16U-c**.

The kinetic results obtained in solvolysis of chloride **31U**, the substrate the most similar to **1**, and in the reaction resembling the biochemical and biomimetic trans-

formation of **1** are very instructive. First, no rate accelerations relative to the saturated analogue are observed. Second, the activation parameters are practically the same for the saturated and unsaturated compounds. However, the secondary β-deuterium KIE are enormouly reduced in magnitude (Table VI). Thus, KIE *again* are the only indication of an extended π-participation. According to this criterion, the participation of two or even three double bonds seems possible.

CONCLUDING REMARKS

1. In the reactions examined, the mechanism involves participation of the double bonds at C5 (with some exceptions).

2. In solvolysis of chlorides with double bonds at positions 5 and 9, an extended π-participation occurs (both double bonds of the aliphatic chain are involved in the rate determining step).

3. Chlorides with more than two double bonds solvolyze by way of extended π-participation. It remains unclear if two or even three double bonds are involved.

4. The results indicate (activation parameters) that derivatives of squalene (**31U**) polycyclize from a favorable prealigned (coiled) conformation, which must be present already in the ground state in polar solvents.

It should be mentioned that it is very likely that there are several coiled conformations of **31U**. However, it is not obvious that participation of the three double bonds must proceed from a unique coiled conformation. The later participation can be considered as an interaction between a carbonioum ion with the positive charge delocalized between C_1, C_5, C_6, C_9 and C_{10} and an aliphatic double bond at C_{13}-C_{14}. This represents a reaction between a very soft acid and the soft base which might not be sensitive to steric arrangements.

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SAŽETAK

Kinetički pristup mehanizmu kationske poliolefinske ciklizacije. Prosta i proširena π-participacija

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U ovom radu istraživan je mehanizam biomimetske olefinske kationske policiklizacije koristeći relativne efekte brzina, aktivacijske parametre, efekte supstituenata, σ,ρ-korelacije i sekundarne deuterijske kinetičke izotopne efekte (KIE) pri solvolizi tercijarnih i benzilnih supstrata koji sadrže jednu, dvije ili više dvostrukih veza koje su smještene u istim položajima

kao kod prirodnih supstrata (C-5, C-9, C-13). Kinetička mjerenja supstrata s dvostrukom vezom na položaju 5 (model za monociklizaciju), koji imaju strukturu **16U** i **22U**, pokazuju da je, uz neke iznimke (**16U** s *p*-OCH_3) nastajanje prvog cikloheksanskog prstena usklađen proces. Solvoliza klorida s dvostrukim vezana u položajima 5 i 9 (**28** i **29U**) odvija se uz proširenu π-participaciju, tj. obje dvostruke veze alifatskog lanca sudjeluju u stupnju koji određuje brzinu reakcije. Pri solvolizi supstrata s više od dvije dvostruke veze (**30** i **31U**) također dolazi do proširene π-participacije. Da li su obuhvaćene dvije ili tri dvostruke veze ostaje zasada nerazjašnjeno. Ovaj rad također jasno dokazuje da je vrijednost β-deuterijskog sekundarnog KIE najosjetljiviji test za utvrđivanje participacije susjedne skupine.