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Solvolytic Behaviour of a Primary Squalene Derivative

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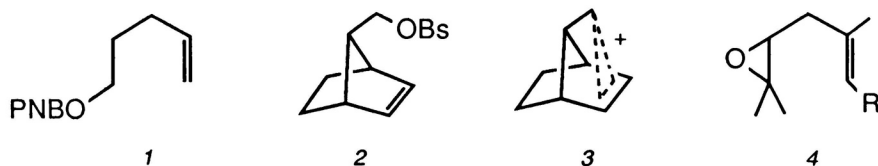
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Compounds **5** (4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenyl chloride and tosylate) were prepared starting from squalene and the solvolysis rates were measured in 80% (v/v) aqueous ethanol. α -Deuterium secondary kinetic isotope effects and activation parameters were calculated, and the products were determined. According to the values obtained ($k_H/k_D = 0.99 \pm 0.06$, $\Delta H^\ddagger = 86.6$ kJ mol⁻¹, $\Delta S^\ddagger = -69.3$ J mol⁻¹ K⁻¹) and on the basis of isolated aliphatic products (**11** and **14**) it is concluded that the substrate follows the S_N2 type displacement reaction with solvent without π -participation of the double bond.

INTRODUCTION

A remote CC double bond which is appropriately placed participates in solvolytic reactions and is therefore usually presumed to stabilize the resulting carbocation.¹ Assistance can result in enhancement of the solvolytic reactivity, in decreasing the secondary α - and β -deuterium kinetic isotope effects (KIE),² and in cyclic or rearranged products.³ There are many published results which support the suggestion that allylic and homoallylic double bonds take part in the rate determining step during solvolysis. Substrates with double bond at C-5 also often proceed by way of participation, forming six-membered rings.⁴ Thus, 5-hexenyl *p*-nitrobenzoate in acid catalyzed reactions shows a slight rate enhancement, also producing a cyclohexyl derivative.⁴

On the other hand, in most of the investigated cases there is no evidence of π -participation if the double bond is at C-4 relative to the leaving group in the substrate. For example, Bartlett⁴ demonstrated that under the same reaction conditions as with the previous substrate, 4-pentenyl *p*-nitrobenzoate (**1**) did not show a rate enhancement like its saturated analog and all the isolated products were uncyclized.

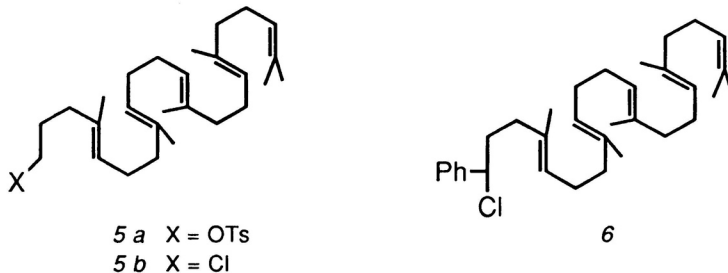


However, there are a few, rather ambiguous, results where π -participation cannot be excluded. Thus, Berson⁵ showed that even though there is an absence of anchimeric rate effects in acetolyses of brosylate 2, the formation of products can be rationalized only if carbonium ion 3 is considered, *i.e.* tricyclic products were isolated. van Tamelen⁶ investigated the biomimetic behavior of 2,3-epoxynorsqualene and found out that 10% of the products were cyclopentane derivatives. Even though the authors suggest that the process is very likely an S_N1 -like ring opening followed by interaction of the resulting carbenium ion with neighboring π -electrons, the result could also be rationalized as an assisted process.

On the basis of regioselectivity toward an oxidizing agent (NBS), van Tamelen⁷ postulated that squalene assumes a coiled conformation in polar solvents. In glyme-water, high selectivity occurred and exclusively terminal double bonds were converted into the bromohydrin (> 95%). Thus, we set out to investigate a possible interaction of the double bond at C-4 with the reaction center in a solvolytic reaction of a primary squalene derivative. Because of the coiled conformation of the substrates, the stereochemical requirements for participation might be fulfilled and the double bond could be located properly relative to the reaction center to make anchimeric assistance possible. In other words, such an open chain substrate could resemble in geometry the strained primary system 2. Substrates 5 (4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenyl chloride and tosylate) were prepared, and their solvolytic behavior was tested in highly polar aqueous ethanol.

RESULTS

Primary tosylate 5a, its α -deuterated analogue 5a-D, primary chloride 5b and the benzylic chloride 6 were prepared according to the Scheme, as described in detail in the Experimental Section.



The rates of solvolysis in 80% (v/v) aqueous ethanol were followed titrimetrically by means of a pH-stat. Typically, 0.05 mmol of the substrate was dissolved in 20 mL of the solvent thermostated to ± 0.05 °C and the libe-

rated acid titrated using a 0.008 M solution of sodium hydroxide in 80% aq. ethanol. Individual measurements followed strictly first-order kinetics up to at least 80% reaction and were repeated three to five times, and for isotope effect six times. First order rate constants were calculated with a nonlinear least-squares program. Activation parameters were calculated from rate constants at three different temperatures. Data obtained by kinetic measurements are presented in Table I.

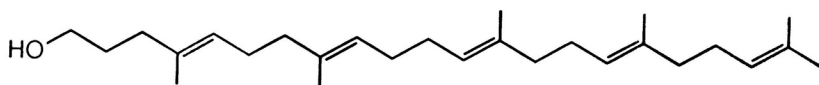
TABLE I

Solvolysis rates, secondary α -deuterium kinetic isotope effect, and activation parameters of tosylate 5a and chloride 6 in 80% aq. (v/v) ethanol^a

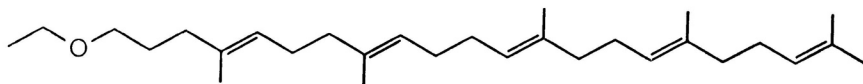
Compound	$t/^\circ\text{C}$	$k/10^{-5} \text{ s}^{-1}$	$k_{\text{H}}/k_{\text{D}}$	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$-\Delta S^\ddagger/\text{J mol}^{-1} \text{ K}^{-1}$
5a	70	10.6 ± 0.2	0.99 ± 0.06	86.6 ± 2.9	69.5 ± 7.9
	60	3.78 ± 0.10			
	50	1.48 ± 0.07			
	25 ^b	8.8×10^{-2}			
6	70	11.2 ± 0.2		68.2 ± 4.6	122.6 ± 13.4
	60	4.78 ± 0.28			
	50	2.39 ± 0.17			
	25 ^b	0.25			

^a Uncertainties are standard deviations; ^b extrapolated values.

In order to determine the products, the ethanolysis of chloride 5b was carried out and the products were isolated. On the basis of ¹³C and ¹H NMR, IR and mass spectra, structures were determined and it was found that the alicyclic alcohol 11 (4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol) and ether 14 (1-ethoxy-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaene) corresponding to the starting material were obtained.



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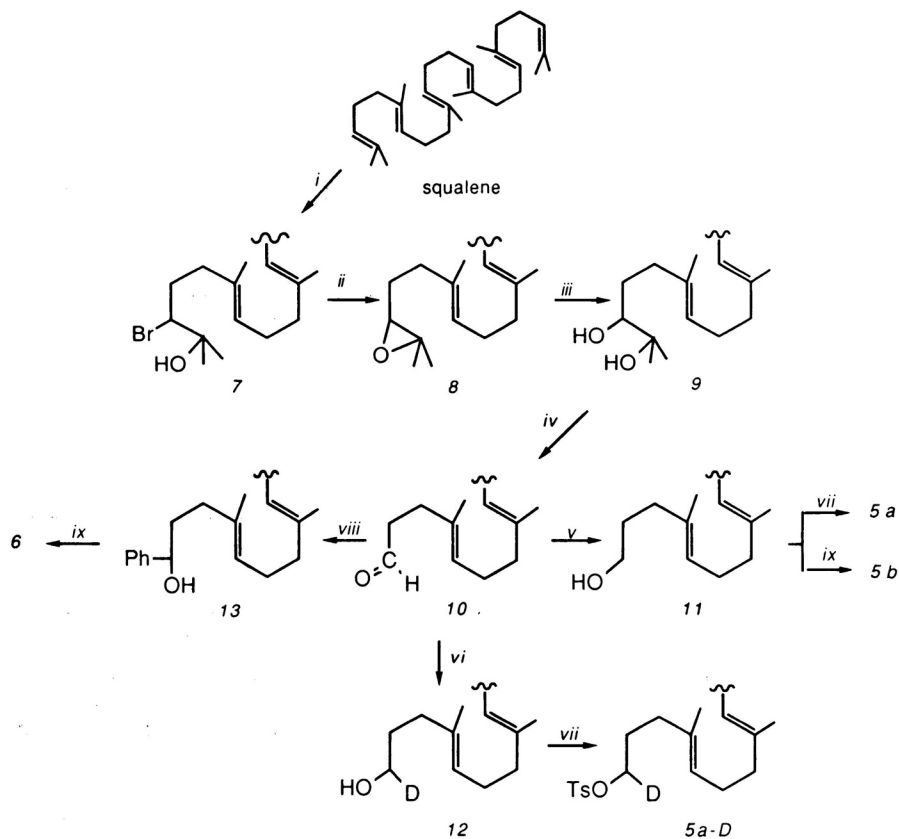


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EXPERIMENTAL

All substances listed below gave IR, ¹H and ¹³C NMR spectra consistent with their structure. Mass spectra were obtained when described in the procedure. Deuterium content was determined by means of mass spectrometry and found to be $\geq 99\%$.

SCHEME



i NBS, glyme-water; ii Na-iPrO, PrOH; iii HClO₄, glyme-water;
 iv Pb(OAc)₄, benzene; v LiAlH₄, ether; vi LiAlD₄, ether; vii TsCl,
 pyridine; viii PhMgBr, ether; ix SOCl₂;

2-Hydroxy-3-bromosqualene (7)

Squalene (20.0 g, 0.049 mol) was dissolved in 400 mL 1,2-dimethoxyethane (glyme) and water was added until the reaction mixture was slightly turbid (≈ 50 mL). *N*-Bromosuccinimide (10 g, 0.057 mol) was added and the reaction mixture was stirred at room temperature overnight. Then, glyme was evaporated, the organic layer separated, some water added and the product extracted three times with ether. Combined organic extracts were dried over anhydrous Na₂SO₄. Ether was evaporated, and the crude product was purified on a silica column by flash chromatography using methylene chloride — petroleum ether. The yield of the bromohydrin obtained was 5.6 g (22%).

2,3-Epoxyqualene (8)

Sodium (277 mg, 0.012 mol) was dissolved in isopropanol (≈ 70 mL) and added to the solution of 2-hydroxy-3-bromosqualene (5.6 g, 0.011 mol) in 30 mL isopropanol. The reaction mixture was stirred at room temperature for one hour. When the bromohydrin was completely converted into epoxide (followed by TLC), isopropanol was evaporated, 20 mL water was added to the residue, and the product extracted three times with ether. The combined ether layers were dried over anhydrous Na_2SO_4 . Ether was evaporated and the crude epoxide (3.5 g, 79%) was pure enough to be used in the next synthetic step.

2,3-Dihydroxysqualene (9)

2,3-Epoxyqualene (4.5 g, 0.010 mol) was dissolved in glyme-water (9:1), and 1 mL HClO_4 (w = 60%) was added. The reaction mixture was stirred for half an hour at room temperature. When the epoxide was completely converted into diol (checked with TLC), glyme was evaporated, some water was added and the product was extracted three times with ether. Ether layers were combined, washed with a saturated solution of NaHSO_4 , brine, and dried over anhydrous Na_2SO_4 . Ether was evaporated, and the crude product was purified on a silica column. Impurities were removed with methylene chloride and the pure diol with ether. Evaporation of the pooled fractions yielded 4.2 g (85%) of the pure product.

4,8,13,17,21-Pentamethyl-4,8,12,16,20-docosapentaenol (10)

In 100 mL of anhydrous benzene 11.9 g (0.026 mol) 2,3-dihydroxysqualene was dissolved. Lead tetraacetate (22.1 g, 0.057 mol) was dissolved in dry benzene and added dropwise into the stirred reaction mixture at room temperature. When tetraacetate is added the reaction is completed. The reaction mixture is then filtered to remove yellow crystals (lead diacetate) formed during the reaction. Water was added into the benzene solution to destroy the excess of lead tetraacetate. The two phase system was filtered again, the layers were separated and the benzene layer was washed with brine and dried over anhydrous Na_2SO_4 . Benzene was evaporated and the crude product was transferred onto a silica column, and eluted with methylene chloride. The yield of pure aldehyde was 8.6 g (80%).

4,8,13,17,21-Pentamethyl-4,8,12,16,20-docosapentaenol (11)

Into a stirred solution of LiAlH_4 (1.18 g, 16.0 mmol) in 80 mL of dry ether, an ether solution (40 mL) of 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol (12.0 g, 0.031 mol) was added dropwise at such a rate as to keep the reaction mixture refluxing. When the aldehyde was completely added, refluxing and stirring of the reaction mixture was continued for one hour. After completion of the reduction (checked with TLC) the reaction mixture was cooled with ice water, and the excess hydride was decomposed with gradual addition of water. The precipitate was collected by filtration, washed with ether, which was added to the filtrate, and dried over anhydrous Na_2SO_4 . Ether was evaporated, and the crude product was purified on silica column. Impurities were removed with methylene chloride and the pure product with ether. The yield of pure alcohol ($M^+ = 386$) was 10.0 g (83%).

4,8,13,17,21-Pentamethyl-4,8,12,16,20-docosapentaenol-1-d₁ (12)

The procedure for the deuterated alcohol is the same as described above. From 5 g (13.0 mmol) 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol and 280 mg (6.66 mmol) LiAlD_4 4.2 g (83%) pure deuterated alcohol was obtained ($M^+ = 387$).

1-Phenyl-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol (13)

Into a three necked flask magnesium (200 mg, 8.33 mmol) and a crystal of iodine was added. The flask was slightly heated. Dry ether was added to cover

the magnesium, and 2-3 drops of bromobenzene were added. The reaction mixture was heated and stirred. When the color caused by iodine disappeared, the solution of bromobenzene (0.6 g, 3.77 mmol) in 20 ml. of dry ether was added dropwise. Then, the reaction mixture was refluxed for one hour. The Grignard reagent was obtained, cooled with ice water, and the solution of 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenal (1.0 g, 2.6 mmol) in 20 mL of dry ether was added dropwise. The reaction mixture was then stirred for one hour at room temperature. Water was added, and the product extracted with ether. Combined ether layers were washed with brine, and dried over anhydrous Na_2SO_4 . Ether was evaporated, and the product was purified by preparative TLC with methylene chloride. The yield was 168 mg (14%).

1-Chloro-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaene (5b)

In 5 mL of hexane, 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol (964 mg, 2.50 mmol) and pyridine (240 mg, 3.00 mmol) were dissolved. The solution was cooled to -10°C and thionyl chloride (328 mg, 2.75 mmol) was added dropwise. During the reaction, a white precipitate of pyridinium hydrochloride formed. After one hour, the alcohol was completely converted into dialkyl sulphite ($M^+ = 818$). The dialkyl sulphite solution was filtered and thionyl chloride (190 mg, 1.0 mmol) was added. The reaction mixture was heated and refluxed for two hours. When the dialkyl sulphite disappeared (checked with TLC), hexane was evaporated, and the crude chloride was purified by preparative TLC with methylene chloride — hexane (1:1). The yield of the pure chloride ($M^+ = 444$) was 430 mg (42%).

4,8,13,17,21-Pentamethyl-4,8,12,16,20-docosapentaenyl tosylate (5a)

To 4 mL of pyridine, 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol (282 mg, 0.73 mmol) and *p*-toluenesulphonyl chloride (181 mg, 0.80 mmol) were added. The solution was left for 15 hours at -15°C . The reaction was then poured onto ice, and extracted three times with ether. Combined ether solutions were washed with NaHSO_4 , brine, and dried over anhydrous Na_2SO_4 . The yield of the crude product, pure enough for kinetic measurements, was 263 mg (49%).

4,8,13,17,21-Pentamethyl-4,8,12,16,20-docosapentaenyl-1- d_1 tosylate (5a-D)

The procedure for deuterated tosylate is the same as described above. From 203 mg (0.52 mmol) 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol-1- d_1 and 130 mg (0.58 mmol) *p*-toluenesulphonyl chloride, the yield of crude product was 230 mg (30%).

1-Phenyl-1-chloro-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaene (6)

In 5 mL of petroleum ether, 1-phenyl-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol (168 mg, 0.36 mmol) was dissolved, cooled to -10°C , and thionyl chloride (42 mg, 0.35 mmol) was added. The reaction mixture was stirred under reduced pressure (≈ 800 – 880 mbar) for one hour. The solvent was then evaporated and the crude product was pure enough for measurements.

Product identification

In 500 mL aqueous ethanol ($\psi = 60\%$), 1-chloro-4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaene (380 mg, 0.94 mmol), and 2,4,6-trimethylpyridine (collidine) (105 mg, 0.094 mmol) were dissolved. The reaction mixture was refluxed for 48 hours then cooled and extracted three times with pentane. The combined pentane extracts were washed with 0.01 M HCl, with a saturated solution of NaHSO_4 and dried over anhydrous MgSO_4 . Pentane was then evaporated, and the products were separated by preparative TLC. The solvent was methylene chloride-hexane (2:1). Aliphatic ether (30 mg), 1-ethoxy-4,8,13,17,21-pentamethyl-

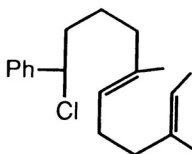
-4,8,12,16,20-docosapentaene 14 and alcohol (48 mg) 4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol 11 were isolated.

(14: MS 81, 95, 109, 111, 121, 123, 135, 136, 137, 141, 147, 149, 163, 203, 299, 343 and 414; ^1H NMR (CDCl_3) 1.25 t, 1.59—1.72 m, 1.87—2.08 m, 3.37 t, 3.46 q, and 5.08—5.14 m; ^{13}C NMR (CDCl_3) 15.26, 15.91, 16.01, 16.04, 17.68, 25.70, 26.66, 26.69, 26.79, 28.04, 28.29, 36.06, 39.75, 66.07, 70.32, 124.30, 124.32, 124.36, 124.43, 124.52, 134.42, and 135.34)

(11: MS 68, 81, 95, 107, 109, 113, 121, 136, 136, 137, 149, 163, 203, 205, 231, 317, 343, and 386; ^1H NMR (CDCl_3) 1.58—1.72 m, 1.85—2.10 m, 3.49 t, and 5.08—5.15 m; ^{13}C NMR (CDCl_3) 16.01, 16.06, 17.68, 25.70, 26.59, 26.69, 26.79, 28.27, 30.76, 36.03, 39.69, 39.75, 39.77, 62.86, 124.30, 124.43, 124.87, 135.16)

DISCUSSION

One of the common criteria for establishing π -participation in solvolysis is an increased reaction rate relative to that of the reference compound, *i.e.* calculating the k_u/k_s ratio (k_u = rate constant of the unsaturated substrate, k_s = rate constant of the saturated analogue). Whenever a large rate effect is observed, it can be taken as a proof of neighboring group participation, but small or even inverse effects can conceal considerable assistance, so other methods should be employed to provide credible information about the reaction mechanism.⁸ It is known that the enlargement of the side chain of substrates in solvolytic reactions influences the rate constant in such a way as to decrease it with increasing size of the alkyl group.⁹ Comparing the observed rate constants of tosylate 5a with the solvolysis rate of methyl tosylate¹⁰ in 80% ethanol ($k_{50\%C} = 1.48 \times 10^{-5} \text{ s}^{-1}$ vs $2.25 \times 10^{-5} \text{ s}^{-1}$) and having in mind the former fact, no rate enhancement caused by the presence of the double bond can be observed.



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Activation parameters should be consistent with the proposed mechanism. In reactions that proceed by way of participation, a high degree of order is required in the transition state because of restricted rotation around single bonds, and the net effect is a large negative entropy of activation (ΔS^\ddagger). On the other hand, charge delocalization in the transition state reduces the enthalpy of activation (ΔH^\ddagger). These effects could be illustrated in the case of ethanolysis of benzyl chloride 15 where, on the basis of activation parameters ($\Delta H^\ddagger = 36 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -195 \text{ J mol}^{-1} \text{ K}^{-1}$), extended π -participation was suggested,¹¹ and was later confirmed by activation volumes in a reaction of the same substrate.¹² However, in $\text{S}_\text{N}2$ type reactions, compared with $\text{S}_\text{N}1$ process, activation parameters are changed in the same direction as for the assisted mechanism, *i.e.* a slight reduction of a ΔH^\ddagger and an increase of $-\Delta S^\ddagger$.¹³ Substrates 5 are primary and the alternative to an assisted mechanism is $\text{S}_\text{N}2$. In order to compare the data for activation parameters, the benzylic chloride 6 was prepared, which is also a squalene

derivative with a double bond at C-4. Reference 6 is suitable because it can solvolyze by way of participation of the double bond/s, or form a benzylic carbocation in the rate determining step of ethanolysis, but it cannot react by way of an S_N2 mechanism. In addition, if the assisted process is operative, activation parameters may be very indicative, like in the case of benzylic chloride 15.

In our previous work, we reported rate constants and activation parameters of a series of saturated chlorides and tosylates which can be used as references for establishing neighboring group participation.⁹ These data were taken into consideration to rationalize the activation parameters of the investigated substrates 5, and 6, and are presented in Table II.

TABLE II
Activation parameters in solvolysis of 5a, 6 and their reference compounds

Substrate	$\Delta H^\ddagger/\text{kJ mol}^{-1}$	$-\Delta S^\ddagger/\text{J mol}^{-1} \text{K}^{-1}$
5a	86.6 ± 2.9	69.5 ± 7.9
16 ^a	93.9 ± 2.2	28.7 ± 6.7
6	68.2 ± 4.6	122.6 ± 13.4
17 ^b	99.5 ± 2.0	22.7 ± 6.1

^a 2-hydroxysqualane; ^b 1-phenyl-1-chloroheptadecane

From Table II it is very obvious that chloride 6 and the saturated benzylic chloride 17 do not solvolyze in the same manner. A drastic increase in negative ΔS^\ddagger (from 22.7 to 122 $\text{J mol}^{-1} \text{K}^{-1}$) and a decrease of ΔH^\ddagger (from 99.5 to 68.2 kJ mol^{-1}) in the case of 6 can be caused only by neighboring π -electrons, *i.e.* participation is tentatively proposed in our previous work, a linear relationship between rate constants and the number of carbon atoms of the side chain was demonstrated and an equation was presented which makes it possible to account for the rate constant of a reference saturated analogue.⁹ These calculations were carried out and $k_u/k_s = 2.5$ was obtained. Lack of rate enhancement cannot prove the results obtained by rationalizing the activation parameters, but it has been shown that even inverse effects cannot be taken as a proof of lack of participation.

It is also obvious from Table II that in the case of tosylate 5a such a dramatic change in activation parameters compared with its reference compound does not exist. Reference compound 17 follows the S_N1 type reaction in 80% (v/v) ethanol, so that decreasing of the $-\Delta S^\ddagger$ for 5 could be rationalized either as an S_N2 process, or as π -participation where only a small amount of substrate reacts by way of the k_A process (k_A = rate constant of assisted reaction), but the larger part follows the S_N2 displacement reaction.

Secondary deuterium KIE are very sensitive probes for neighboring group participation.² Unfortunately, the value obtained for the secondary α -effect ($k_H/k_D = 0.99 \pm 0.06$) cannot be interpreted unequivocally. Small or inverse secondary KIE are typical for S_N2 displacement reactions,¹⁴ but also a considerable decrease in the effect is observed in assisted reactions, for they can be interpreted as intramolecular S_N2 processes. Anyhow, due to

the lack of rate and secondary KIE, as well as the activation parameters, it is more likely that substrate 5a follows the S_N2 type displacement reaction. To test this conclusion, chloride 5b was subjected to ethanolysis and the products were isolated. Only noncyclic products, ether 14, and alcohol 11, were found. With that additional data, it is clear that, although the coiling of the substrate in polar ethanol-water might occur, it does not assume the conformation that favours participation of the double bonds during solvolysis, and that the primary substrates 5 react with solvent in a concerted displacement reaction (S_N2).

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SAŽETAK

Solvolitička svojstva primarnog derivata skvalena

Olga Kronja, Stanko Borčić, Krešimir Humski i Christopher S. Foote

Polazeći od skvalena, pripremljeni su spojevi 5 (4,8,13,17,21-pentametil-4,8,12,16,20-dokosapentaenil-klorid i -tosilat), te su izmjerene konstante brzine reakcije u 80% (v/v) vodenom etanolu. Izračunani su sekundarni α -deuterijski kinetički izotopni efekt i aktivacijski parametri, te su određeni produkti solvolize (11 i 14). Iz dobivenih podataka ($k_H/k_D = 0.99 \pm 0.06$, $\Delta H^\ddagger = 86.6 \text{ kJ mol}^{-1}$, $\Delta S^\ddagger = -69.3 \text{ J mol}^{-1} \text{ K}^{-1}$) slijedi da supstrat solvolizira po S_N2 tipu reakcije bez π -participacije dvostruke veze.