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Extended π-Participation in Biomimetic Cyclization of Squalene Derivatives†

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Chlorides **4** (1-aryl-1-chloro-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenes) with various phenyl substituents were prepared, and solvolysis rates were measured in aqueous ethanol (φ = 95% and 80%) and in aqueous 2,2,2-trifluoroethanol (w = 97%). Hammett ρ^+ values obtained are –1.86, –1.81 and –1.56, respectively, suggesting concerted cyclization of at least two double bonds in the rate determining step.

INTRODUCTION

Steroid hormones and polycyclic triterpenes arise in nature from 2,3-epoxysqualene in enzymatic polycyclization reactions.[1] The first step is the epoxy-ring opening, followed by nucleophilic attack of the double bonds. A great deal of work has been done to clarify the role of the enzymes in these highly stereospecific reactions, and also to find out whether and to what extent nature can be imitated. Van Tamelen *et al.*[2] demonstrated that biomimetic conditions can be used to rationalize the formation of the first three rings, since the epoxyde-ring opening of the 2,3-epoxysqualene, initiated with Lewis acid, produced tricyclic products. Investigations of the biomimetic polycyclization reactions led to the development of elegant synthetic methods for the preparation of stereospecifically fused rings.[3–6] However, the mechanism of polycyclization has not yet been completely clarified. The main question, whether cyclization occurs in a stepwise or concerted manner, is still unsolved. It is not certain whether the final product arises

† Dedicated to the memory of Professor Stanko Borčić.

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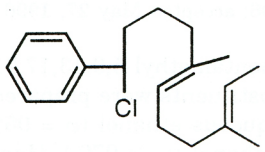
by way of formation of an initial carbenium ion intermediate, which then cyclizes in a stepwise manner through discrete partially cyclized intermediates, whether only the formation of the first ring is concerted with the departure of the leaving group, or whether the whole polycyclization process is concerted, *i.e.* whether extended π-participation occurs.

In chemical literature there is evidence for both concerted and stepwise mechanisms. Of the two pioneers in this field, Johnson[4] considered that the concerted mechanism is possible, while van Tamelen[6,7] stated that only monocyclization might be a concerted process, and further cyclization should be stepwise.

Borčić *et al.* used a kinetic approach to investigate the mechanism of olefinic cyclizations. They showed unambiguously that the formation of the first ring is a concerted process.[9,10]



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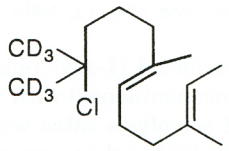

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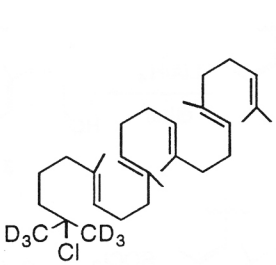
Investigation of the model substrates **1** and **2**, with two appropriately located double bonds, demonstrated that extended π-participation is operative.[11,12] Rather unusual values for activation parameters were obtained in solvolysis of chloride **1** ($\Delta H^{\#}$ = 36 ± 4 kJ mol^{-1} and $\Delta S^{\#}$ = −195 ± 12 J K^{-1} mol^{-1}). These values were considered to be consistent with the extended π-participation mechanism, in which the high degree of order, which is required in the transition state (unfavourable change in $\Delta S^{\#}$), is overcompensated by a rather small $\Delta H^{\#}$.[11] The proposed extended π-participation mechanism in solvolysis of **1** was supported by Le Noble *et al.*[13] on the basis of the activation volumes of the same reaction. A very sensitive probe for proving the existence of the neighbouring group participation is the reduced secondary β-deuterium kinetic isotope effect (KIE). In the solvolysis reaction with the saturated analog of **2**, the KIE was found to be k_H/k_D = 1.80 ± 0.03; with the corresponding reactant with one double bond, the effect was considerably reduced (k_H/k_D = 1.37 ± 0.03). However, under the same conditions (aqueous ethanol, φ = 80%; 80E), chloride **2** solvolyzed without a significant β-deuterium KIE (k_H/k_D = 1.01 ± 0.04), indicating extended π-participation of both double bonds in the rate determining step.

The β-deuterium KIE obtained with chloride **3**, a substrate directly related to the natural precursor, also suggested that at least two double bonds take part in the rate determining step.[14] However, even though the absence of the effect (k_H/k_D = 1.02 ± 0.01) strongly supported the extended π-partici-

pation mechanism, neither an enhancement of the reaction rate of the unsaturated substrate compared with the saturated analog (k_U/k_S), nor the activation parameters supported extended π-participation.



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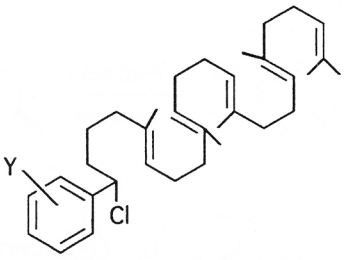

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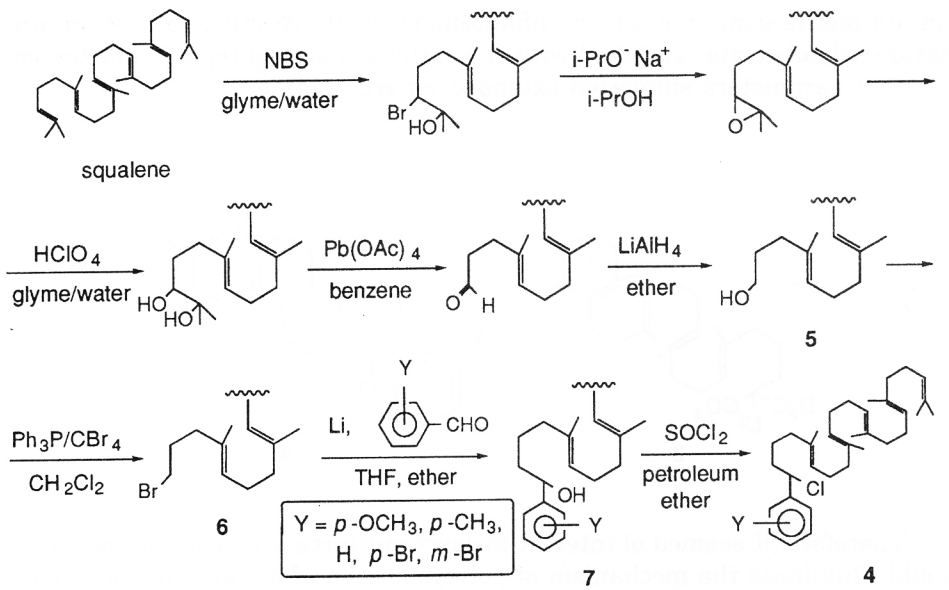
Therefore, it seemed of interest to carry out further investigations which could illuminate the mechanism of polycyclization of a substrate closely related to the natural precursor under biomimetic conditions. We have chosen to investigate the solvolytic behaviour of aryl derivatives of **3**, chlorides **4**. We pointed out in the preliminary communication[15] that only a moderate rate enhancement (k_U/k_S = 15.8 in 80E at 25 °C) was observed with substrate **4** with Y = H, which cannot be taken as a proof of extended π-participation. The magnitudes of the activation parameters do not support the concerted bicyclization either. We expected that the Hammett ρ^+ values for chlorides **4**, with various substituents on the phenyl ring, would provide some new information which would unambiguously prove or disprove the proposed concerted mechanism in the biomimetic polyene cyclization. Thus, in this paper we would like to report some important results obtained in the solvolysis of chlorides **4**.

RESULTS

The series of chlorides **4** with variously substituted phenyl rings were prepared by reaction of the parent alcohols **7** with thionyl chloride. The alcohols were prepared according to the Scheme 1.[16] Procedures are described in detail in the Experimental section. Preparation of the organolithium compound from bromide **6** was carried out in an ultrasonic bath. This was followed by addition of the corresponding benzaldehyde at 0 °C.

Chlorides **4** were subjected to solvolysis in aqueous ethanol, φ = 80% and 95% (80E and 95E, respectively), and in aqueous 2,2,2-trifluoroethanol, w = 97% (97T). Reaction rates were followed by titration of the liberated acid with an automatic pH-state. Activation parameters were calculated from



Scheme 1.

rate constants determined at three different temperatures. Data obtained by kinetic measurements are presented in Table I. Hammett ρ^+ values were calculated using the simple regression analysis. Regression lines for reactions in all three solvents are shown in Figure 1. Also, the calculated ρ^+ values for the chlorides **4**, as well as for some reference benzylic chlorides (**8** and **9**) are presented in Table II.

EXPERIMENTAL

Substrate Preparation

Primary alcohol **5** (4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol) was prepared according to the Scheme 1 using the procedures already published.[16]

In all cases, carbon and proton NMR spectra as well as IR spectra are consistent with the expected structure of the product.

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

Into a stirred solution of primary alcohol **5** (4,8,13,17,21-pentamethyl-4,8,12,16,20-docosapentaenol, 10.5 g, 27.16 mmol) and carbon tetrabromide (11.71 g, 35.31 mmol) in 100 mL of anhydrous methylene chloride, a solution of triphenylphosphine (8.55 g, 32.60 mmol) in 50 mL of the same solvent was added dropwise at room temperature. After the addition was completed, refluxing and stirring of the reaction mixture was continued

TABLE I

Solvolysis rate constants and activation parameters for 1-aryl-1-chloro-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaens (**4**)

Compound [a]	Solvent [b]	t/°C	$k/10^{-5}$ s^{-1} [c]	$\Delta H^{\#}$/kJ mol^{-1} [d]	$-\Delta S^{\#}$/J K^{-1} mol^{-1} [d]
4-*p*-OCH_3	95E	50	61.9 ± 0.9	85 ± 2	44 ± 6
		40	21.0 ± 0.7		
		30	7.18 ± 0.08		
		25	3.96		
	80E	50	264 ± 8	70 ± 1	79 ± 3
		40	114 ± 5		
		30	44.7 ± 0.6		
		25	27.8		
	97T	25	240 ± 9		
4-*p*-CH_3	95E	60	14.7 ± 0.4	84 ± 3	66 ± 10
		50	5.22 ± 0.06		
		40	1.97 ± 0.05		
		25	0.360		
	80E	60	94.8 ± 0.7	76 ± 3	75 ± 9
		50	36.9 ± 0.3		
		40	15.3 ± 0.9		
		25	3.27		
	97T	50	577 ± 8	72 ± 12	67 ± 38
		40	185 ± 3		
		30	92.5 ± 0.8		
		25	52.1		
4-H	95E	70	14.1 ± 0.1	88	63
		60	5.42 ± 0.07		
		25	0.116		
	80E	70	73.0 ± 0.5	77 ± 16	82 ± 46
		60	23.5 ± 0.3		
		50	12.8 ± 0.5		
		25	0.966		
	97T	50	164 ± 3	68 ± 11	90 ± 36
		40	56.0 ± 0.6		
		30	29.1 ± 0.3		
		25	16.9		
4-*p*-Br	95E	70	10.5 ± 0.4	92	54
		60	3.87 ± 0.09		
		25	0.070		

TABLE I

(Continued)

Compound[a]	Solvent[b]	t/°C	$k/10^{-5}$ s^{-1} [c]	$\Delta H^{\#}$/kJ mol^{-1} [d]	$-\Delta S^{\#}$/J K^{-1} mol^{-1} [d]
4-*p*-Br	80E	70	35.9 ± 0.7	77 ± 12	87 ± 35
		60	12.4 ± 0.4		
		50	6.3 ± 0.1		
		25	0.486		
	97T	50	107 ± 2	73 ± 6	77 ± 19
		40	38.3 ± 0.4		
		30	16.7 ± 0.5		
		25	9.70		
4-*m*-Br	95E	25	0.0229		
	80E	70	23.3 ± 0.7	87 ± 1	62 ± 3
		60	9.21 ± 0.04		
		50	3.33 ± 0.07		
		25	0.205		
	97T	60	106 ± 3	79 ± 1	66 ± 1
		50	42.6 ± 0.7		
		40	16.1 ± 0.6		
		25	3.33		

[a] Substituents on the phenyl ring.

[b] 95E and 80E are aqueous ethanol (φ = 95% and 80%) respectively, and 97T is aqueous 2,2,2-trifluoroethanol (w = 97%).

[c] Uncertainties are standard errors. The rate constants lacking standard errors are extrapolated values.

[d] Uncertainties are standard deviations.

for 2–3 hours. After completion of the reaction (checked with TLC), petroleum ether was added into the reaction mixture and after decantation the volatiles were evaporated. The crude product was purified on silica column. Nonpolar product **6** was eluated with petroleum ether (R_f = 0.9). The yield of pure bromide was 8.82 g (72.2%).

*1-Phenyl-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenol (**7**-H)*

Lithium powder (50 mg, 7.2 mmol), granulated lithium (250 mg, 36 mmol), dry THF (20 mL) and dry *n*-hexane (10 mL) were placed in a three necked flask fitted with a magnetic stirrer, dropping funnel and reflux condenser with a drying tube at the top, under a slow stream of argon. The flask was placed in an ultrasonic bath (100 W, 30 KHz) and the reaction mixture was stirred for about one hour at room temperature. Then, a solution of bromide **6** (1.5 g, 3.34 mmol) in 15 mL of dry ether was added dropwise to the stirred mixture, which was then, in turns, stirred with the magnetic stirrer and the ultrasonic bath. Ultimately, the ultrasonic stirring was

used exclusively during the last 3–4 hours. During that period, the colour of the lithium surface changed from dull matt to a golden silvery sheen. The organolithium reagent obtained was then cooled in ice water bath and the solution of benzaldehyde (0.295 g, 2.78 mmol) in 15 mL of dry ether was added dropwise. The reaction mixture was then stirred for additional one hour at room temperature. The progress of the reaction was checked with TLC.

The excess lithium was filtered off, and the solvent was evaporated. The residue was hydrolyzed with a saturated aqueous solution of NH_4Cl and alcohol **7** was extracted with ether. Ether layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. The ether was evaporated and the product was purified on a silica column. Unreacted bromide was removed with petroleum ether, other impurities were removed with petroleum ether/methylene chloride mixture (4 : 1) and the pure alcohol was eluated with petroleum ether/methylene chloride mixture (1 : 1). Evaporation of the pooled alcohol containing fractions yielded 210 mg (13.2%) of the pure product.

*1-(4-methoxyphenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenol (***7**-p-OCH_3*)*

The procedure is the same as described above. From 50 mg (7.2 mmol) of lithium powder, 250 mg (36 mmol) of granulated lithium, 1.2 g (2.67 mmol) of bromide **6** and 0.303 g (2.22 mmol) of anisaldehyde, 75.9 mg (5.6%) of pure alcohol was obtained.

*1-(4-methylphenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenol (***7**-p-CH_3*)*

The procedure is the same as described above. From 50 mg (7.2 mmol) of lithium powder, 250 mg (36 mmol) of granulated lithium, 1.2 g (2.67 mmol) of bromide **6** and 0.267 g (2.22 mmol) of *p*-toluylaldehyde, 160 mg (12.2%) of pure alcohol was obtained.

*1-(4-bromophenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenol (***7**-p-*Br)*

The procedure is the same as described above. From 100 mg (14.4 mmol) of lithium powder, 500 mg (72 mmol) of granulated lithium, 1.2 g (2.67 mmol) of bromide **6** and 0.412 g (2.22 mmol) of 4-bromobenzaldehyde, 98.7 mg (6.7%) of pure alcohol was obtained.

*1-(3-bromophenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaenol (***7**-m-*Br)*

The procedure is the same as described above. From 50 mg (7.2 mmol) of lithium powder, 250 mg (36 mmol) of granulated lithium, 0.8 g (1.78 mmol) of bromide **6** and 0.274 g (1.48 mmol) of 3-bromobenzaldehyde, 103.5 mg (10.5%) of pure alcohol was obtained.

Chlorides ***4***

(1-chloro-1-phenyl-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaene, **4**-H, 1-chloro-1-(4-methoxyphenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaene, **4**-*p*-OCH_3, 1-chloro-1-(4-methylphenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaene, 4-*p*-CH_3, 1-chloro-1-(4-bromophenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaene, **4**-*p*-Br and 1-chloro-1-(3-bromophenyl)-5,9,14,18,22-pentamethyl-5,9,13,17,21-tricosapentaene, **4**-*m*-Br, respectively) were prepared from the corresponding alcohols **7** and thionyl chloride.

The appropriate alcohol **7** was dissolved in 10–15 mL of petroleum ether (b.p. 50–60 °C), the solution was cooled to –10 °C, and thionyl chloride was added drop-

wise. The reaction mixture was stirred for two hours under reduced pressure (about 520–560 mmHg, 693–747 mbar) to remove the liberated hydrogen chloride and sulphur dioxide continuously. Then, the petroleum ether was evaporated and crude chloride **4** was used for kinetic measurements. Further purifications proved to be unnecessary since the solvolysis rates were found to be independent of contamination.

Kinetic Measurements

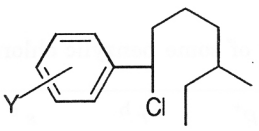
Solvolysis rates were followed in aqueous ethanol, φ = 80% and 95% (80E and 95E, respectively) and aqueous 2,2,2-trifluoroethanol, w = 97% (97T) titrimetrically by means of a pH-stat. Typically, 0.01 mmol of the substrate was dissolved in 20 mL of the solvent at the required temperature thermostated ±0.05 °C, and the liberated hydrochloric acid was continuously titrated by using a 0.004 M solution of sodium hydroxide in the same solvent mixture. Individual measurements could be decribed by the first-order low from 15% up to at least 80% completion. First order rate constants were calculated from about 100 determinations by using a nonlinear least-squares program. Measurements were usually repeated 3–7 times. Activation parameters were calculated from rate constants at three different temperatures.

DISCUSSION

The results presented in Table I and Table II show some extraordinary features. The rate constants in all three solvents correlate well with σ^+ constants as it is shown in Table II and in Figure 1. It is also very obvious that the negative ρ^+ values are extremely low. Such small ρ^+ values could suggest that the leaving group is displaced by the solvent in the rate determining step.[17] However, the ρ^+ values obtained in three different solvents are essentially the same. This observation shows that the direct displacement by the solvent (S_N2) does not represent a major reaction pathway.

Most of the information concerning the mechanism of a reaction obtained from linear free energy relationship (LFER)[18] comes from the interpretation of the reaction constant, ρ. The magnitude of the Hammett ρ value is generally used as a measure of the charge »seen« by the aromatic ring at the reaction centre.[19] The ρ value can be also interpreted in terms of electron demand,[20] and charge delocalization.[21] Even though the ρ value can be rationalized in different terms, the comparison of a ρ value with those generated by related substrates, which have only minor differences in the structure, can be decisive for choosing the right reaction mechanism. For establishing the possible extended π-participation, we found it very useful to compare the ρ^+ values for **4** with the published results for the related chlorides **8** and **9**.[9] Chlorides **8** are without the neighbouring double bonds, while in chlorides **9** only one double bond exists and can take part in the rate determining step.

If π-participation of the neighbouring double bond(s) occurs, it ultimately leads to charge delocalization on the reaction centre. Thus, a lower negative



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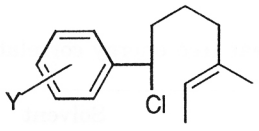

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ρ^+ value demonstrates that positive charge is delocalized from the reaction centre. In the case of chlorides **9**, for all substituents but the *p*-methoxy group, the ρ^+ value obtained is considerably lower than ρ^+ for the saturated chlorides **8** (–3.93 *vs.* –6.28). In the case of *p*-anisyl, the participation of the neighbouring double bond is eliminated by the strongly electron donating *p*-methoxy substituent. Both, the coefficient of correlation (r) and the statistical test (Ψ) demonstrate that a worse fit is obtained if the *p*-methoxy variant of **9** was included in a correlation (Table II). Therefore, in the case of substrates **9**, a breakdown of the linear relation occurs, as shown in Figure 2, suggesting that the k_Δ (assisted) process is the major reaction pathway for all the variants except the *p*-methoxy substrate. Therefore, the π-participation mechanism is operative for all cases except for *p*-methoxy, which uses the k_c (unassisted process) mechanism. The ability of the *p*-anisyl group to

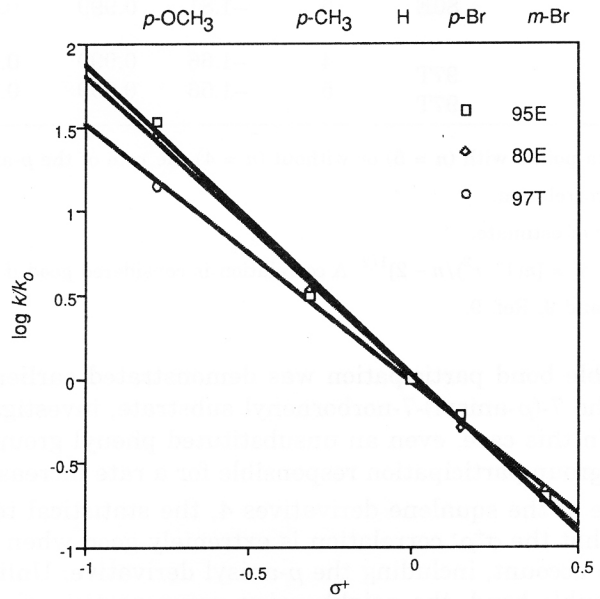
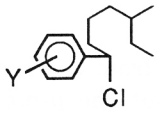
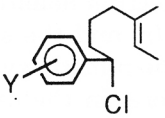
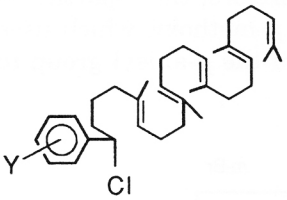


Figure 1. $\sigma^+\rho^+$ plots for chlorides **4** in three different solvents (95E and 80E are aqueous ethanol, φ = 95% and 80% respectively, and 97T is aqueous 2,2,2-trifluoroethanol, w = 97%).

TABLE II

Linear free energy correlation at 25 °C of some benzylic chlorides

Compound	Solvent	n [a]	ρ^+	r [b]	s [c]	Ψ [d]
 **8** [e]	97T	5	–6.28	0.997	0.25	0.100
 **9** [e]	97T	4	–3.93	0.998	0.10	0.089
		5	–4.76	0.992	0.31	0.163
 **4**	95E	4	–1.66	0.998	0.03	0.089
	95E	5	–1.86	0.997	0.08	0.100
	80E	4	–1.70	0.999	0.03	0.063
	80E	5	–1.81	0.999	0.05	0.058
	97T	4	–1.66	0.999	0.02	0.063
	97T	5	–1.56	0.999	0.04	0.058

[a] Number of data points with (n = 5) or without (n = 4) the rate of the p-anisyl derivative.

[b] Coefficient of correlation.

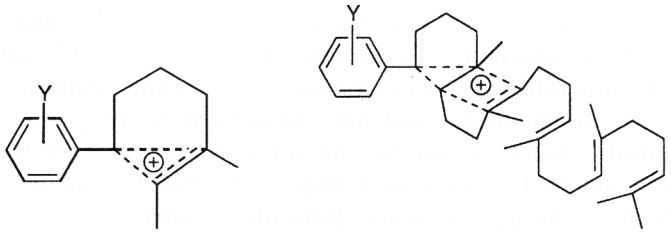
[c] Standard error of estimate.

[d] Statistical test $\Psi = [n(1 - r^2)/n - 2]^{1/2}$. A correlation is considered good if $\Psi \leq 0.1$.[22]

[e] Compounds **8** and **9**, Ref. 9.

eliminate double bond participation was demonstrated earlier, for example solvolysis of the 7-(p-anisyl)-7-norbornenyl substrate, investigated by Gassman *et al.*..[23] In this case, even an unsubstituted phenyl group overcomes a neighbouring group participation responsible for a rate increase of 2.4×10^9.

In the case of the squalene derivatives **4**, the statistical tests (Table II) demonstrate that the $\sigma^+\rho^+$ correlation is extremely good when all the points are taken into account, including the p-anisyl derivative. Unlike substrates **9**, with one double bond, the neighbouring group participation is not overcome by the p-methoxy group. This fact suggests a somewhat different mechanism of anchimeric assistance with **4** than with chlorides **9**. This can be rationalized by the extended π-participation mechanism. Drastically re-



10 **11**

duced values of the ρ^+ (Figure 2) slope of the $\sigma^+\rho^+$ plots, *i.e.* lower $-\rho^+$ values as compared with substrates **9**, support this conclusion. In the case of extended π-participation in **4**, the positive charge must be delocalized to at least five carbon atoms, unlike in **9**, where only three carbon atoms take part in the rate determining step, as it is shown in structures **10** and **11**. Larger charge delocalization from the reaction centre in the transition state of **4** is consistent with the less negative value of ρ^+. It is worth mentioning that comparably low $-\rho^+$ values were obtained with substrates in which the electron donating group is directly attached on the reaction centre.[24]

At first sight, it seems that the activation parameters for solvolysis of substrates **4** are not in accord with the extended π-participation mechanism,

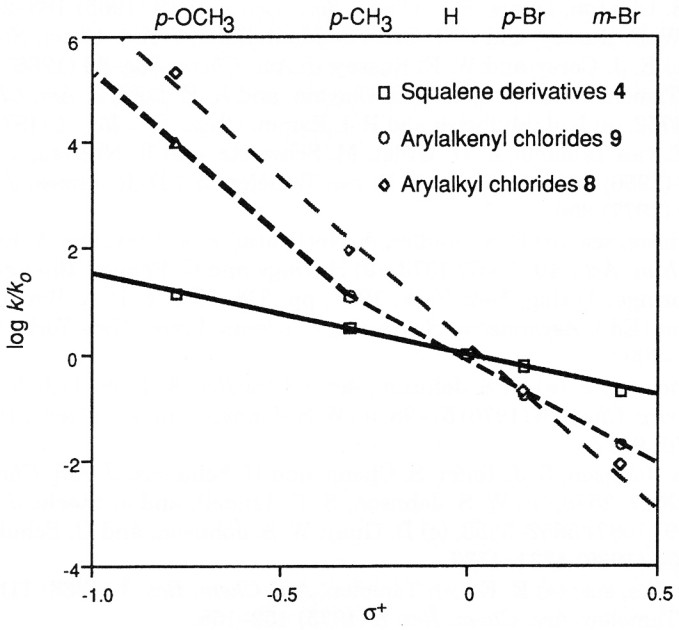


Figure 2. $\sigma^+\rho^+$ plots for some benzylic chlorides in aqueous 2,2,2-trifluoroethanol (w = 97%).

as they are with compound **1**. The values for $\Delta H^{\#}$ and $\Delta S^{\#}$ (Table I) are comparable with those obtained with chlorides **9**.[9b] Van Tamelen[6a] proposed that squalene and some other polyenes assume a coiled conformation in polar solvents. Since all the solvents used here have high polarity, it is likely that the investigated substrates assume one of the many coiled conformations in which, in contrast to **1**, a necessary degree of order for participation is already achieved in the ground state. Extended π-participation would therefore be favoured since there is no requirement for the loss of many degrees of freedom in the transition state.

The ρ^+ values for substrates **4** in all three different solvents, and also the lack of leveling with the *p*-anisyl substrate, unambiguously suggest extended π-participation mechanism. Also, the secondary β-deuterium KIE near unity, with the related substrate **3**, supports this conclusion. Whether two or even three double bonds take part in the rate determining step cannot be decided on the basis of these experiments, and remain to be clarified with additional investigations.

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SAŽETAK

Proširena π-participacija pri biomimetskoj ciklizaciji derivata skvalena

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Pripravljeni su kloridi **4** (1-aril-1-klor-5,9,14,18,22-pentametil-5,9,13,17,21-trikosapentaeni) s različitim supstituentima na fenilnom prstenu. Izmjerene su konstante brzine solvolize u vodenom etanolu (φ = 80% i 95%) te u vodenom 2,2,2-trifluoretanolu (w = 97%). Dobivene Hammettove ρ^+ vrijednosti od –1.86. –1.81, odnosno –1.56 upućuju na usklađeni proces ciklizacije najmanje dviju dvostrukih veza u stupnju koji određuje brzinu reakcije.