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Preliminary Communication

Reactivity of Some Tertiary Chlorides with Methoxy and Olefinic Neighboring Group*,#

Stanko Borčić,† *Olga Kronja, Krešimir Humski, and Sandra Miletić*

Faculty of Pharmacy and Biochemistry, University of Zagreb,
A. Kovačića 1, P. O. Box 156, 10000 Zagreb, Croatia

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Solvolysis rates of tertiary chlorides **1**–**6** and their hexadeuterated analogs **1**-d_6–**6**-d_6 were measured in ethanol (φ = 80%) and 2,2,2-trifluoroethanol (w = 97%). The β-deuterium KIE calculated showed that chloride **1** solvolyzes with n-participation of the methoxy group in the rate determining step, while chloride **2** solvolyzes mainly by way of a k_c process. Based on the reduced β-deuterium isotope effect, it was also concluded that in the solvolysis of chloride **5** π-electrons take part in the rate-determining step.

The n-participation of the methoxy group in solvolytic reactions has been established without ambiguity in many cases.[1] One of the oldest, but also one of the most apparent cases is the solvolysis of 4-methoxy-1-pentyl brosylate and 5-methoxy-2-pentyl brosylate, in which the product can be derived from the same intermediate oxonium ion.[2] However, there are only a few examples of direct comparison in which a double bond's ability to donate its π-electrons in the rate-determining step in solvolysis is compared with the donating abilities of n-electrons. Borčić *et al.*[3] pointed out that the solvolysis of 1-phenyl-4-methoxy-1-butyl chloride proceeds by way of the oxonium ion. The benzylic cation, which is formed in the rate-determining step of this reaction, is stabilized by the participation of the n-electrons of the methoxy group in a similar manner to the formation of the benzylic cation which arises in the solvolysis of 1-phenyl-4-methoxy-1-butyl chloride with π-electron participation.

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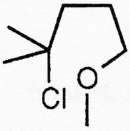
* Dedicated to Professor Vladimir Prelog on the occasion of his ninetieth birthday.

\# Part of projected master of science thesis of S. Miletić.

† Deceased on December 21, 1994.

We have prepared tertiary chlorides **1** and **2**, the model compounds for studying the possible n-electrons participation of the methoxy group. Also, π-participation in the solvolysis with similar substrates possessing a double bond instead of the methoxy group has been studied in detail.[4,5] In this way, the study of the solvolytic behavior of chlorides **1** and **2** and the direct comparison of reactivities of substrates with methoxy groups and double bonds are possible.



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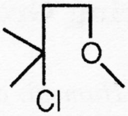

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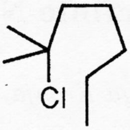

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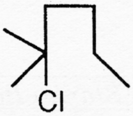

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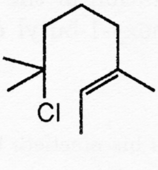
Neighboring group assistance can result in enhancement of the solvolytic reactivity, a decrease of the secondary β-deuterium kinetic isotope effects (KIE)[6] and also in cyclic or rearranged products. It was pointed out earlier that the β-secondary deuterium KIE are the most sensitive probe for proving the neighboring group participation.[7] Recognizing that the kinetic isotope effects are cumulative, the magnitudes of β-deuterium KIE with hexadeuterated substrates can show the extent of the participation most clearly.

Protio and hexadeuterated analogs of chloride **1** and **2** (**1**-d_6 and **2**-d_6) were prepared using standard Grignard reactions, starting with nondeuterated and hexadeuterated acetone and the corresponding methoxy alkyl bromides, followed by chlorination of the alcohols obtained with thionyl chloride. Prior to this procedure, the methoxy group was introduced into the molecules by methylation of the corresponding haloalkanols with dimethylsulfate. The corresponding reference substrates **3**, **3**-d_6, **4** and **4**-d_6 , respectively, in which alkyl groups replace the methoxyalkyl groups, were also prepared according to the same general procedure. These reference substrates not having a neighboring group solvolyze without participation in the rate-determining step.



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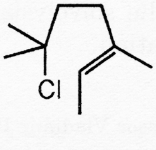

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For direct comparison of n- and π-participation, the unsaturated counterpart to substrate **1** is chloride **5** (the double bond is at C-5 relative to the reaction center) which was very intensively examined earlier.[5] However, the unsaturated analog substrate **2** is the alkenyl chloride **6** in which the double bond is at C-4 from the reaction center, which has not been studied yet. Thus, chloride **6** and its hexadeuterated analog **6**-d_6 were prepared by reaction of trans-ethyl 4-methyl-hexenoate[8] with methylmagnesium iodide and methylmagnesium iodide-d_3, respectively.

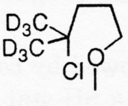
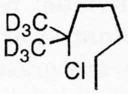
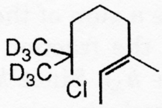
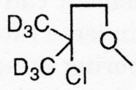
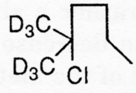
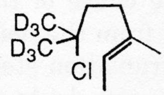
Solvolysis rates of substrates **1–4** and **6** were followed by continuous titration of the liberated hydrochloric acid by means of a pH-stat, alternating deuterated and protio substrates in ($\varphi = 80\%$) ethanol (80 E) and ($w = 97\%$) 2,2,2-trifluorethanol (97 TFE), respectively. Each individual measurement was repeated four to six times. First order rate constants were calculated using a nonlinear least-squares program. The results are presented in the Table.

The experimentally measured solvolysis rate constant for systems which proceed by way of participation can be considered as a sum of the unassisted process k_c and the assisted process k_Δ. Therefore, the fraction of products arising by way of participation is given by $k_\Delta/(k_c + k_\Delta)$. Since k_c cannot be measured directly, it is approximated from the solvolysis rate of the reference compound of similar structure which lacks the neighboring group. Because of this approximation, only a large rate enhancement can be taken as a proof of participation. However, since small or even inverse rate effects can conceal some considerable participation of the neighboring group, therefore it cannot be taken as a proof for the lack of participation. As it can be seen from the Table, there is no rate enhancement of the chlorides **1** and **2** compared with saturated analogs **3** and **4**, but there is rather a slight inverse effect in both cases. In the case of **1** and **2**, the rate decrease is likely to originate in the electrion-withdrawing inductive effect of the methoxy group.

Substrates deuterated at β-position relative to the reaction center show rate depression relative to the protio analogs. The cause of this KIE has been shown to be hyperconjugative electron release from the neighboring C-H(D) bond to the incipient empty p orbital in the transition state. β-Deuterium KIE of the saturated compounds **3** and **4** with two deuterated methyl groups gave the expected values for the maximum KIE in the system investigated ($k_H/k_D = 1.8$), as it has been established for hexadeuterated tertiary chlorides with side chains ranging from 6 to 22 carbon atoms.[9,10] If neighboring group participation is operative, then the orbital vacancy is delocalized away from the reaction center and a less hyperconjugative interaction occurs, resulting in a lower β-deuterium KIE. As it can be seen from the Table, the value is significantly reduced for chloride **1** in both solvents ($k_H/k_D = 1.34$). Essentially, the same value of the β-effect was obtained for the alkenyl analog **5** where the participation of the π-electrons in the rate determining step

TABLE I

Relative solvolysis rates and β-deuterium secondary kinetic isotope effects of some tertiary chlorides

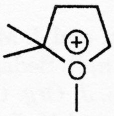
Compound	Solvent	k_u/k_s[a]	k_H/k_D[b]
 *1-d6*	80 E	0.93	1.34 (1)
	97 TFE	0.52	1.35 (1)
 *3-d6*	80 E	–	1.79 (1)
	97 TFE	–	1.81 (1)
 *5-d6*	80 E	18.9[c]	1.37 (3)[c]
	97 TFE	–	–
 *2-d6*	80 E	0.15	1.62 (1)
	97 TFE	0.07	1.69 (1)
 *4-d6*	80 E	–	1.81 (1)
	97 TFE	–	1.82 (1)
 *6-d6*	80 E	0.6[d]	1.30 (3)
	97 TFE	–	1.29 (2)

[a] k_u stands for the rate constant of the substrate with the neighboring group, k_s stands for substrate with adequate length of the alkyl side chain; k_u/k_s at 25 °C;

[b] at 50 °C, the uncertainty of the last reported figures (standard deviation of the mean) is shown in the parentheses; the standard deviation of the mean of k_H and k_D values themselves are within 2% of the rate constants;

[c] Ref. 5;

[d] $k_s = 1{,}25 \times 10^{-5}\ s^{-1}$, Ref. 10.



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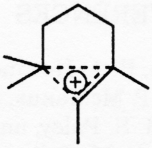

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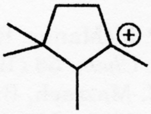

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in ethanolysis was established. Therefore, in the case of **1**, the considerably reduced isotope effects strongly support the conclusion that the structure of the transition state is closely related to the five-membered ring **7** *i.e.*, the n-electrons of the methoxy group take part in the rate determining step in a manner similar to the participation of the π-electrons in **5** to form the intermediate carbonium ion **8**.

Quite different results were observed in the case of chloride **2**, in which the side chain is shorter by one carbon than in chloride **1**. The β-deuterium KIE (Table) is only slightly reduced in comparison with its saturated counterpart in both solvents. In this case if solvolysis proceeded with participation of the methoxy group, the intermediate, as well as the transition state, according to the Hammond postulate,[11] should contain a four-membered ring that is energetically unfavorable. A slightly reduced β-deuterium KIE indicates that n-participation may be operative to some extent, but the majority of the substrate solvolyzes through a k_c process, *i.e.* the charge developed in the transition state is concentrated mainly at the reaction center.

Rather unexpected isotope effects in both solvents were obtained with chloride **6**, which was expected to behave like **2**. Substrate **6** showed the smallest isotope effects of all the examples measured here (k_H/k_D = 1.30 in both solvents), which unambiguously demonstrates the assistance of the double bond in the rate-determining step. This result is even more unexpected since there are a number of cases in the chemical literature when placement of a double bond at C-4 relative to the reaction center is known to favor the k_c over the k_Δ process.[12] These conclusions were based on product analysis and on the lack of rate effects ($k_u/k_s \approx 1$). Therefore, the β-deuterium KIE obtained for the solvolysis of chloride **6** shows again that the lack of a rate effect cannot be taken as a proof for the lack of participation. The fact that the effect is smaller than with chloride **5** can be rationalized in terms of the charge distribution in the reaction transition state. In the case of **5**, the transition state is like carbonium ion **8**. Since forming the four-membered ring in the transition state is unfavorable for chloride **6**, the transition state may be more akin to tertiary cyclopentyl cation **9** with relatively less charge at the reaction center, *i.e.*, a »late« transition state.

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SAŽETAK

Reaktivnost nekih tercijarnih klorida s metoksi- i olefinskom susjednom skupinom

Stanko Borčić, Olga Kronja, Krešimir Humski i Sandra Miletić

Mjerene su brzine solvolize tercijarnih klorida **1–6** i njihovih heksadeuteriranih analoga **1**-d_6–**6**-d_6 u etanolu (φ = 80%) i 2,2,2-trifluoretanolu (w = 97%). Izračunani β-deuterijski KIE pokazuju da pri solvolizi klorida **1** dolazi do n-participacije metoksi-skupine u stupnju koji određuje brzinu reakcije, dok klorid **2** uglavnom solvolizira po procesu k_c. Na temelju smanjenih β-deuterijskih izotopnih efekata također se vidi da pri solvolizi klorida **5** π-elektroni sudjeluju u sporom stupnju reakcije.