Evidence for extended π,n-participation in solvolysis of some benzyl chlorides

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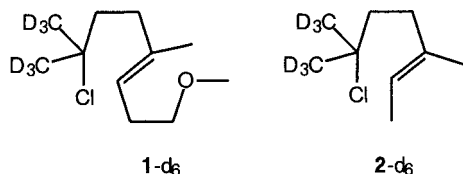Faculty of Pharmacy and Biochemistry, University of Zagreb, A. Kovačića 1, P.O. Box 156, 10000 Zagreb, Croatia

ABSTRACT: Chlorides **3** (1-aryl-1-chloro-4-methyl-7-methoxy-4-heptene) and **4** (1-aryl-1-chloro-4-methyl-4-hexene) with various phenyl substituents were prepared (Y = p-OCH$_3$, p-CH$_3$, H and m-Br) and the solvolysis rates were measured in 80% (v/v) aqueous ethanol. The rate constants of **3** correlate well with σ^+, and the ϱ^+ value obtained is -1.45 ± 0.15, whereas with **4** breakdown of the Hammett plot occurs, and the ϱ^+ value without the p-anisyl group is -2.55 ± 0.20, indicating extended π,n-participation in **3** and simple π-participation in **4**. The drastically smaller activation parameters obtained with **3** than with **4** are consistent with the proposed mechanism in which the high degree of order required in the transition state (large negative $\Delta S^{\ddagger}$) is overcompensated by a small $\Delta H^{\ddagger}$. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: π,n-participation; solvolysis; benzyl chlorides

INTRODUCTION

The term 'extended participation' in solvolytic reactions refers to the simultaneous assistance of at least two neighboring groups in the rate-determining step. Typical cases are those in which π-electrons stabilize the positive charge generated in displacement reactions. In one of the first examples that kinetically proved this phenomenon, Bartlett *et al.*[1] studied a substrate in which the substituent on the remote aromatic ring influences the reaction rate, and that influence is transferred through the isolated *trans* double bond, suggesting that concerted bicyclization occurs in the rate-determining step. A concerted bicyclization mechanism was also established with great certainty in the investigation of biomimetic polyolefinic cyclization carried out in our group, in which the extended π-participation of appropriately located two double bonds was demonstrated.[2,3,4]

1-d$_6$ 2-d$_6$

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In previous work, we showed that solvolysis of chloride **1** presumably proceeds via an extended π,n-participation mechanism, involving simultaneous assistance of the double bond and n-electrons of the methoxy group. This is, to the best of our knowledge, the first ever reported case of this phenomenon.[5] Chloride **2** was used as a reference model for simple π-participation, since the assistance of its double bond has been established both kinetically and theoretically.[5] In comparison with **2** [$k_H/k_D = 1.30 \pm 0.03$ in 80% (v/v) aqueous ethanol (80E); $k_H/k_D = 1.29 \pm 0.02$ in 97% (w/w) aqueous 2,2,2-trifluoroethanol (97T)], chloride **1** shows considerably reduced secondary β-deuterium kinetic isotope effects (KIE) in solvolysis ($k_H/k_D = 1.16 \pm 0.01$, 80E; $k_H/k_D = 1.12 \pm 0.01$, 97T), showing less charge on the reaction center in the transition state.[6] This result was taken as an indication of the extended π,n-participation mechanism. The reduced enthalpy and entropy of activation in ethanolysis of **1** are in accord with this conclusion.

In order to confirm the presumed mechanism, we have examined benzyl substrates in which π,n-electrons can take part. The chosen structures are chlorides **3**, which are the corresponding benzyl derivatives of **1**, and chlorides **4**, which are the corresponding benzyl derivatives of the reference compound **2**. The substitution of the two methyl groups with substituted or non-substituted benzyl groups is advantageous, since the ϱ^+ values could be measured and used as a reference in testing for concertedness of the mechanism. It was shown earlier that each additional double bond that takes part in stabilization of the positive charge generated in the transition state lowers

the negative value of the reaction constant (ϱ^+) by ~2 units.[3]

3   **4**
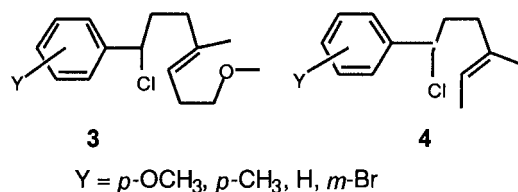
Y = *p*-OCH$_3$, *p*-CH$_3$, H, *m*-Br

RESULTS AND DISCUSSION

Series of benzyl chlorides **3** (1-aryl-1-chloro-4-methyl-7-methoxy-4-heptene) and **4** (1-aryl-1-chloro-4-methyl-4-hexene) were prepared (Y = *p*-OCH$_3$, *p*-CH$_3$, H and *m*-Br) according to the Scheme 1 starting from esters **5**[5,7] and **6**,[4,7] respectively. Chlorides were subjected to solvolysis in 80E. Reactions were monitored by titration of the liberated acid with an automatic pH-stat. Activation parameters were calculated from rate constants determined at three temperatures. The measured and extrapolated rate constants and the activation parameters are presented in Table 1. The Hammett ϱ^+ values for the chlorides **3** and **4**, which were calculated using simple regression analysis, are presented in Table 2 together with some other important relevant data.

Participation of the neighboring group(s) leads to charge delocalization away from the reaction center. Thus, the magnitude of the Hammett ϱ^+ value, which can be used as a measure of the charge 'seen' by the aromatic ring at the reaction center, should be indicative of assistance by neighboring groups.[8] The solvolysis of the saturated chloride **7**, as with numerous other benzyl and tertiary chlorides, proceeds by way of a k_S process, in which nucleophilic solvation occurs.[9,10] The rate constants of **7** correlate well with the σ^+ constants, and the corresponding Hammett ϱ^+ parameter is −6.3.[11] Statistical analysis revealed that for series **4** a good fit was obtained only if the point for the *p*-anisyl derivative was

i = LAH/ether
ii = PyCrO$_3$·HCl/methylene chloride
iii = SOCl$_2$/petroleum ether
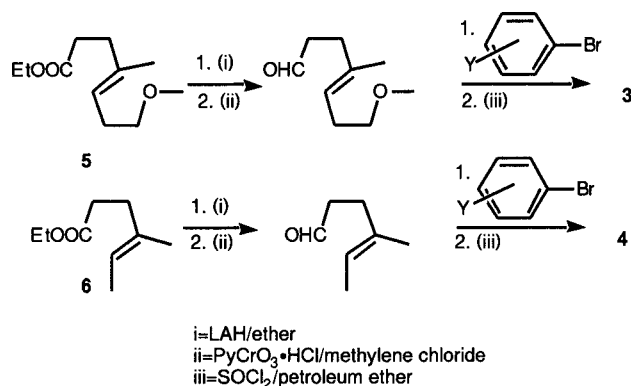
Scheme 1

Table 1. Solvolysis rate constants and activation parameters of some benzyl chlorides in 80% (v/v) aqueous ethanol

	t (°C)	k $(10^{-4}\,\mathrm{s}^{-1})^{\mathrm{a,b}}$	$\Delta H^{\ddagger}$ (kJ mol^{-1})$^{\mathrm{a}}$	$\Delta S^{\ddagger}$ (J K^{-1} mol^{-1})$^{\mathrm{a}}$
4-*m*-Br	70	1.56 ± 0.2	75 ± 2	−98 ± 7
	60	0.714 ± 0.10		
	50	0.285 ± 0.05		
	25	0.0252		
4-H	70	11.5 ± 0.1	71 ± 10	−95 ± 29
	60	4.38 ± 0.02		
	50	2.29 ± 0.01		
	25	0.214		
4-*p*-CH$_3$	50	16.7 ± 0.5	70 ± 3	−83 ± 9
	40	6.67 ± 0.08		
	30	2.83 ± 0.06		
	25	1.72		
4-*p*-OCH$_3$	25	(4.04 ± 0.03)$^{\mathrm{c}}$ 4876$^{\mathrm{d}}$		
3-*m*-Br	70	8.96 ± 0.08	68 ± 5	−107 ± 15
	60	3.86 ± 0.02		
	50	1.93 ± 0.02		
	25	0.207		
3-H	50	8.29 ± 0.01	51 ± 8	−140 ± 25
	40	4.04 ± 0.0		
	30	1.88 ± 0.01		
	25	1.26		
3-*p*-CH$_3$	50	13.5 ± 0.3	58 ± 1	−126 ± 1
	40	8.36 ± 0.07		
	30	3.56 ± 0.02		
	25	2.62		
3-*p*-OCH$_3$	50	56.2 ± 0.2	47 ± 2	−143 ± 6
	40	29.9 ± 0.9		
	30	16.6 ± 0.1		
	25	11.79		

$^{\mathrm{a}}$ The uncertainties are standard deviations of the mean.
$^{\mathrm{b}}$ The rate constants lacking standard errors are extrapolated.
$^{\mathrm{c}}$ Measured in 93% aqueous (v/v) acetone.
$^{\mathrm{d}}$ Estimated rate constant in 80% aqueous (v/v) ethanol.[12]

Table 2. Linear free energy correlations for some benzyl chlorides at 25 °C

Compound	Solvent$^{\mathrm{a}}$	$\varrho^{+\mathrm{b}}$
7	97T	−6.28 ± 0.25
8	97T	−3.93 ± 0.10$^{\mathrm{c}}$
4	80E	−2.55 ± 0.20$^{\mathrm{c}}$
3	80E	−1.45 ± 0.15
11	80E	−1.45 ± 0.03

$^{\mathrm{a}}$ 97T = 97% (w/w) aqueous 2,2,2-trifluorethanol; 80E = 80% (v/v) aqueous ethanol.
$^{\mathrm{b}}$ Uncertainties are standard errors.
$^{\mathrm{c}}$ Without the data for the rate constant of the *p*-anisyl derivative.

excluded. Thus, without taking the rate constant for the *p*-methoxy group into account, $\varrho^+ = -2.55$ is obtained for the reference chlorides **4** (Table 2, Fig. 1). This significant decrease in $-\varrho^+$ is caused by participation of the neighboring double bond. A breakdown of the linear Hammett relation in the case of the *p*-anisyl compound (Fig. 1) suggests that an assisted process is the major reaction pathway for all the variants except the *p*-anisyl substrate. In the case of the *p*-anisyl group, the double bond assistance is much attenuated
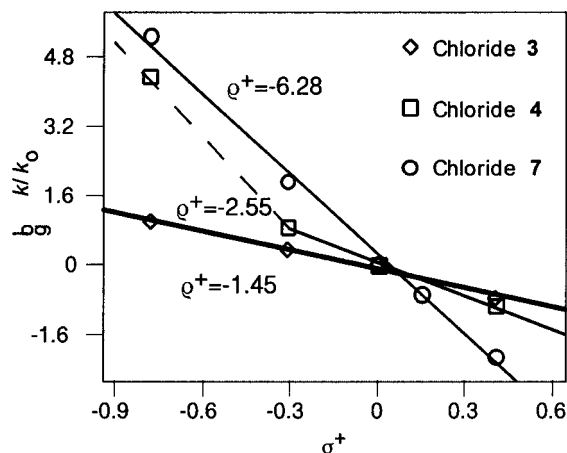
Figure 1. Hammett plots for some benzyl chlorides at 25 °C

by the strongly electron-donating *p*-methoxy substituent. This result is not surprising, since a similar breakdown of the Hammett plot was obtained earlier with unsaturated chlorides **8**.[10]

It should be noted that the $-\varrho^+$ value for substrates **4** is even smaller than the $-\varrho^+$ value for **8** [$\varrho^+ = -3.9$ in 97% (w/w) TFE]. The comparison of the ϱ^+ of **4** measured in 80E and the ϱ^+ of **8** obtained in 97T is here justified, since in numerous cases related compounds solvolyzed with the exactly same ϱ^+ parameter in both solvents.[3,12] Comparison of ϱ^+ values can be taken as indicating that chlorides **4** proceed through a 'later' transition state along the reaction coordinate, whereas **8** proceed through an 'earlier' transition state, i.e. the structure of **4** is more akin to the carbocation intermediate than that of the structure **8**, which is closer to the starting chloride. This conclusion is completely in accord with theoretical calculations at the MP2/6–31(G,p) level of theory obtained with the corresponding dimethyl derivatives **2** and **9**.[4] It has been shown that the transition state in displacement reactions with **9** is a π-complex-like structure, whereas the transition state in reactions with **2** is more akin to a tertiary cyclopentyl cation. Consequently, the positive charge on the reaction center in the transition structure of **2** is less pronounced than that in the transition state of **9** (calculated charges +0.23 for **2** and +0.58 for **9**). Experimental β-deuterium KIEs obtained with tertiary substrates **2** and **9** (1.30 for **2** vs 1.37 for **9**) also support the conclusion that 4-alkenyl derivatives solvolyze via a later transition state. The larger depression of KIE in **2** demonstrates less charge on the reaction center.
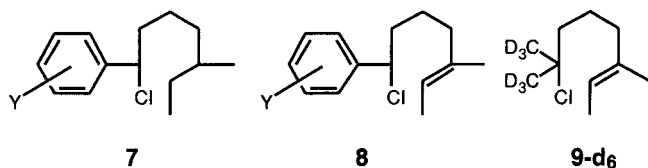
A value of $\varrho^+ = -1.45 \pm 0.15$ was obtained in ethanolysis of substrates **3**. The slope of the Hammett plot is significantly lower than that of the reference **4**, indicating that the methoxy group plays an important role in the charge delocalization. It is important to note that, as with benzyl chloride **11**, a better fit is obtained if the *p*-methoxy variant of **3** was included in the correlations (Table 2 and Fig. 1). The facts that the $-\varrho^+$ value is considerably lower and the neighboring group participation for substrates **3** is not overcome by the *p*-methoxy group support a different, extended π,n-participation mechanism in which decrease of the positive charge occurs in the reaction transition state (**3-TS**).
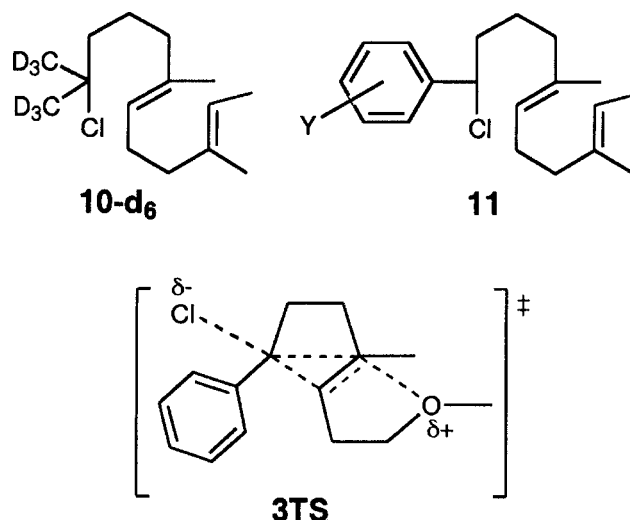
The activation parameters presented in Table 1 are also in accord with the proposed extended participation mechanism of **3**. All derivatives of **3** and all derivatives of **4** have essentially the same activation parameters. Furthermore, substrates **3** have lower $\Delta H^{\ddagger}$ and lower $\Delta S^{\ddagger}$ values than compounds **4**, which solvolyze by way of simple π-participation. Finally, substrates **3** have the same activation parameters as the aliphatic derivative **1** ($\Delta H^{\ddagger} = 56 \pm 6$ kJ mol^{-1}, $\Delta S^{\ddagger} = -142 \pm 17$ J mol^{-1} K^{-1} in 80E).[5]

Because of the extended π, *l*n-electron delocalization in the transition state of **3**, $\Delta H^{\ddagger}$ is lower than that in the simple π-electron delocalization process with **4** (see Table 1). Delocalization involves bridging in the transition state, which causes a conversion of some internal rotations to stiffer vibrations, and therefore a very negative $\Delta S^{\ddagger}$, as is the case with all chlorides **3**. The largest contribution in decreasing the value of $\Delta S^{\ddagger}$ is caused by the loss of two internal rotations around the two single C—C bonds located between the two double bonds and the methoxy group in **3**. Extended π-participation mechanism fits excellently with the values of $\Delta S^{\ddagger}$, since it is known that the loss of one internal rotation in the transition state decreases $\Delta S^{\ddagger}$ for 15–20 J mol^{-1} K^{-1}.[13]

On the basis of the β-deuterium KIEs obtained in solvolysis of **1** ($k_H/k_D = 1.16 \pm 0.01$, 80E),[5] it was concluded that substrate **1** reacts by way of an 'earlier' transition state than **10**, since in the latter lack of the β-deuterium KIE occurs ($k_H/k_D = 1.01 \pm 0.02$, 80E). This assumption cannot be verified for the benzyl chlorides, since **3** and **11** have the same Hammett ϱ^+ value. Nevertheless, same values of ϱ^+ for **3** and **11** indicate that chloride **3** solvolyzes by way of an extended π,n-participation mechanism, probably through a **3-TS**-like transition structure.

EXPERIMENTAL

Substrate preparation

4-Methyl-7-methoxy-4-heptenal. To a stirred solution of LiAlH$_4$ (1.90 g, 0.05 mol) in 25 ml of dry diethyl ether, a solution of ethyl 4-methyl-7-methoxy-4-heptenoate (**5**) (10.0 g, 0.05 mol) in 30 ml of diethyl ether was added dropwise. Refluxing and stirring were continued for 3 h. The excess of hydride was decomposed with gradual addition of water. The precipitate was washed with diethyl ether and the combined organic layers were dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica gel. Impurities were removed with methylene chloride and the pure product with diethyl ether. The yield of pure alcohol was 6.10 g (77.2%).

4-Methyl-4-hexenol. The procedure is the same as described above. From 2.69 g (0.07 mol) of LiAlH$_4$ and 11.0 g (0.07 mol) of ethyl 4-methyl-4-hexenoate (**6**), 7.25 g (90.8%) of pure alcohol were obtained.

4-Methyl-7-methoxy-4-heptenal. Pyridinium chlorochromate (8.32 g, 0.04 mol) was suspended in methylene chloride (25 ml) and 6.10 g (0.04 mol) of 4-methyl-7-methoxy-4-heptenol were rapidly added at room temperature. After 2 h, the oxidation was complete. The dark reaction mixture was diluted with 40 ml of dry diethyl ether, the solvent was decanted and the dark solid was washed twice with diethyl ether. The product was isolated by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure. The crude product was distilled (b.p. 120–125 °C), yielding 3.51 g (56.1%) of the pure product.

4-Methyl-4-hexenal. The procedure is the same as described above. From 13.7 g (0.06 mol) of pyridinium chlorochromate and 7.25 g (0.06 mol) of 4-methyl-4-hexenol, 3.12 g (46.4%) of pure aldehyde were obtained (b.p. 105–107 °C).

1-Phenyl-7-methoxy-4-methyl-4-heptenol. A suspension of Li powder (223 mg, 32.13 mmol), granulated Li (223 mg, 32.13 mmol) and dry THF (10 mL) was refluxed under a slow stream of argon for 10–15 min in an ultrasonic bath. A solution of 4-methyl-7-methoxy-4-heptenal (1.00 g, 6.41 mmol) and bromobenzene (1.00 g, 6.41 mmol) was added dropwise to the stirred mixture at 0 °C. The reaction mixture was alternately stirred with the magnetic stirrer and in the ultrasonic bath for 3 h. The excess of Li was filtered off and the filtrate was treated with a saturated aqueous solution of NH$_4$Cl. The alcohol was extracted with diethyl ether and dried over anhydrous Na$_2$SO$_4$. The diethyl ether was evaporated, and the product was purified on a silica gel column. Unreacted bromide was removed with light petroleum and the pure alcohol was eluted with dichloromethane. The yield of pure alcohol was 0.53 g (35.3%).

1-Phenyl-4-methyl-4-hexenol. The procedure is the same as described above. From 223 mg (32.13 mmol) of Li powder, 223 mg (32.13 mmol) of granulated Li, 1.20 g (10.7 mmol) of 4-methyl-4-hexenal and 2.02 g (12.84 mmol) of bromobenzene, 0.21 g (10.3%) of pure alcohol was obtained.

1-(4-Methoxyphenyl)-7-methoxy-4-methyl-4-heptenol. The procedure is the same as described above. From 223 mg (32.13 mmol) of Li powder, 223 mg (32.13 mmol) of granulated Li, 1.00 g (6.41 mmol) of 4-methyl-7-methoxy-4-heptenal and 1.20 g (6.41 mmol) of 4-bromoanisole, 0.17 g (10.0%) of pure alcohol was obtained.

1-(4-Methoxyphenyl)-4-methyl-4-hexenol. The procedure is the same as described above. From 343 mg, (49.40 mmol) of Li powder, 343 mg (49.40 mmol) of granulated Li, 1.20 g (10.70 mmol) of 4-methyl-4-hexenal and 2.06 g (11.00 mmol) of 4-bromoanisole, 0.92 g (38.0%) of pure alcohol was obtained.

1-(4-Methylphenyl)-7-methoxy-4-methyl-4-heptenol. The procedure is the same as described above. From 223 mg (32.13 mmol) of Li powder, 223 mg (32.13 mmol) of granulated Li, 1.00 g (6.41 mmol) of 4-methyl-7-methoxy-4-heptenal and 1.10 g (6.41 mmol) of 4-bromotoluene, 0.23 g (14.5%) of pure alcohol was obtained.

1-(4-Methylphenyl)-4-methyl-4-hexenol. The procedure is the same as described above. From 343 mg (49.40 mmol) of Li powder, 343 mg (49.40 mmol) of granulated Li, 1.20 g (10.70 mmol) of 4-methyl-4-hexenal and 2.19 g (12.80 mmol) of 4-bromotoluene, 0.16 g (7.30%) of pure alcohol was obtained.

1-(3-Bromophenyl)-7-methoxy-4-methyl-4-heptenol. The procedure is the same as described above. From 223 mg (32.13 mmol) of Li powder, 223 mg (32.13 mmol) of granulated Li, 1.00 g (6.41 mmol) of 4-methyl-7-methoxy-4-heptenal and 1.51 g (6.41 mmol)

of 1,3-dibromobenzene, 0.55 g (27.5%) of pure alcohol was obtained.

1-(3-Bromophenyl)-4-methyl-4-hexenol. The procedure is the same as described above. From 223 mg (32.13 mmol) of Li powder, 223 mg (32.13 mmol) of granulated Li, 2.00 g (17.8 mmol) of 4-methyl-4-hexenal and 4.20 g (17.8 mmol) of 1,3-dibromobenzene, 1.02 g (21.3%) of pure alcohol was obtained.

*1-Aryl-1-chloro-4-methyl-7-methoxy-4-heptene (**3**) and 1-aryl-1-chloro-4-methyl-4-hexene (**4**).* The appropriate alcohol was dissolved in 10–15 ml of light petroleum, the solution was cooled to $-15\,^{\circ}$C and SOCl$_2$ was added dropwise. The reaction mixture was stirred for 2 h under reduced pressure (about 520–560 mmHg) to remove the liberated HCl and SO$_2$ continuously. The light petroleum ether was then evaporated and crude chloride was used for kinetic measurements.

Kinetic measurements

Solvolysis rates were followed in 80E titrimetrically by means of a pH-stat (end-point titration, pH = 6.85). The solvolysis rate of the methoxy variant of chloride **4** was measured in 93% aqueous acetone, and the rate in 80E was estimated according to experimental data for phenyl ethyl chloride.[14] Typically, 0.02 mmol of the chlorides **3** and **4** were dissolved in 20 ml of the solvent at the required temperature thermostated at $\pm 0.05\,^{\circ}$C, and the liberated HCl was continuously titrated with a 0.008 M solution of NaOH in the same solvent mixture. Individual measurements could be described by a first-order law from 15% up to at least 80% completion. First-order rate constants were calculated from about 100 determinations by using a non-linear least-squares program. Measurements were usually repeated 3–7 times. Activation parameters were calculated from rate constants at three temperatures.

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