Research Article

Lack of the neighboring group rate effect in solvolytic reactions that proceed via participation

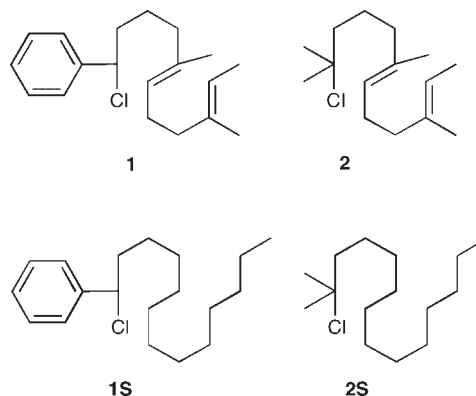## Sandra Jurić[a] and Olga Kronja[a]*

In order to investigate the influence of solvent polarity on the rate effect of double bonds in reactions that proceed via an extended π-participation mechanism, the solvolysis rates (k_U) of the benzyl chloride derivative 1 and tertiary chloride 2 that have doubly unsaturated side chains were measured in absolute ethanol, 80% v/v. aq. ethanol and 97% wt. aq. trifluoroethanol. The rates of the corresponding saturated analogs 1S and 2S (k_S) were measured in 80% aq. ethanol and 97% wt. aq. trifluoroeth'anol, while those in pure ethanol were calculated according to LFER equation log $k = s_f (E_f + N_f)$. In solvents with moderate ionizing power (ethanol and 80% aq. ethanol) the expected rate effects were obtained ($k_U/k_S > 1$), while in solvent with high ionizing power (2,2,2-trifluoroethanol) absence of the rate effect was observed ($k_U/k_S \approx 1$), indicating that in the k_S process the solvation of the transition state is very important, while in k_Δ process the breaking of the C—Cl bond is not appreciably developed in the transition state and the solvent effect is marginal. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: neighboring group assistance; extended participation; inverse neighboring group rate effect

INTRODUCTION

Neighboring group participation in S_N1 reactions occurs when the group adjacent to the reaction center acts as an intramolecular nucleophile. Assistance of the neighboring group may cause charge delocalization and thus lower the reaction barrier. The fact that solvolysis of a compound with a suitably located neighboring group is enhanced in comparison to the solvolysis of a corresponding compound lacking that group has been taken as important evidence for the existence of the anchimeric assistance. Probably the most cited example is the acetolysis of *anti*-7-norbornenyl tosylate, which is 10^{11} faster than the acetolysis of the saturated analog.[1] Furthermore, the lack of rate enhancement was often taken as proof that solvolysis follows the k_C route (unassisted process) rather than the k_Δ pathway (assisted process).[2]

Assistance of the double bond(s) located properly to participate in forming hexa- or pentacyclic transition states in solvolytic displacement reactions has been investigated widely.[3] Even though other kinetic methods indicate that the π-participation of double bond(s) is operative, solvolysis rates (80% aq. ethanol) of several substrates with unsaturated side chains (k_U) are virtually equal to the rates of their saturated analogs (k_S) or are only moderately enhanced.[4] In this work, we set out to re-examine the solvolytic behavior of benzyl and tertiary substrates 1 and 2, and to find out how the ratio of the rates of a compound that solvolyses by way of double bond assistance and by the S_N1 route (k_U/k_S) depends on the solvent. Solvolysis rates of chlorides 1S and 2S having the same number of carbon atoms in the alkyl side chains were used as a reference for the unassisted S_N1 process.

Compounds 1/1S and 2/2S have been chosen because the extended π-participation of both double bonds for 1 and 2 were established unambiguously.[5] Thus, both substrates solvolyse with smaller entropy and enthalpy of activation than

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do the corresponding reference compounds that proceed by way of one π-bond participation ($\Delta\Delta H^{\ddagger} = -36\,kJ\,mol^{-1}$, $\Delta\Delta S^{\ddagger} = -95\,J\,K^{-1}\,mol^{-1}$ for **1**; $\Delta\Delta H^{\ddagger} = -21\,kJ\,mol^{-1}$, $\Delta\Delta S^{\ddagger} = -88\,J\,K^{-1}\,mol^{-1}$ for **2**; the side chain in the reference compounds with one neighboring double bond is E-4-methyl-4-hexenyl) indicating that the second double bond also participates in the rate determining step. The slope of the Hammett plot obtained with the series of **1** is considerably smaller ($\rho^{+} = -1.76 \pm 0.04$; substituents on the phenyl ring were: p-methoxy, p-methyl, H, m-bromo, and p-bromo) than that obtained with the corresponding reference chlorides with one double bond in the side chain ($\rho^{+} = -3.93 \pm 0.10$) and saturated side chain **1S** ($\rho^{+} = -6.28 \pm 0.25$), supporting considerably less charge at the reaction center. Similarly, the β-deuterium kinetic isotope effects (KIEs) indicate pronounced charge delocalization from the reaction center for chloride **2**. Thus, ethanolysis of the hexadeuterated saturated analog **2S** (two deuteromethyl groups adjacent to the reaction center) produced reference KIE ($k_H/k_D = 1.80 \pm 0.03$). The effect was reduced ($k_H/k_D = 1.37 \pm 0.03$) for the corresponding hexadeuterated tertiary chloride with one double bond suggesting a concerted monocyclization, while the hexadeuterated chloride **2** solvolysed without a significant secondary β-deuterium KIE ($k_H/k_D = 1.01 \pm 0.04$).

RESULTS AND DISCUSSION

In order to investigate the influence of solvent ionizing power on the k_U/k_S ratio, the solvolysis rates of the unsaturated compounds **1** and **2** were measured by potentiometric titration in absolute ethanol (EtOH), 80% aq. ethanol (80EtOH) and 97% wt. aq. 2,2,2-trifluorethanol (97TFE), or were taken from the literature (Table 1). The solvolysis rates of **1S** and **2S** in 80EtOH and 97TFE have been measured or taken from literature.[6] However, the rates of the reference compounds **1S** and **2S** in pure ethanol are too slow to be measured by conventional methods at conventional temperatures. In order to get data for solvolysis rates in pure ethanol, recent findings have been employed to calculate the solvolysis rates of the substrates that follow an S_N1 pathway (**1S** and **2S**).

According to a general reactivity scale developed by studying the solvolysis rates of a large variety of benzhydryl substrates with different leaving groups in different solvents, the absolute rate of the heterolysis reaction (S_N1) can be calculated according to the following equation:[7]

$$\log\ k = s_f(E_f + N_f) \qquad (1)$$

in which: k is the first-order rate constant (s^{-1}); s_f is the nucleofuge specific slope parameter; N_f is the nucleofugality parameter; and E_f is the electrofugality parameter. The nucleofugality (N_f) is defined for a leaving group and solvent pair, while the electrofugality parameters E_f are independent variables and refer to the carbocation generated in heterolysis reaction (S_N1). E_f parameters for the corresponding carbocation of the saturated model compounds **1S** and **2S** were easily calculated from the known reaction rates (k_S) for **1S** and **2S** in 80EtOH and in 97TFE at 25°C (Table 1), and from earlier determined nucleofuge specific parameters for chloride ($N_f = 3.28$ and $s_f = 0.98$ in 80EtOH and $N_f = 5.56$ and $s_f = 0.82$ in TFE). By applying Eqn (1), the following average electrofugality parameters were obtained: $E_f = -9.38 \pm 0.34$ for corresponding carbocation of **1S** and $E_f = -8.81 \pm 0.37$ for the corresponding carbocation of **2S**. From these E_f values and

Table 1. Solvolysis rates of chlorides **1**, **2**, **1S**, and **2S** and k_U/k_S ratios

Compound	Solvent[a]	t (°C)	$k \times 10^{-4}$ (s^{-1})[b]	k_U/k_S[c]
1S	EtOH	25	3.05×10^{-4} [d]	
	80EtOH	68	2.72 (3)	
		62	1.36 (2)	
		58	94.5 (3)	
		25	0.0200[e]	
	97TFE	19	1.81 (4)	
		25	4.16 (1)	
		30	7.48 (2)	
		35	13.0 (2)	
1	EtOH	25	0.626 (3)	**2050**
	80EtOH	25	2.24[f]	**112**
	97TFE	25	4.61[g]	**1.1**
2S	EtOH	25	1.14×10^{-3} [d]	
	80EtOH	25	0.123[h]	
	97TFE	25	8.03 (3)	
2	EtOH	70.7	11.3 (5)	
		60.8	3.97 (5)	
		51.6	1.42 (1)	
		25	0.0507[e]	**44**
	80EtOH	60	16.6 (7)	
		50	8.74 (5)	
		35	3.25 (1)	
		25	1.59[e]	**13**
	97TFE	25	17.1 (1)	**2.1**

[a] EtOH is absolute ethanol, 80EtOH is 80% v/v aqueous ethanol, 97TFE is 97% wt. 2,2,2-trifluoroethanol.
[b] The uncertainties of the last reported figure (standard deviation of the mean) are shown in parentheses; the rate constants lacking standard errors are extrapolated or taken from literature.
[c] k_U is the rate of the compound with an unsaturated side chain, k_{S-} is the rate of the compound with an saturated side chain.
[d] Rates calculated according to equation $\log k = s_f (E_f + N_f)$.
[e] Extrapolated value.
[f] Reference [5c].
[g] Reference [5a].
[h] Reference [5b].

from the nucleofuge specific parameters for chloride ($N_f = 1.87$ and $s_f = 1.00$), the solvolysis rates of **1S** and **2S** in pure ethanol were calculated.

Let us discuss the reliability of the calculated rate constants in pure ethanol obtained for the saturated reference compounds **1S** and **2S** by using the Eqn (1). The LFER presented above has been developed using benzhydryl derivatives.[7a] Because of the different steric and electronic interactions between the electrofuge and the nucleofuge in the substrates **1S** and **2S**, as well as the different solvation of differently delocalized carbocations, deviation from the correlation may occur. The scope of the above equation has been examined for various electrofuges by calculating the E_fs for a variety of carbocations from the solvolysis rates of different chlorides or bromides in standard solvents.[7b] It was demonstrated that for aryl substituted carbocations, as is generated in solvolysis of **1S**, the agreement of E_fs are better

than ± 0.3. Therefore, the rate constant calculated for **1S** is reasonably reliable and can be taken as a valid reference value. The largest scatter in E_f was obtained for *tert*-butyl cation ($E_f = -8.21 \pm 0.68$). Since compound **2S** produces a tertiary aliphatic carbocation, it can be predicted that the deviations of E_f in different solvents is up to ± 0.7. Nevertheless, even though the calculated rate constant for **2S** is less reliable, the error is below one order of magnitude.

The absolute reaction rates (measured and calculated) and k_U/k_S ratios are presented in Table 1. In a solvent with moderate ionizing power, like absolute ethanol, participation of the double bonds causes enhancement of the reaction rate in both cases. However, as the ionizing power of the solvent increases, the k_U/k_S ratio decreases, so in 97TFE no rate effects were observed. A similar observation that the k_U/k_S ratio is decreased in a solvent with larger ionizing power was reported for biomimetic cyclization of substrates with triple bond.[8]

The fact that the k_U/k_S ratio depends on the solvent can be rationalized if the manner of stabilization in the k_C and k_Δ processes is considered. In the k_C route that **1S** and **2S** follow, solvation is the most important variable that influences the reaction rates. Therefore, the solvolysis rates of the saturated substrates increase with ionizing power of the solvent, because of the more efficient stabilization of the carbocation and the leaving group generated in the transition state. On the other hand, even at the first glance it is obvious that the rate constants of the substrates that proceed via assistance of the double bonds depend only marginally on the solvent ionizing power. For example, solvolysis of benzyl chloride **1** is only about eight times faster in 97TFE than in EtOH, while the difference of the ionizing power of those solvents is well above 4 ($\Delta Y = 4.49$, $\Delta Y_{OTs} = 5.36$). The stabilization of the intermediate carbocation generated from **1** and **2** comes from charge delocalization, which lowers the energy of the carbocation intermediate. Therefore, according to the Hammond postulate, the reaction proceeds through an earlier transition state. In this earlier transition state, the breaking of the C—Cl bond is less advanced than in the transition state of solvolysis of the saturated model, and the solvation is less important. If the charge is delocalized to more atoms, the transition state is more shifted toward to starting structure. Since in the carbocation intermediate generated from chloride **1** the charge is additionally delocalized to the phenyl group by resonance, it is easy to understand why the solvolysis rates of benzyl chloride **1** are even less influenced by solvent ionizing power than that of tertiary substrate **2**.

If the energy of stabilization by solvation in the saturated substrates is close in magnitude to the energy of stabilization

caused by charge delocalization in substrates that proceed via the neighboring group participation mechanism, then the enhancement of the reaction rate of the substrates in which participation occurs is only moderate. Since the transition state stabilization caused by charge delocalization depends very little on the solvent used, the existence or absence of the neighboring rate effect is determined by the efficiency of the carbocation and leaving group stabilization via an unassisted process. Thus, in EtOH whose ionizing power is the smallest, the barrier difference between the nonassisted and assisted process is the largest because of the least effective stabilization of the transition structure produced from **1S** and **2S**, and the k_U/k_S ratio is the largest (Table 1). Enhancement of the rate of the saturated substrates due to solvation causes a less pronounced rate effect (k_U/k_S) in 80EtOH. Absence of the rate effect ($k_U/k_S \approx 1$) is observed in 97TFE whose ionizing power is the largest among three solvents used, caused by electrostatic and electrophilic solvation of the developing chloride ion.[9]

The lack of the rate effect or even an inverse rate effect can be rationalized if the Eyring plots are considered (Fig. 1). The slope of the unassisted process is much steeper than that of the assisted process, due to the relatively small $\Delta H^\ddagger$ of the later caused by intramolecular bond formation. In Fig. 1 log k of **1** and **1S** in 97TFE and 80EtOH are plotted against 1/T. Intersection of the plots in 97TFE is at 29°C, indicating that above this temperature the saturated reference solvolyses faster than the unsaturated analog ($k_U/k_S < 1$). Even though only a moderate rate effect is obtained with **1** in 80EtOH, the plot indicates that in all possible experimental conditions $k_U/k_S > 1$, since the intercept of the plots is at 109°C, which is above the boiling point of the solvent mixture. As the barrier between the assisted and unassisted process increases, the intersection of Eyring plots are shifted to higher temperatures and normal rate effects can be observed at all experimental temperatures ($k_U/k_S > 1$).

In order to rule out the possibility that the lack of the rate effect in 97TFE indicates a qualitative change in the mechanism of solvolysis, we have considered the relevant parameters earlier measured with benzyl chloride **1**. Thus, if the fraction of the reaction that proceeds by extended participation is considerably decreased in 97TFE, ρ^+ for **1** would be decreased up to -4, as is obtained for a compound that proceeds via simple π-participation. However, in both solvents measured, 80EtOH and 97TFE, those parameters are essentially the same ($\rho^+ = -1.45 \pm 0.03$ in 80EtOH and $\rho^+ = -1.76 \pm 0.04$ in 97TFE), indicating a similar amount of the positive charge on the reaction center.

In conclusion, according to the findings above it can be predicted that for reactions that proceed via distinct neighboring participation, the k_Δ/k_S ratio is sensitive to solvent ionizing power. Therefore, only a large rate effect ($k_\Delta/k_S \gg 1$) can be taken as valid proof for neighboring group participation. Moderate or even inverse rate effects can conceal some considerable participation, and ambiguous results can be clarified if the changes in k_Δ/k_S are considered after switching to a different solvent, or by changing the experimental temperature.

Figure 1. Eyring plots obtained with **1** and **1S** in 97TFE and 80EtOH

EXPERIMENTAL SECTION

Substrate preparation

Substrate **1** was prepared according to known reaction scheme.[5a,5c]

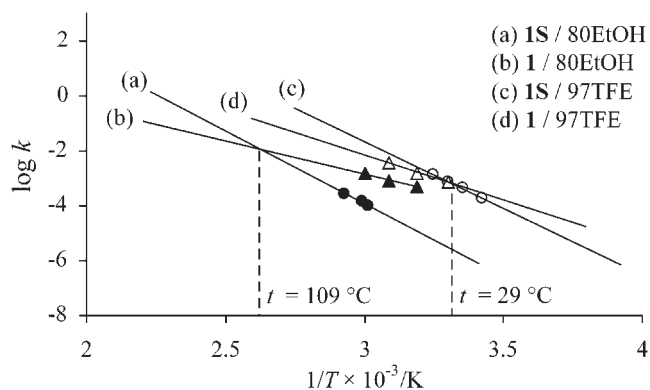### 2,6,10-trimethyl-6,10-dodecadiene-2-ol

The Grignard reagent, prepared from Mg (120 mg, 4.9 mmol) and 1-bromo-4,8-dimethyl-4,8-decadiene[5c] (690 mg, 2.82 mmol) in ether (10 mL) was cooled to 0°C and a solution of acetone (164 mg, 2.82 mmol) in 10 mL ether was added dropwise. Stirring was continued at room temperature for 1 h. The Grignard complex was hydrolyzed with saturated aqueous NH$_4$Cl. The water layer was washed with ether three times and the combined ether layers were dried over Na$_2$SO$_4$. The crude product was purified by column chromatography on silica gel. The pure 2,6,10-trimethyl-6,10-dodecadienol obtained (22.5%) was in the form of viscous oil.

^{1}H NMR (CDCl$_3$) = δ 1.22 (s, 6H, (CH$_3$)$_2$COH), 1.56–1.62 (m, 9H, C=CCH$_3$), 1.99–2.08 (m, 10H, CCH$_2$C), 5.16–5.22 (m, 2H, C=CH); ^{13}C NMR (CDCl$_3$) = δ 13.07, 15.36, 15.76, 26.32, 30.33, 34.30, 39.39, 41.67, 70.99, 118.34, 124.39, 135.32, 135.58.

2-methyl-tetradecan-2-ol

The procedure is the same as described above. From 120 mg (4.9 mmol) of Mg, 702 mg (2.82 mmol) of 1-bromododecane and 164 mg (2.82 mmol) of acetone was obtained 205 mg (31.8%) of pure alcohol.

^{1}H NMR (CDCl$_3$) = ^{TM}0.96 (t, 3H, CH$_3$CH$_2$), 1.26 (s, 6H, (CH$_3$)$_2$COH), 1.29–1.40 (m, 22H, CCH$_2$C), ^{13}C NMR (CDCl$_3$) = ^{TM}14.09, 21.33, 23.18, 30.33, 32.39, 39.39, 72.11.

1-phenyl-tridecanol

The procedure is the same as described above. From 120 mg (4.9 mmol) of Mg, 702 mg (2.82 mmol) of 1-bromododecane and 299 mg (2.82 mmol) of benzaldehyde, 505 mg (64.8%) of pure alcohol was obtained.

^{1}H NMR (CDCl$_3$) = ^{TM}0.96 (t, 3H, CH$_3$CH$_2$), 1.29–1.53 (m, 22H, CCH$_2$C), 4.50 (t, 1H, Ar-CHOH), 7.19 (s, 5H, Ar-H); ^{13}C NMR (CDCl$_3$) = ^{TM}14.18, 23.50, 23.94, 30.15, 40.00, 71.15, 126.31, 129.32, 133.66.

2-chloro-2,6,10-trimethyl-6,10-dodecadiene (**2**), 2-chloro-2-methyl-tetradecan (**2S**), and 1-phenyl-tridecanylchloride (**1S**) were prepared from the corresponding alcohol and thionyl chloride. The alcohol was dissolved in 10–15 mL of petroleum ether (bp 40–60°C) and the solution was cooled to −15°C, and SOCl$_2$ was added dropwise. The reaction mixture was stirred for 2 h under reduced pressure (about 520–560 mmHg) to remove liberated HCl and SO$_2$ continuously. Then, the petroleum ether was evaporated and crude chloride was used for kinetic measurements. Further purification proved to be unnecessary since the solvolysis rates were found to be independent of contamination.

Kinetic measurements

Solvolysis rates were followed in absolute ethanol (EtOH), 80% (v/v) aqueous ethanol (80EtOH) and 97% (wt.) aqueous 2,2,2-trifluoroethanol (97TFE) titrimetrically by means of a pH-stat (end-point titration, pH = 6.85). Typically, 0.02 mmol of the chloride was dissolved in 20 mL of the solvent that was thermostated at the required temperature (± 0.05°C), and the liberated HCl was continuously titrated by using a 0.008 M solution of NaOH in the same solvent mixture. Individual measurements could be described by the first-order law from 15% up to at least 85% completion. First-order rate constants were calculated from about 100 determinations using a nonlinear least-squares program. Measurements were usually repeated 3–4 times.

Acknowledgements

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