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Mechanism of Solvolyses of Substituted Benzyl Bromides in 80 % Ethanol

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Abstract: The mechanism of solvolysis of activated and deactivated benzyl bromides in 80 % ethanol at 25 °C has been investigated by using the Yukawa-Tsuno treatment and by correlating measured kinetic data with relative stabilities of corresponding benzyl carbocations calculated at the IEFPCM-M06-2X/6-311+G(3df,3pd) level of theory. Both correlation methods demonstrate that only benzyl bromides substituted with strong *para*-π-donors solvolyze by the S_N1 mechanism whereas other activated and deactivated substrates solvolyze by the S_N2 mechanism.

Keywords: benzyl bromide, IEFPCM, M06-2X, S_N1, S_N2, solvolysis, Yukawa-Tsuno.

INTRODUCTION

NUMEROUS kinetic and mechanistic studies on substitution reactions of benzyl derivatives in both protic and aprotic solvents have been carried out in order to elucidate the mechanisms of nucleophilic substitution at saturated carbon.[1–4] Nevertheless, some questions concerning solvolysis reactions of these substrates remain unanswered. Different types of Hammett correlations referring to solvolysis of substituted benzyl tosylates in various solvents have shown a break with decreased ρ values in the electron-withdrawing region of plots.[1a,1b,2–4] The observed break in the plots have been interpreted as clear evidence for the duality of nucleophilic substitution mechanisms in the solvolysis of benzyl tosylates.[2,3] In addition, the plots have indicated that activated benzyl tosylates solvolyze by the S_N1 mechanism, whereas those substituted with electron-withdrawing groups solvolyze by the S_N2 mechanism.[2,3] As solvolysis reactions of benzyl derivatives bearing other leaving groups have not been systematically investigated, one may have a notion that the activated primary benzylic substrates always solvolyze via the S_N1 route.[1h]

In our previous work, we have studied the solvolysis of activated *para*- and *meta*-substituted benzyl chlorides in 80 % ethanol by using the Hammett-Brown and Yukawa-Tsuno treatments of solvolysis rate constants.[5] In order to involve *ortho*-substituted benzyl derivatives in the study, we have correlated logarithms of solvolysis rate constants with relative stabilities of corresponding benzyl carbocations calculated at the IEFPCM-M06-2X/6-311+G(3df,3pd) level of theory. The correlations have revealed that only benzyl chlorides activated by strong conjugative electron-donors in the *para*-position solvolyze by the S_N1 mechanism. Accordingly, it appears that the position of the S_N1 to S_N2 mechanistic changeover in the solvolysis of the series of substituted benzyl substrates with a common leaving group is determined by the ability (i.e., nucleofugality) of the leaving group.

This observation has further prompted us to investigate the solvolysis of benzyl bromides, that is, the benzyl substrates containing the leaving group which is, according to the N_f nucleofugality scale,[6] approximately one order of magnitude more reactive than chloride and three orders of magnitude less reactive than tosylate. In addition, we intend to study the influence of a solvent on the mechanistic change in the solvolysis of the series of benzyl bromides. In this paper, we present results for solvolyses in 80 % ethanol.

EXPERIMENTAL

Preparation of Benzyl Bromides

Benzyl bromides were prepared from the corresponding benzyl alcohols and either acetyl bromide or phosphorus tribromide according to the procedures described in the Supporting Information.

Kinetic Methods

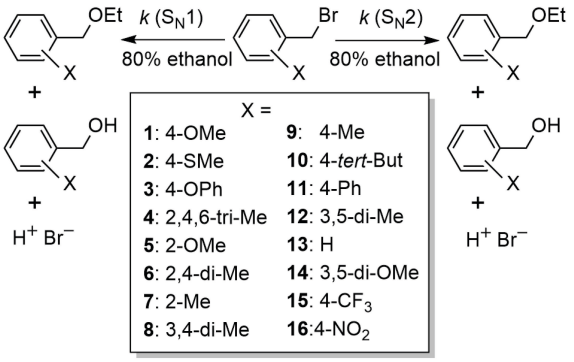
Solvolysis rate constants were determined conductometrically by using the WTW LF 530 conductometer, ME-2600 PC-DAQ board, ME-RedLab 1208FS-PLUS DAQ Minilab and Radiometer 2-pole conductivity cell (CDC641T). An 80 % ethanol-water mixture (*v*/*v*) for kinetic measurements was prepared from pure ethanol (Carlo Erba) and deionized water. Prior to each run, 30 mL of the freshly prepared mixture was thermostated at a given temperature (± 0.1 °C). Typically, 5 mg of a substituted benzyl bromide was dissolved in 0.10 mL of dichloromethane, and then injected into the mixture. Individual rate constants were obtained by least-squares fitting of conductivity data to the first-order kinetic equation for three to four reaction half-lives. Final rate constants at 25 °C were averaged from at least three kinetic runs, whereas those at other temperatures were averaged from at least two runs.

Computational Methods

Calculations were carried out with the GAUSSIAN 16 (A.03)[7] software package. Geometry optimizations were performed using the M06-2X[8] DFT method, 6-311+G(3df,3pd) basis set and the IEFPCM[9] model with water as a solvent. The solvation model was utilized with default parameters of GAUSSIAN 16. Frequency calculations were performed upon the optimized geometries at the same level of theory to compute thermal corrections at 298.15 K. The ultrafine grid and tight convergence criteria were applied in all computations. Using the vibrational analysis, all stationary points were verified as minima (no imaginary frequencies). Coordinates of optimized geometries and calculated energies are given in the Supporting Information (Table S4). When calculating entropy contributions to the free energy of each conformer, a quasiharmonic correction[10] has been applied by setting all vibrational frequencies that are lower than 100 cm^{-1} to 100 cm^{-1}.[5] Corrected free energies are listed in Table S4.

RESULTS AND DISCUSSION

First-order rate constants for solvolyses of sixteen variously substituted benzyl bromides (**1Br–16Br**) in 80 % ethanol (Scheme 1) were determined conductometrically at 25 °C (Table S1) and at higher temperatures (Table S2). As some activated and all deactivated benzyl bromides were shown



Scheme 1. Solvolyses of X-benzyl bromides (1Br–16Br) in 80 % ethanol.

to solvolyze very slowly at ambient temperature (**7Br–16Br**), in these cases, solvolysis rate constants at 25 °C were extrapolated from data obtained at higher temperatures by using the Eyring equation (Table S1).

Comparison of first-order rate constants at 25 °C (Table S1) generally shows that the solvolysis rate in the series of benzyl bromides increases as the electron-donating ability of the ring substituents increases. In order to investigate the mechanism of solvolyses in the ethanol-water mixture, that is, to locate the position of the S_N1 to S_N2 mechanistic changeover in the series, the rate constants at 25 °C for *meta*- and *para*-substituted derivatives (**1Br–3Br**, **8Br–16Br**) have been analyzed in terms of the Yukawa-Tsuno treatment [Equation (1)].[11]

$$\log (k / k_0) = \rho [\sigma^\circ + r (\sigma^+ - \sigma^\circ)] \quad (1)$$

Parameters σ^+ and σ° are well-known substituent constants, whereas the *r* parameter represents a measure of the extent of resonance demand for a given reaction. An *r* value of 1.3 for the solvolysis of benzyl tosylates had been determined earlier by Tsuno and coworkers,[3] and we have already applied the same value for analyzing solvolysis rate constants of substituted benzyl chlorides.[5] The Yukawa-Tsuno correlation for the solvolysis of benzyl bromides in 80 % ethanol at 25 °C is presented in Figure 1.

As in the case of the solvolysis of benzyl chlorides in 80 % ethanol at 60 °C,[5] the correlation exhibits a breakdown of the linear relationship in the region of solvolyses of activated substrates. A clearly separated steep line ($\rho^+ = -5.1$) indicates that solvolyses of benzyl bromides activated by the strong *para*-π-donors proceed by the S_N1 mechanism. Regardless of whether distribution of data points in the region of alkyl-substituted and deactivated derivatives exhibits a further break in linearity or curvature, ρ^+ obviously decreases with decreasing electron-donating ability of the substituents. This trend reveals that S_N2 solvolyses of activated benzyl derivatives (**8Br–11Br**) occur via loose transition states, that is, via

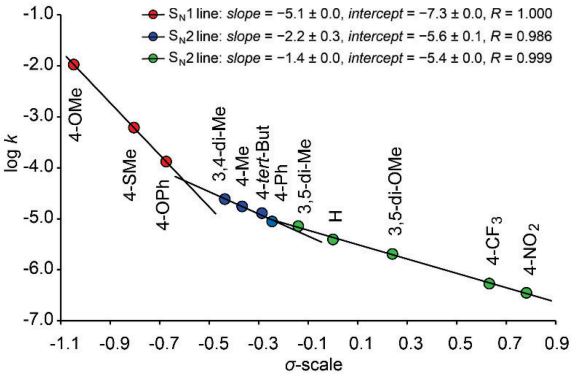
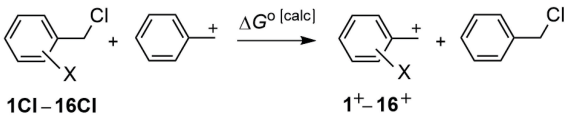


Figure 1. Yukawa-Tsuno correlation for solvolyses of X-benzyl bromides (**1Br**–**3Br**, **8Br**–**16Br**) in 80 % ethanol at 25 °C. σ° and σ^+ values were taken from reference [11]. Errors shown are standard errors.

transition states characterized by considerable ionic character. In addition, transition states for the solvolysis of weakly activated and deactivated bromides (**12Br**–**16Br**) are obviously tighter, however, a certain amount of the positive charge is still delocalized into the ring π-system.

Ortho-substituted derivatives of all types of benzylic substrates (i.e., primary–tertiary) have been regularly omitted in solvolysis studies including Hammett correlations due to unpredictable *ortho*-effect.[12] In our previous study, we have demonstrated that the logarithms of rate constants for S_N1 and S_N2 solvolyses of benzyl chlorides in 80 % ethanol correlate very well with relative stabilities of the corresponding benzyl carbocations calculated as standard free energies {$\Delta G^{\circ\,[calc]}$} of isodesmic reactions in Scheme 2.[5] Furthermore, the correlation has confirmed the S_N1–S_N2 mechanistic changeover observed in the Yukawa-Tsuno plot and additionally shown that even benzyl chlorides activated by substituents in *ortho*-positions solvolyze via the S_N2 route. In order to calculate standard free energies, the M06-2X/6-311+G(3df,3pd) level of theory including the IEFPCM model with water as a solvent was employed.[5] It had been demonstrated earlier that this combination provides both kinetic and thermodynamic data that correlate very well with measured solvolytic kinetic data.[13] Water has been shown to be a good medium for attenuating strong electronic effects present in the gas phase. For example, the above mentioned log *k* versus $\Delta G^{\circ\,[calc]}$ correlation for S_N1 solvolyses of benzyl chlorides in 80 % ethanol has provided a slope of almost unity, which is in accordance with presumption that these solvolyses proceed through very late transition states. In addition to that, to reduce errors when calculating standard free energies, entropy contributions to the free energies of conformers were corrected by using the quasiharmonic approximation.[10]

Almost the same set of $\Delta G^{\circ\,[calc]}$ values is used here for correlation with log *k* values for the solvolysis of benzyl



1Cl – **16Cl** **1$^+$** – **16$^+$**

X =	**6**: 2,4-di-Me	**12**: 3,5-di-Me
1: 4-OMe	**7**: 2-Me	**13**: H
2: 4-SMe	**8**: 3,4-di-Me	**14**: 3,5-di-OMe
3: 4-OPh	**9**: 4-Me	**15**: 4-CF_3
4: 2,4,6-tri-Me	**10**: 4-*tert*-But	**16**: 4-NO_2
5: 2-OMe	**11**: 4-Ph	

Scheme 2. Isodesmic reactions used for determining stabilities of substituted benzyl carbocations (**1$^+$**–**16$^+$**) relative to the parent benzyl carbocation (**13$^+$**).

bromides in 80 % ethanol at 25 °C. To include the least reactive bromides (Scheme 1, **14Br**–**16Br**) in the correlation, standard free energies of the corresponding isodesmic reactions for chlorides (Scheme 2, **14Cl**–**16Cl**) were calculated as described above and in more detail in Ref. [5] (Table S3). The plot is shown in Figure 2. This correlation, as well as the Yukawa-Tsuno correlation (Figure 1), indicates that only benzyl bromides activated by the strong conjugative *para*-electron-donors solvolyze by the S_N1 mechanism in 80 % ethanol. Thus, even the substrates activated by the methyl and methoxy substituents in *ortho*-positions (i.e., relatively reactive substrates which cannot be included in Hammett correlations) solvolyze in 80 % ethanol with the nucleophilic assistance of the solvent. The correlation also indicates a relatively good and long linear correlation in the region of S_N2 solvolyses. A break in the region of low reactivity can be rationalized in terms of increasing tightness of the corresponding S_N2 transition states. The analogous pattern of the correlation was also observed in the above-mentioned log *k* versus $\Delta G^{\circ\,[calc]}$ plot for solvolyses of benzyl chlorides.[5]

The correlation in Figure 2 implies that solvolyses of *ortho*-substituted derivatives (**4Br**–**6Br**) represent borderline cases as the corresponding rates are close to rates for S_N1 solvolyses of **2Br** and **3Br**. Moreover, **4Br** solvolyzes in 80 % ethanol even faster than **3Br**. However, rates for the S_N1 solvolysis of the *ortho*-derivatives (**4Br**–**6Br**) can be predicted from the S_N1 line (Figure 2, dashed lines) and those predictions indicate that the S_N2 route of these substrates is appreciably more favorable than the S_N1 route. Consequently, regardless of the relative rates of solvolyses, the most reactive *ortho*-substituted benzyl bromides (**4Br**–**6Br**) solvolyze in 80 % ethanol either predominantly or exclusively via the S_N2 route. On the other hand, the S_N2 line cannot be used for analogous predictions since the nature of S_N2 transition states (loose-tight) affects the linear relationship between solvolysis kinetic data and calculated relative stabilities of benzyl carbocations.

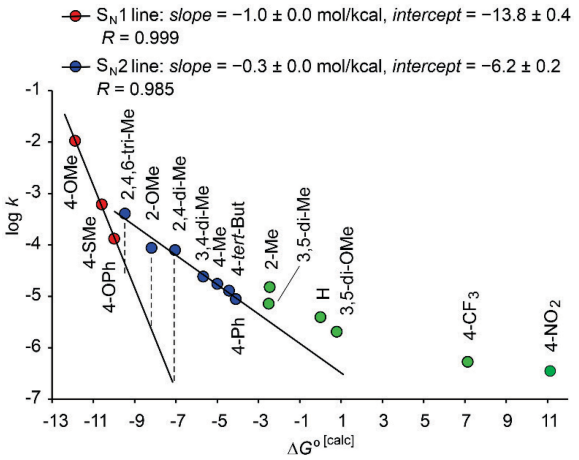


Figure 2. Correlation of logarithms of rate constants for the solvolysis of X-benzyl bromides in 80 % ethanol at 25 °C versus relative stabilities of X-benzyl cations in water (at 25 °C) calculated by using the isodesmic reactions given in Scheme 2. Values of $\Delta G°$ [calc] for **1Cl**–**12Cl** were taken from Ref. [5]. Errors shown are standard errors.

CONCLUSION

Both the Yukawa-Tsuno treatment of first-order rate constants for solvolyses of substituted benzyl bromides in 80 % ethanol at 25 °C and the correlation of the logarithms of solvolysis rate constants (including those for solvolyses of activated *ortho*-substituted derivatives) with relative stabilities of the corresponding benzyl carbocations calculated at the IEFPCM-M06-2X/6-311+G(3df,3pd) level of theory have shown that only benzyl bromides activated by conjugative *para*-electron-donors (i.e., –OMe, –SMe and –OPh) solvolyze by the S_N1 mechanism. Accordingly, even the 2,4,6-trimethyl- and 2-methoxy-substituted derivatives solvolyze via the S_N2 route. The same pattern of the S_N1-S_N2 mechanistic change in a series has previously been observed in solvolyses of benzyl chlorides, i.e., the series bearing approximately one order of magnitude less reactive leaving group.[5] On the other hand, other authors had reported earlier that the solvolysis of all activated benzyl tosylates proceeds through the S_N1 route.[2,3] Thus, the nature of a leaving group (i.e., nucleofugality) is a mechanism-determining factor in the solvolysis of a series of activated benzyl substrates.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: https://doi.org/10.5562/cca3885.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from Adobe's web site.

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