A Study of Solvolyses of *ortho-* and *para* Carboxybenzyl Bromides Using the Extended Grunwald-Winstein Equation

Jin-Woo Ra, Jin Burm Kyong,* and Dennis N. Kevill[†]

Department of Chemistry and Applied Chemistry, Hanyang University, Ansan, Gyunggi-Do 425-791, Korea
[†]Department of Chemistry and Biochemistry, Northern Illinois University, Dekalb, Illinois 60115-2862, U.S.A.
*Received August 29, 2002*

Solvolyses of benzyl halides have been studied extensively.[1] However, the reaction mechanism of the isomeric carboxybenzyl halides is not well established. Accordingly, a study of the mechanism of the isomeric carboxybenzyl bromides under solvolytic conditions is one of the subject of continuing interest.

Recently, the extended Grunwald-Winstein equation [eqn. (1)] has been applied to a very useful mechanistic tool for solvolysis reactions.[2-5]

$$\log(k/k_o) = lN_T - mY_X - c \qquad (1)$$

In equation (1), k and k_o are the specific rates of solvolysis in a given solvent and in the standard solvent (80% ethanol), respectively; l is the sensitivity towards changes in solvent nucleophilicity (N_T);[6] m is the sensitivity towards changes in solvent ionizing power (Y_X);[3,7] c is a residual term. The equation is a very useful indicator of the extent of nucleophilic participation by the solvent, as expressed in the parameter, l, which, in turn, is directly related to whether a substitution reaction is unimolecular (S_N1) or bimolecular (S_N2). Also, there is a general tendency for a decrease in m values as l values increase.

For *para* carboxybenzyl bromide (*p*-isomer, 1), it is to be expected that the electron withdrawing carboxylic acid group will favor S_N2 reaction, which is already known to be the favored pathway for benzyl bromide in the absence of substituents. Applying the extended Grunwald-Winstein equation [eqn. (1)] using N_T and Y_{Br} values, one would expect an l value approaching unity and an m value in the 0.4 to 0.5 range.[8] There are indications that, in 80% aqueous dioxane as solvent, the *ortho* carboxybenzyl bromide (*o*-isomer, II) reacts about 80 times faster than the *p*-isomer(I), which suggests the possibility of an intramolecular assistance to the substitution process.[9] If intramolecular assistance operates, it would be expected to operate as in eqn. (2):
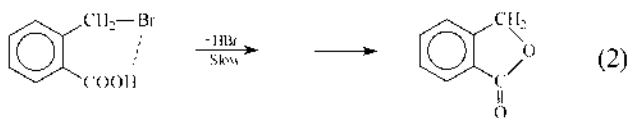
If the mechanism operates according to eqn. (2), or some closely related variant, one would expect the influence of ionizing power (ion-pair-like species). If intramolecular

assistance should not operate for solvolyses of *o*-isomer(II), one would predict an *l*-value close to that operating for solvolyses of *p*-isomer(I), reflecting extensive nucleophilic assistance from a solvent molecule.

In the present study, we report concerning the application of the extended Grunwald-Winstein equation [eqn. (1)] to the solvolyses of *para* and *ortho* carboxybenzyl bromides in wide variety of hydroxylic solvents. This is the first time that this eqn. (1) has been used as a tool in a study of possible intramolecular nucleophilic participation during solvolyses.

Results and Discussion

The specific rate constants, k_{obs} of solvolyses for *p*-isomer (I) and *o*-isomer(II), at 25.0 °C or 45.0 °C, in binary solvent mixtures are reported in Table 1, together with the N_T and Y_{Br} values. The solvents consisted of ethanol (EtOH), binary mixtures of water with ethanol, methanol (MeOH), 2,2,2-trifluoroethanol (TFE) and acetone. As shown in Table 1, the k_{obs} for reaction of the *o*-isomer(II) in all the solvents is solvolyzed much more rapidly than its *p*-isomer(I). The high reactivity of *o*-isomer(II) reverses the usual order of reactivity among isomers of this type. Andrews and coworkers[9] have demonstrated that the high reactivity of the *o*-isomer(II) is rationalized in terms of internal participation by a neighboring carboxylic acid group (*o*-COOH). Such participation is not possible for *p*-isomer(I) because of unfavorable molecular geometry.

An analysis in terms of the simple Grunwald-Winstein equation [eqn. (1) without the lN_T term] to the specific rates of solvolysis of *p*-isomer(I) (from Table 1) leads to an extremely poor correlation with value of 0.170 for the correlation coefficient(r). Again, analysis of the data using the extended Grunwald-Winstein equation [eqn. (1)] leads to a good linear correlation with values of 1.24 ± 0.09 for l, 0.59 ± 0.05 for m, 0.10 ± 0.05 for c, 0.973 for the correlation coefficient, and 107 for the F-test value (Figure 1). These l and m values (or l/m ratio) are similar to those obtained to reflect the bimolecular pathway within the analyses of the solvolyses of *p*-nitrobenzyl *p*-toluenesulfonates[10] and haloformates.[5(c)]

Application of the equation (1) to solvolyses of *o*-isomer(II) leads to a poor correlation with values of 0.90 ± 0.14 for l, 0.49 ± 0.10 for m, 0.007 ± 0.14 for c, 0.933 for the

Notes

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Table 1. Specific rate constants (k_{obs}) for the solvolyses of *p*-carboxybenzyl bromide[a](1) (at 45.0 °C) and *o*-carboxybenzyl bromide[b](11) (at 25.0 °C) in binary hydroxylic solvents

Solvent[c]	$10^5 k_{obs}$ (sec^{-1})$_p$	$10^4 k_{obs}$ (sec^{-1})$_o$	N_T[d]	Y_{Br}[e]
100EtOH[f]	0.188 ± 0.003	3.04 ± 0.1	0.37	-2.40
90EtOH	0.455 ± 0.02	4.92 ± 0.06	0.16	-0.84
80EtOH[f]	0.752 ± 0.03[h]	15.1 ± 0.2[j]	0.00	0.00
70EtOH	1.09 ± 0.04	27.1 ± 0.2	-0.20	0.68
50EtOH[f]	2.45 ± 0.08	-	-0.58	1.88
90MeOH	0.853 ± 0.02	3.93 ± 0.2	-0.01	-0.14
80MeOH	1.46 ± 0.01	10.7 ± 0.3	-0.06	0.70
60MeOH	3.76 ± 0.09	47.7 ± 0.4	-0.54	2.04
50MeOH	5.21 ± 0.2	-	-0.75	2.61
80Acetone	0.127 ± 0.009	4.25 ± 0.1	-0.37	-0.70
60Acetone	0.606 ± 0.02	25.3 ± 0.2	-0.52	1.03
50Acetone	1.06 ± 0.08	-	-0.7	1.74
97TFE[g]	-	0.275 ± 0.03	-3.3	2.53
90TFE[g]	0.0127 ± 0.002	0.385 ± 0.02	-2.55	2.58
70TFE[g]	0.210 ± 0.01[i]	11.3 ± 0.3[k]	-1.98	2.79
50TFE[g]	0.781 ± 0.03	-	-1.73	3.04

[a]Substrate concentration of *ca.* 5.40×10^{-4} M. [b]Substrate concentration of *ca.* 5.00×10^{-4} M. [c]Volume/volume basis at 25.0 °C, except for TFE-H$_2$O mixtures, which are on a weight/weight basis. [d]Based on the specific rates of solvolysis of the S-methyldibenzothiophenium ion, from ref. 6 and ref. 8. [e]Y_{Br} values of 1-adamantyl bromidefrom ref. 3 and ref. 7. [f]Percentage of products for the solvolysis of these substrates: *p*-isomer. 100%EtOH: *p*-carboxybenzyl ethyl ether (retention time:44.86 min. 100%o), 80%EtOH: *p*-carboxybenzyl ethyl ether (retention time: 44.86 min, 4.70%o), *p*-carboxybenzyl alcohol (retention time: 71.24 min, 95.3%o), *o*-isomer: 100%EtOH: *o*-carboxybenzyl ethyl ether (retention time: 41.61 min, 8.52%o), phthalide (retention time: 49.11 min, 91.5%o). 80%EtOH: *o*-carboxybenzyl ethyl ether (retention time: 41.61 min), phthalide (retention time: 49.11 min, 97.7%o), 50%EtOH: phthalide (retention time: 49.11 min, 100%o). [g]TFE is 2,2,2-trifluoroethanol. [h]At 55 °C, 68 °C, and 73 °C, values of 1.87×10^{-5} sec^{-1}, 5.76×10^{-5} sec^{-1}, and 8.97×10^{-5} sec^{-1}, respectively, were obtained. $\Delta H^{\neq} = 19.6$ kcal·mol^{-1} and $\Delta S^{\neq} = -20.7$ cal·K^{-1}·mol^{-1}. [i]At 55 °C, 68 °C, and 73 °C, values of 0.602×10^{-5} sec^{-1}, 1.09×10^{-5} sec^{-1}, and 1.43×10^{-5} sec^{-1}, respectively, were obtained. $\Delta H^{\neq} = 13.8$ kcal·mol^{-1} and $\Delta S^{\neq} = -41.3$ cal·K^{-1}·mol^{-1}. [j]At 35 °C and 45 °C, values of 30.6×10^{-4} sec^{-1} and 44.2×10^{-4} sec^{-1} were obtained. $\Delta H^{\neq} = 9.49$ kcal·mol^{-1} and $\Delta S^{\neq} = -39.6$ cal·K^{-1}·mol^{-1}. [k]Value of 33.0×10^{-4} sec^{-1} at 45 °C was obtained. $\Delta H^{\neq} = 9.52$ kcal·mol^{-1} and $\Delta S^{\neq} = -40.1$ cal·K^{-1}·mol^{-1}.

correlation coefficient, and 20 for the F-test value. Accordingly, we applied the use of a new term, aromatic ring parameter *I*, together with N_T and Y_X in the extended Grunwald-Winstein equation to examine the solvolytic behavior of benzylic substrates.[11] To study the nucleophilic solvent participation in benzylic solvolysis, a three-term equation [eqn. (3)] should be applied.

$$\log(k/k_o) = lN_T + mY_X + hI + c \qquad (3)$$

h is the sensitivity to changes in aromatic ring parameter values. Application of eqn. (3) shows a good linear correlation [$\log(k/k_o) = 0.73N_T + 0.41Y_{Br} - 0.78I$, r = 0.952] for the specific rates of solvolysis of *o*-isomer(II) in a variety of binary solvent mixtures. This result can also be predicted that the delocalization of the developing positive charge on the methylene (α-carbon) of the *o*-isomer(II) will be larger than in the case of the *p*-isomer(I). Accordingly, it is shown that the solvolysis of *o*-isomer(II) in the transition state can
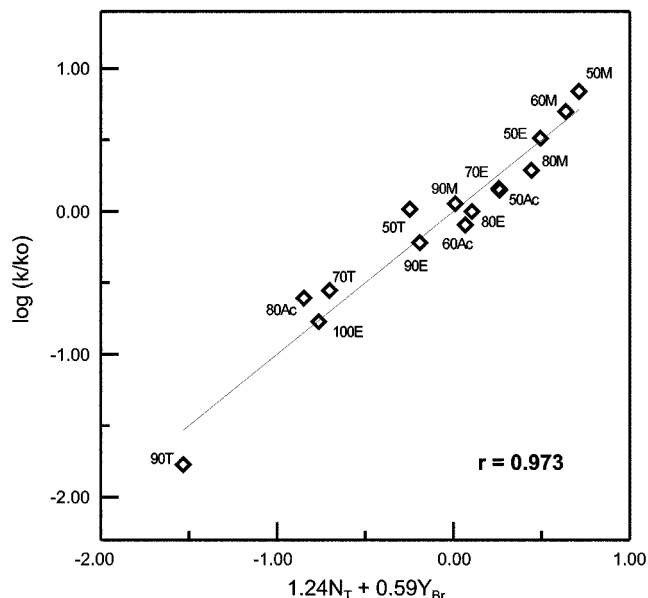
Figure 1. Plot of $\log(k/k_o)$ for solvolysis of *p*-carboxybenzyl bromide against ($1.24N_T + 0.59Y_{Br}$) in binary solvents.

be affected not only by the structure of the R-group (RX) and the nature of the leaving group but also by the effects involving changes in solvation of the aromatic ring (the *hI* term).

The values of the enthalpies and entropies of activation for the solvolyses of *p*-isomer(I) and *o*-isomer(II) in 80% aqueous ethanol and 70% aqueous 2,2,2-trifluoroethanol are reported in the footnotes to Table 1. These values are consistent with the finding by Andrews.[9] Priebat[12] and our previous study[13,14], with the very negative entropies of activation, and with the bimolecular nature of the proposed rate-determining step. From the data of $\Delta H^{\neq}$ for *p*-isomer(I) and *o*-isomer(II), it appears the energy barrier for reaction of *o*-isomer(II) is significantly less than *p*-isomer(I), and this is presumed to reflect the contribution of the *o*-carboxylic acid group.

For reactions of *p*-isomer(I) and *o*-isomer(II), product studies were carried out in ethanol, 80% and 50% aqueous ethanol with the analyses employing gas chromatography and those results are reported in the footnotes to Table 1. The fact that the product obtained from the *o*-isomer(II) was identified as phthalide supports the possibility of an intramolecular participation due to assistance of the carboxyl group. From *p*-isomer(I), *p*-carboxybenzyl ethyl ether and alcohol were obtained.

In conclusion, the specific rates of solvolyses of *p*-isomer (I) and *o*-isomer(II) are very well correlated by the equation (1) and (3) over a wide range of solvents, respectively. The solvolysis of *p*-isomer(I) (*l* = 1.24, *m* = 0.59, *l/m* = 2.1), where bond making (*l*-value) is more progressed than bond breaking (*m*-value), is indicated to proceed by the bimolecular pathway(associated S_N2), reflecting nucleophilic assistance from a solvent molecule. The bond making (*l*-value) of *o*-isomer(II)(*l/m* = 1.8) is less progressed than *p*-isomer(I) (*l/m* = 2.1). Therefore, the solvolysis of *o*-isomer(II) is

considered to reflect the operation of both the intramolecular assistance of o-carboxylic acid group (ion-pair like species) and the nucleophilic assistance from a solvent molecule.

Experimental Section

o-Carboxybenzyl bromide (o-HOOCC$_6$H$_4$CH$_2$Br) was prepared from the corresponding o-toluic acid(Aldrich, o-HOOCC$_6$H$_4$CH$_3$) according to previously published procedures.[15] p-Carboxybenzyl bromide (Aldrich, p-HOOCC$_6$H$_4$-CH$_2$Br) was recrystallized from benzene (Aldrich) before using. Solvents were purified and the kinetic runs carried out as previously described.[13] All runs were performed at least in duplicate. The l, m and h values were calculated using the multiple regression analyses. The products were directly analyzed by gas chromatography as previously described.[5(b)]

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