European Journal of Chemistry

Journal webpage: www.eurjchem.com

Correlation analysis of the rates of solvolysis of 4-bromopiperidine: A reaction following a Grob fragmentation pathway

Dennis Neil Kevill [1], Zoon Ha Ryu [2] and Malcolm John D'Souza [3,*]

[1] *Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, Illinois 60115-2862, USA*
[2] *Department of Chemistry, Dong-Eui University, 995 Eomgwango, Busan-Jin-Gu, Busan 614-714, Republic of Korea*
[3] *Department of Chemistry, Wesley College, 120 North State Street, Dover, Delaware 19901-3875, USA*

** Corresponding author at: Department of Chemistry, Wesley College, 120 North State Street, Dover, Delaware 19901-3875, USA. Tel.: +1.302.7362528. Fax: +1.302.7362301. E-mail address: malcolm.dsouza@wesley.edu (M.J. D'Souza).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.8.2.162-167.1566

Received: 13 March 2017
Received in revised form: 11 April 2017
Accepted: 19 April 2017
Published online: 30 June 2017
Printed: 30 June 2017

KEYWORDS

Solvolysis
Mechanism
Correlation
4-Bromopiperidine
Grob fragmentation
Grunwald-Winstein equation

ABSTRACT

A Grunwald-Winstein treatment of the specific rates of solvolysis of 4-bromopiperidine gives for aqueous ethanol, methanol, acetone, and dioxane a very good logarithmic correlation against the Y_{Br} solvent ionizing power values with a slope (*m* value) of 0.46±0.02, consistent with the operation of a synchronous Grob fragmentation mechanism. When the organic component of the solvent is 2,2,2-trifluoroethanol (TFE), the data points show a negative deviation, consistent with an appreciable deactivating interaction of the acidic TFE component of the solvent with the lone-pair of electrons present on the nitrogen.

Cite this: *Eur. J. Chem.* **2017**, *8(2)*, 162-167

1. Introduction

A study by D'Arcy, Grob, Kaffenberger and Krasnobajew [1] found that, in 80% ethanol-20% water (volume/volume), 4-chloropiperidine (**1**) undergoes solvolysis by a pathway involving fragmentation, which was best described as being synchronous in nature. This is a reaction where a study of the variation of the rate, with changes in the solvent composition for the solvolysis, can give valuable information. In particular, analysis in terms of a two-term [Equation 1] or one-term (lN_T or mY_X omitted) Grunwald-Winstein equation [2,3] can indicate the relative importance of solvent ionizing power [4] and solvent nucleophilicity [5] within the mechanistic pathway.

$$\log (k/k_o)_{RX} = lN_T + mY_x + c \quad (1)$$

In Equation (1), k and k_o are the specific rates (first-order rate coefficients) for solvolysis RX in a given solvent and in 80% ethanol (the arbitrarily chosen standard solvent), respectively, l is the sensitivity to changes in solvent nucleophilicity (N_T), m is the sensitivity to changes in solvent ionizing power (Y_X for a leaving group X) and c is a constant (residual) value. The l and m values reflect the relative importance of nucleophilicity and ionizing power for a given solvolysis.

Grob and coworkers have carried out extensive studies of a variety of fragmentation reactions with the results largely published in German in *Helvetica Chimica Acta.* Fortunately, for readers not well versed in the German language, there are two excellent reviews, which were published in both German and English [6,7]. The first deals with the general principles of heterolytic fragmentations and the second reviews the mechanistic and stereochemical considerations of the fragmentations.

The solvolyses of 4-chloropiperidine (**1**), although 113 times as rapid in 80% ethanol at 100 °C as the corresponding solvolysis of cyclohexyl chloride [1], were still quite slow and, to lower the temperature required, we substituted the corresponding bromo-derivative, which would be expected to react some one or two orders of magnitude faster at a given temperature [8]. In this way, the solvolysis rates in a wide variety of hydroxylic solvents could be conveniently studied at 55 °C. The 4-bromopiperidine (**2**) is commercially available as its hydrobromide and, since we add triethylamine and/or hydroxide ion to neutralize the acid produced in the solvolysis [1] (so as to prevent protonation of the nitrogen of the

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.8.2.162-167.1566

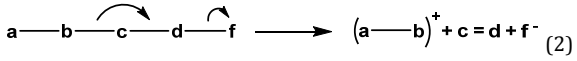
Table 1. Effect of varying the concentration of triethylamine, in the presence or absence of one equivalent of tetraethylammonium hydroxide, on the first-order rate coefficient (k, s^{-1}) [a] for solvolysis of 2.0×10^{-4} mol/dm^3 4-bromopiperidine, as formed *in situ* from the hydrobromide at 55.0 °C, tabulated as 10^4 k values.

Solvent [b,c]	[Et_3N], mol/dm^3			
	0.00040	**0.00060**	**0.00040 (+0.00020 NEt_4OH)**	**0.00080**
80E-20W (v/v)	1.03±0.02	0.99±0.02	1.06±0.06	1.08±0.02
30M-70W (v/v)	32.1±0.90	32.7±0.70	37.3±0.50	40.4±0.30
80T-20W (w/w)	1.10±0.05	1.08±0.08	1.14±0.06	1.22±0.01
70T-30W (w/w)	1.31±0.03	1.79±0.08	1.84±0.04	1.94±0.04

[a] Average of at least duplicate determinations, reported together with the standard deviation.
[b] E, W, M, T represent ethanol, water, methanol, 2,2,2-trifluorethanol.
[c] The (v/v) indicates volume-volume (at 25.0 °C) and the (w/w) indicates weight-weight.

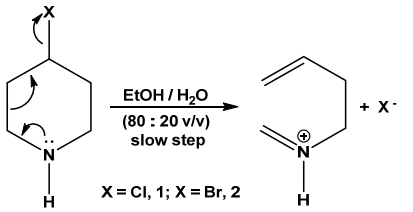
unreacted 4-halopiperidine), we added the substrate to the solvent under consideration as the hydrobromide and employed sufficient base to both liberate **2** and to neutralize all of the acid subsequently produced during its solvolysis.

A general scheme for a Grob fragmentation [1,6,7] is shown in Equation (2).



(2)

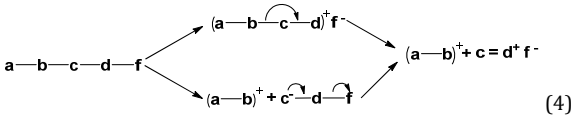
This is the mechanism that was applied [1,6,7] to the fragmentation of 4-chloropiperidine in 80% ethanol-20% water, Equation (3).



(3)

The carbimonium ion formed is then spontaneously hydrolyzed to 1-amino-3-butene which, after treatment with *p*-toluenesulfonyl chloride and sodium hydroxide, was isolated [1] as the ditosyl derivative [CH_2=CH-CH_2-CH_2-N($SO_2C_6H_4$-*p*-CH_3)$_2$], which could be stabilized by hydrogenation of the double bond.

In a study of the trifluoroacetolysis of variously substituted tetrahydropyranyl methanesulfonates (mesylates) [9], it was demonstrated that the tetrahydropyranyl cation was a common intermediate for Grob fragmentation [following the upper pathway of Equation (4)], Prins cyclizations [10] and 2-oxonia-Cope rearrangements [11]. This suggested that it would be worthwhile to see if any evidence for this type of non-synchronous pathway could be found in the solvolyses of 4-bromopiperidine (**2**).



(4)

2. Experimental

The 4-bromopiperidine hydrobromide (Aldrich, 98%), triethylamine (Aldrich ≥ 99.5%) and tetraethylammonium hydroxide (Aldrich, 35% by weight in water) were used as received. The purifications of acetone [12], acetonitrile [13], dioxane [12], ethanol [12], methanol [12], and 2,2,2-trifluoro ethanol [14] were carried out as previously described.

The aqueous-organic solvents were prepared by the mixing of appropriate volumes of the purified organic solvent and water at 25 °C, except for the aqueous TFE solvents, of known N_T [5] and Y_{Br} [4,15] values, which were prepared on a weight-weight basis.

Initial experiments to determine the best reaction conditions as regards the amount of excess base are summarized in Table 1. Both triethylamine alone and triethylamine plus one equivalent (as regards the concentration of 4-bromopiperidine (**2**)) tetraethylammonium hydroxide were considered. It was found that, within reasonable limits, the amount of excess base was not critical. The concentration chosen for the conductometric determination of the specific rates of solvolysis of 4-bromopiperidine at 55.0 °C and the procedure for preparing 2.0 mL of solution are presented in footnote (a) to Table 2. Details of the conductivity apparatus and the computer procedure for calculation of the specific rates have previously been reported [16,17]. The regression analyses were performed using commercially available statistical packages.

3. Results and discussion

In Table 1 is shown the effect of varying the triethylamine concentration on the first-order rate coefficient (specific rate) for solvolysis when the 4-bromopiperidine (**2**) is introduced as its hydrobromide to four typical aqueous-organic solvents at 55.0 °C. Also shown is the effect of including one equivalent of tetraethylammonium hydroxide for the initial deprotonation of the 4-bromopiperidinium ion, to liberate the free **2**. The first vertical column in the table is for addition of two equivalents of triethylamine, the minimum amount for the initial deprotonation followed by complete neutralization of the acid produced during the solvolysis. The next two vertical columns would each have an excess of one equivalent of triethylamine and the final vertical column is for an excess of two equivalents of triethylamine over the minimum required to allow a complete solvolysis of the unprotonated **2**.

In all four solvent systems, the highest specific rate values are for the runs with the largest triethylamine concentration, but the increases in specific rate with increases in excess amine concentration are small. This aspect of the study indicates that a modest excess of triethylamine, assuring an essentially complete deprotonation of the 4-bromopiperidine throughout the solvolysis, would afford the best conditions for a study of its solvolysis reactions.

In Table 2, the specific rates (first-order rate coefficients) are presented for the solvolysis of 2.0×10^{-4} mol/dm **2**, in the presence of 6.0×10^{-4} mol/dm triethylamine, in 100% H_20 and in thirty-two aqueous-organic solvents, all of which have tabulated values for both N_T and Y_{Br} available. These known N_T and Y_{Br} values are also tabulated in Table 2, and their sources indicated as footnotes.

When the original (one-term) Grunwald-Winstein equation [4,18] [Equation (1) without the l N_T term] is applied to the data of Table 2, it is found that the specific rates of solvolysis in the 29 solvents not containing a 2,2,2-trifluoro fluoroethanol (TFE)-component give a linear plot (Figure 1) and correlation analysis leads to Equation (5).

$$\log (k/ko)_2 = (0.46 \pm 0.02)\, Y_{Br} - (0.02 \pm 0.04) \quad (5)$$

n = 29; Correlation Coefficient (r) of 0.987; F-test value of 967.

Table 2. First-order rate coefficients for the solvolyses of 4-bromopiperidine at 55.0 °C [a] and the appropriate solvent nucleophilicity (N_T) and solvent ionizing power (Y_{Br}) values.

Solvent [b]	$10^4\ k/s^{-1}$ [c]	N_T [d]	Y_{Br} [e]
90% EtOH	0.72±0.01	0.16	-0.84
80% EtOH	0.99±0.02	0.00 [f]	0.00 [f]
70% EtOH	1.72±0.02	-0.20	0.68
60% EtOH	4.40±0.04	-0.38	1.26
50% EtOH	8.98±0.11	-0.58	1.88
40% EtOH	16.7±0.3	-0.74	2.62
30% EtOH	29.3±0.5 [g]	-0.93	3.40
20% EtOH	54.9±0.6 [g]	-1.16	3.92
10% EtOH	82.9±0.6	-1.31	4.17
100% H_2O	181±7 [h]	-1.38	4.44
90% MeOH	0.53±0.01	-0.01	-0.14
80% MeOH	1.32±0.02	-0.06	0.70
70% MeOH	3.30±0.04	-0.40	1.42
60% MeOH	6.62±0.13	-0.54	2.04
50% MeOH	11.7±0.2	-0.57	2.61
40% MeOH	25.2±0.5 [g]	-0.87	3.14
30% MeOH	32.7±0.7 [h]	-1.06	3.61
20% MeOH	53.3±0.6 [g]	-1.23	3.94
10% MeOH	90.1±1.5 [g]	-1.36	4.17
70% Acetone	1.88±0.01	-0.42	0.20
60% Acetone	3.64±0.02	-0.52	1.20
50% Acetone	9.50±0.08	-0.70	1.82
40% Acetone	22.6±0.8	-0.83	2.43
30% Acetone	31.4±0.2	-0.96	2.99
20% Acetone	49.1±0.8	-1.11	3.66
10% Acetone	85.1±0.7	-1.23	4.05
80% Dioxane	0.60±0.01	-0.46	-0.60
70% Dioxane	0.95±0.01	-0.37	-0.01
60% Dioxane	2.68±0.06	-0.54	0.82
80% TFE	1.08±0.08	-2.19	1.95
70% TFE	1.79±0.08 [g]	-1.98	2.21
60% TFE	2.62±0.02	-1.85	2.53
50% TFE	4.23±0.05	-1.73	2.97

[a] Determined conductimetrically after injecting 20 μL of a solution in acetonitrile that was 2×10^{-2} mol/dm^3 in the hydrobromide of the substrate and 6×10^{-2} mol/dm^3 in triethylamine into 2.0 mL of the indicated solvent maintained at 55.0 °C, to give an initial substrate concentration of 2.0×10^{-4} mol/dm^3 in the presence of 4.0×10^{-4} mol/dm^3 of triethylamine.
[b] Binary solvents on a volume-volume basis at 25.0 °C, except for the TFE-H_2O mixtures, which are on a weight-weight basis. The second component in addition to that indicated, is water.
[c] With standard deviations and, unless otherwise indicated, the average of duplicate determinations.
[d] Values from refs. [5] and [20].
[e] Values from refs. [4] and [15].
[f] By definition.
[g] Average of four determinations.
[h] Average of six determinations.

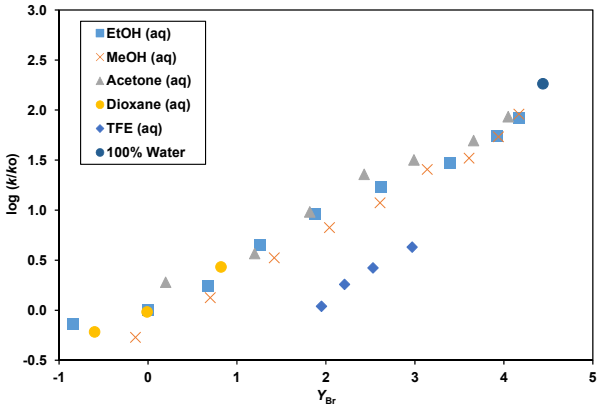


Figure 1. Plot of log (k/k_o) for solvolyses of 4-bromopiperidine (**2**) in 29 solvents against Y_{Br} values (slope of 0.46±0.02). The four data points for TFE-H_2O are not included in the correlation but are added to the plot to show the extent of their deviation from the regression line.

Application of the two-term equation [2,4,5,19,20] [Equation (1)] to the same 29 solvents leads to Equation (6).

$$\log (k/ko) = (-0.38 \pm 0.14)N_T + (0.36 \pm 0.04)Y_{Br} - (0.05 \pm 0.04) \quad (6)$$

n = 29; Multiple Correlation Coefficient (R) of 0.989; F-test value of 600.

The negative l values in Equation (6) almost certainly result from the 29 solvents showing appreciable multicollinearity as regards the N_T and Y_{Br} values. Moving from use of the one-term to the two-term equation (Equation (5) to Equation (6)) leads to only a very modest increase in the correlation coefficient, coupled with an appreciable reduction in the m value and an appreciably negative l value. These are exactly the effects to be expected from the presence of an appreciable degree of multicollinearity in the absence of fluoroalcohol-containing solvents.

Table 3. Correlation of the specific rates of solvolyses of 4-bromopiperidine (**2**) and other compounds solvolyzing with an internal nucleophilic assistance, plus cyclohexyl tosylate, against Y_x values [a] and Y_x plus N_T values, using the one-and-two-term Grunwald-Winstein equations. [b]

Compound	*n* [c]	*l* [d,e]	m [d,e]	R [f]
2	29[g]		0.46±0.02	0.986 [h]
		-0.38±0.14	0.36±0.04	0.989 [h]
$MeS(CH_2)_2Cl$ [i]	11		0.41±0.04	0.964
		0.11±0.07	0.47±0.05	0.973
$PhS(CH_2)_2Cl$ [i]	6		0.39±0.04	0.984
		0.07±0.05	0.44±0.05	0.990
$PhS(CH_2)_2OTs$ [i]	8		0.52±0.04	0.984
		-0.10±0.02	0.44±0.02	0.997
$PhSe(CH_2)_2Cl$ [i]	7		0.42±0.03	0.991
		-0.01±0.05	0.42±0.04	0.991
$Ph_2P(CH_2)_3Cl$ [i]	8		0.47±0.04	0.980
		-0.05±0.06	0.43±0.06	0.983
$PhS(CH_2)_4Cl$ [i]	6		0.34±0.02	0.993
		0.01±0.03	0.36±0.04	0.993
$C_6H_{11}OTs$ [j]	18		0.59±0.07	0.914
		0.35±0.03	0.81±0.03	0.991

[a] The Y_x scale used is the appropriate one for X=Br, Cl, or OTs (OTs is the *p*-toluenesulfonate leaving group).
[b] Equation (1), without and with the N_T term.
[c] Number of solvents.
[d] Sensitivity to changes in solvent nucleophilicity and solvent ionizing power.
[e] With associated standard error.
[f] Correlation coefficient.
[g] With the fluoroalcohol-containing solvents omitted.
[h] With constant (residual) *c* values of 0.02±0.04 and 0.05±0.04.
[i] Values from Tables 1 and 2 of ref. [25].
[j] From ref. [32].

The desirability of a wide variety of solvents being employed during applications of the Grunwald-Winstein equation has previously been emphasized [21]. Unfortunately, changes in mechanisms from one involving a dominant nucleophilic attack by solvent towards one involving ionization of the substrate as the solvent nucleophilicity is decreased and the solvent ionization power is increased, by a fluoroalcohol being incorporated within the solvent, can complicate this goal [22,23]. For the 29 solvents incorporated, the specific rates can be adequately correlated by the one-term equation and there is only a negligible increase in the correlation coefficient on going to the two-term equation, accompanied by an appreciable reduction in the *F*-test value. A plot of log (k/k$_o$) against Y_{Br} is shown in Figure 1. The correlations reported in Equation (5) and (6), and shown graphically for application of Equation (5) in Figure 1, exclude the TFE-containing solvents. The data points for the TFE-containing solvents are added to Figure 1 to show the extent and nature of their deviation from the plot. They gave a separate, and almost linear, plot lying at about one log *k* unit below the above discussed plot. In Table 3, the values in the 29 solvents are compared with the values for other substrates also believed to involve an internal nucleophilic assistance.

What is unusual as regards Figure 1 is that the points for the solvolyses in TFE-H_2O solvents of high ionizing power, lie below the correlation line based on the solvents not containing fluoroalcohol. The Grunwald-Winstein measure of solvent ionizing power will be a composite of several components, with the major ones expected to be that a generalized increased polarity will favor ionization and specific electrophilic solvation effects will assist the departure of an anionic leaving group. However, with 4-bromopiperidine as the substrate, the electrophilic solvation aspect can also involve an interaction with the lone-pair of electrons on the nitrogen and here the influence will be to make this lone-pair less effective in promoting the concerted Grob fragmentation, with a reduction in the specific rate of the concerted process. This is consistent with the positioning of the TFE-H_2O data points in Figure 1.

The four TFE-H_2O solvent mixtures together with the 100% H_2O have been plotted using equation 7, where k_o refers to the value which would apply in 80% ethanol if the same pathway as in TFE-H_2O was followed.

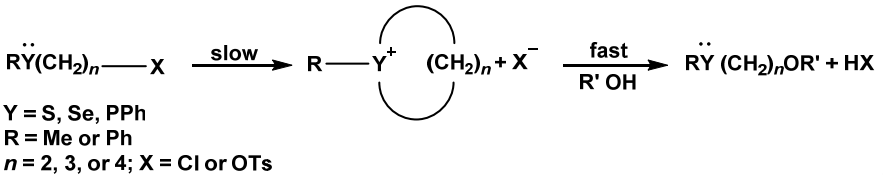
$$\log k = mY_{Br} + (c + \log k_o) \quad (7)$$

The value for *m* was found to be 0.89±0.08 and for *c*+log k_0 a value of -5.80±0.24. Since *c* is a, usually small, residual term, the -5.80 will closely approximate the predicted log k_o value in 80% ethanol, leading to a k_o value of 1.58×10^{-6}. This value is lower than the experimental value (Table 2) in ethanol of 9.9×10^{-5}. The slope of 0.89 is within the region commonly observed for a unimolecular ionization reaction.

When all of the 33 solvents of Table 1 are correlated using Equation (1), with and without the lN_T term, the one-term equation gives a correlation coefficient of 0.923, which increases to 0.971 when the two-term equation is used. These values are considerably lower the values of 0.986 and 0.989 for the 29 solvents, excluding the TFE-H_2O solvents. Further, the values for *l* and *m* would vary as the mix of solvents following the upper and lower correlations of Figure 1 was varied and the composite (averaged) values obtained are of little assistance in the establishment of a mechanistic framework.

The low value for *m* of 0.46±0.02 using the simple (one-term) equation for 29 solvents (Table 3) is consistent with the "internal" S_N2 nature proposed for synchronous Grob fragmentation. The solvolysis of methyl *p*-toluenesulfonate is the usual model chosen for a bimolecular S_N2 solvolysis and, when N_T and Y_{OTs} values are incorporated into the extended (two-term) Grunwald-Winstein equation [Equation (1)] an *l* value of 0.96±0.04 and an *m* value of 0.53±0.04 have been obtained [3,24], this *m* value is similar to that obtained in the present study.

It is useful to compare the conclusions from the present study with those from other studies of the influence of solvent variation on the specific rates of "internal S_N2-type" nucleophilic substitution reactions. One such reaction, which we have analyzed earlier [25] in terms of the Grunwald-Winstein equation approach involves the ring closure reaction of substrates related to mustard chlorohydrin. The specific rates as the solvent is varied at constant temperature have previously been reported, for several substrates of this type [26-31]. These reactions are of the general type illustrated in Equation (8).



(8)

It was found [25] for six substrates of this general type that the *m* values of the simple Grunwald-Winstein equation were in the range of 0.34±0.02 to 0.52±0.04 and with application of the extended Grunwald-Winstein equation, negligible *l* values were observed (-0.10±0.02 to 0.11±0.07), with little change in the *m* values. These results are summarized and compared to those for solvolyses of **2** in Table 3, where it is also shown that solvolyses of cyclohexyl tosylate, with no electron pairs available for participation in an intramolecular process, involve *l* and *m* values typical for a reaction proceeding with a developing carbocation, which is assisted by nucleophilic solvation in the rate-determining step [32]. Alternatively, the transition rate of the rate-determining step can be considered in terms of lying towards the (S_N1+E1) extreme of an (S_N1+E1) to (S_N2+E2) spectrum of mechanisms [19,33].

Grob defined a measure of the assistance given by fragmentation, termed the frangomeric effect, from a consideration of the ratio of the specific rates of solvolysis for the compound with the leaving group at the 4-position of a piperidine ring relative to the leaving group departing from the molecule with the nitrogen atom replaced by a CH grouping. For example, in 80% ethanol at 100 °C, the ratio favoring 4-chloropiperidine (**2**) relative to cyclohexyl chloride is 113 [1,7]. Since we have demonstrated that, in terms of the Grunwald-Winstein correlations, the response to the solvent variations is very different for the cyclohexyl and the corresponding 4-substituted piperidine derivatives, one would expect this value for the frangomeric effect to vary appreciably as the solvent is varied.

In comparing the Grob fragmentation of **2** to the ring closure reactions of the mustard-type compounds [25] the lack of a statistically significant response (*l*) to changes in solvent nucleophilicity in both cases, supports the pathways outlined in Equations (3) and (8). One further point of similarity is that a plot of log *k* for the solvolyses of the mustard compound $CH_3SCH_2CH_2Cl$ against log *k* for the solvolyses of 1-AdCl (equivalent to plotting against Y_{Cl} values) shows that the specific rates in TFE-$H_2$0 mixtures, lie below the linear plot of the specific rates in EtOH-H_2O and acetone-H_2O mixtures [34], paralleling the observation for the data plotted in Figure 1 of the present manuscript. In the consideration of the influence of solvent on a methoxy group, it has been convincingly shown [35] that the electron-withdrawing capacity of a non-participating methoxy in the solvolysis of a 2-methoxy substituted 2-cyclohexenyl *p*-nitrobenzoate is strongly influenced by the hydrogen-bond donation from the solvent to the oxygen of the substituent, and the effect is much greater in solvents rich in TFE than in aqueous acetone or aqueous ethanol.

There have also been studies of ring closure reactions based on the intramolecular attack by the lone-pair of electrons on the nitrogen atom of 2-halogenoethylamines to give the aziridinium halide [36,37]. Correlation analysis of the kinetic response to changes in solvent composition was considered [36] to show substantial carbon-nitrogen bond formation at the transition state, consistent with the low *m*-value observed in the present study of a Grob fragmentation and in earlier analyses [25] of the kinetic data available [26-31] for the influence of solvent variation on the ring-closing intramolecular nucleophilic attack which is initiated by attack of a neighboring sulfur, selenium, or phosphorus.

4. Conclusions

The first-order rate coefficients (specific rates) for solvolysis of 4-bromopiperidine in a wide variety of aqueous-organic solvents have been determined at 55.0 °C. Application of the simple (one-term) Grunwald-Winstein equation shows that, when the organic component is acetone, dioxane, ethanol or methanol a good correlation against Y_{Br} values is obtained, with a slope of 0.46±0.02, consistent with a synchronous Grob fragmentation pathway.

When the organic component is 2,2,2-trifluoroethanol (TFE), the data points for this mixed solvent show a negative deviation from the plot. This deviation can be considered to result from a hydrogen-bonding interaction of the acidic TFE component of the solvent with the lone pair of electrons on the nitrogen, reducing their ability to promote a synchronous Grob fragmentation.

Parallel behavior in TFE-H_2O solvents has been observed for internal nucleophilic attack leading to ring formation [34]. Examples of nucleophilic substitution reactions changing from bimolecular to unimolecular character on going to solvents of high Y_x value are quite common [38]. The observation [9] of a non-synchronous route *via* a carbocation for the Grob fragmentation within the solvolysis in trifluoroacetic acid (a solvent of very high ionizing power) of a derivative of tetrahydropyranyl mesylate is consistent with such a dichotomy of mechanism.

Acknowledgments

Support is acknowledged from the donors of the American Chemical Society Petroleum Research Fund (PRF# 38163-AC4); the National Institute of General Medical Sciences-NIGMS (P20GM103446) IDeA program from the National Institutes of Health (DE-INBRE); the National Science Foundation (NSF) EPSCoR grant IIA-1301765 (DE-EPSCoR program); and the Delaware (DE) Economic Development Office (DEDO program). In addition, Zoon Ha Ryu thanks Dong-Eui University for support of this work by grant 2006AA089. The content is solely the responsibility of the authors and does not necessarily represent the official views of the granting agencies.

References

[1]. D'Arcy, R.; Grob, C. A.; Kaffenberger, T.; Krasnobajew, V. *Helv. Chim. Acta.* **1966**, *49*, 185-203.
[2]. Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700-2707.
[3]. Kevill, D. N.; D'Souza, M. J. *J. Chem. Res.* **2008**, 61-66.
[4]. Bentley, T. W.; Llewellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, 121-158.
[5]. Kevill, D. N. in *Advances in Quantitative Structure-Property Relationships*; Charton, M. Ed.; JAI Press: Greenwich, CT, USA, 1996; Volume 1, pp. 81-115.
[6]. Grob, C. A.; Schiess, P. W. *Angew. Chem.* **1967**, *79*, 1-14; *Angew. Chem. Int. Ed.* **1967**, *6*, 1-15.
[7]. Grob, C. A. *Angew. Chem.* **1969**, *81*, 543-554; *Angew. Chem. Int. Ed.* **1969**, *8*, 535-546.
[8]. Lowry, T. H.; Richardson, K. S. Mechanism and Theory in Organic Chemistry, 3rd. ed.; Harper and Row: New York, NY, USA, 1987; pp. 373-375.
[9]. Jasti, R.; Rychonovsky, S. D. *Org. Lett.* **2006**, *8*, 2175-2178.
[10]. Snider, B. B. The Prins Reaction and Carbonyl Ene Reactions, eds. Trost, B. M. , Fleming, I. , and Heathcock, C. H. Pergamon Press, New York, NY, 1991, Vol. 2, pp. 527-561.

[11]. Lee, C. L. K.; Lee, C. H. A.; Tan K. T.; Loh, T. P. *Org. Lett.* **2004**, *6*, 1281-1283.
[12]. Kevill, D. N.; Kolwyck K. C.; Weitl, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 7300-7306.
[13]. Kevill, D. N.; Dorsey, J. E. *J. Org. Chem.* **1969**, *34*, 1985-1987.
[14]. Rappoport, Z.; Kaspi, J. *J. Am. Chem. Soc.* **1974**, *96*, 4518-4530.
[15]. Bentley, T. W.; Carter, G. E. *J. Am. Chem. Soc*. **1982**, *104*, 5741-5747.
[16]. Lee, I.; Lee, H. W.; Uhm, T. S.; Sung D. D.; Ryu, Z. H. *J. Korean Chem. Soc.* **1988**, *32*, 85-93.
[17]. Koh, H. J.; Han, K. L.; Lee H. W.; Lee, I. *J. Org. Chem.* **1998**, *63*, 9834-9839.
[18]. Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846-854.
[19]. Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667-7675.
[20]. Kevill, D. N.; Anderson, S. W. *J. Org. Chem.* **1991**, *56*, 1845-1850.
[21]. Kevill, D. N.; Rissmann, T. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 717-720.
[22]. Kevill, D. N.; D'Souza, M. J. *J. Org. Chem.* **1998**, *63*, 2120-2128.
[23]. D'Souza, M. J.; Sandosky, B.; Fernandez-Bueno, G. A.; McAneny M. J.; Kevill, D. N. *Can. Chem. Trans.* **2014**, *2*, 160-174.
[24]. Kevill, D. N.; D'Souza M. J.; Ren, H. *Can. J. Chem.* **1998**, *76*, 751-757.
[25]. Kevill, D. N.; D'Souza, M. J. *J. Chem Res. (S)* **1994**, 190-191.
[26]. McManus, S. P.; Neamati-Mazrach, N.; Hovanes, B. A.; Paley M. S.; Harris, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 3392-3393.
[27]. McManus, S. P.; Sedaghat-Herati, M. R.; Karaman, R. M.; Neamati-Mazrach, N.; Cowell, S. M.; Harris, J. M. *J. Org. Chem*. **1989**, *54*, 1911-1918.
[28]. McManus, S. P.; Sedaghat-Herati, M. R.; Harris, J. M. *Tetrahedron Lett.* **1987**, *28*, 5299-5300.
[29]. McManus, S. P.; Neamati-Mazrach, N.; Karaman, R. M.; Harris, J. M. *J. Org. Chem.* **1986**, *51*, 4876-4878.
[30]. McManus, S. P.; Lam, D. H. *J. Org. Chem.* **1978**, *43*, 650-651.
[31]. Neamati-Mazrach, N.; McManus, S. P. *Tetrahedron Lett.* **1987**, *28*, 837-840.
[32]. Kevill, D. N.; Abduljaber, M. H. *Croatica Chemica Acta* **1992**, *65*, 539-546.
[33]. Bentley, T. W.; Schleyer, P. v. R. *J. Am Chem. Soc.* **1976**, *98*, 7658-7666.
[34]. Harris, J. M.; McManus, S. P.; Sedaghat-Herati, M. R.; Neamati-Mazrach, N.; Kamlet, M. J.; Doherty, R. M.; Taft, R. W. Abraham, M. H. in Nucleophilicity, ed. Harris, J. M. and McManus, S. P. Advances in Chemistry No 215, American Chemical Society, Washington, D. C. , 1987, pp. 249.
[35]. Jursic, B.; Ladika, M.; Sunko, D. E. *Tetrahedron* **1986**, *42*, 911-916.
[36]. Chechik, V. O.; Bobylev, V. A. *J. Gen. Chem. USSR. (Engl. Transl.)* **1992**, *62*, 814-820.
[37]. Chechik, V. O.; Bobylev, V. A. *Acta. Chem. Scand.* **1994**, *48*, 837-842.
[38]. D'Souza, M. J.; Kevill, D. N. *Recent Res. Devel. Organic Chem*. **2013**, *13*, 1-38.