JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2001; **14:** 819–822
DOI:10.1002/poc.434

Concerning the extent of nucleophilic participation in solvolyses of glucopyranosyl derivatives[†]

Dennis N. Kevill[1]* and Malcolm J. D'Souza[2]

[1]Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115-2862, USA
[2]Department of Chemistry, Wesley College, 120 N, State Street, Dover, DE 19901-3875, USA

Received 25 April 2001; revised 23 June 2001; accepted 16 July 2001

ABSTRACT: The specific rates of solvolysis of 2-deoxy-α- and -β-D-glucopyranosyl-4′-bromoisoquinolinium ions (1 and 2) give excellent correlations in a Grunwald–Winstein equation approach for solvents with N_T values more positive than -1.4; the sensitivity to changes in N_T value is considerably reduced in less nucleophilic solvents. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: Grunwald–Winstein equation; solvent nucleophilicity; solvolysis

INTRODUCTION

Insertion of an α-alkoxy group accelerates enormously the solvolyses of alkyl derivatives. For example, ethoxymethyl chloride solvolyzes about 10^9 times faster than *n*-butyl chloride.[1] The generally accepted mechanism involves a rate-determining ionization (Eqn. (1)), to give a resonance-stabilized carbocation.[1–4]

$$\mathrm{ROCH_2Cl} \xrightarrow{-\mathrm{Cl}^-} \left[\mathrm{R{-}O{-}CH_2}^+ \longleftrightarrow \mathrm{R{-}\overset{+}{O}{=}CH_2}\right] \qquad (1)$$

One cannot, however, assume a unimolecular mechanism purely on the basis of the appreciable acceleration, since it was also found[3] that the ethanolysis of methoxymethyl chloride was accelerated by the addition of ethoxide ion and the second-order rate coefficient for the superimposed process was 10^5 times that for the corresponding reaction of ethoxide ion with methyl chloride. Such a bimolecular process has been proposed to proceed with a loose (open) transition state, with appreciable oxocarbenium ion character.[3,5–8]

Knier and Jencks studied[5] the reactions of *N*-methoxymethyl-*N,N*-dimethylanilinium ions with nucleophilic reagents in water at constant ionic strength. They observed well-behaved second-order reactions with a variety of neutral and anionic nucleophiles. For solvolyses of the *N*-methoxymethyl-*N,N*-dimethyl-*m*-nitroanilinium ion (**3**), a study was made of the effect of solvent variation on the specific rates of solvolysis and a reasonable logarithmic correlation with the corresponding specific rates of solvolysis of the triethyloxonium ion[9] was found.

A well-established technique for obtaining mechanistic information from the influence of solvent variation on the specific rates of a solvolysis reaction involves use of the Grunwald–Winstein approach. For reactions with the possibility of appreciable nucleophilic assistance, the extended (two-term) Grunwald–Winstein equation (Eqn. (2)) is recommended:[10]

$$\log(k/k_0)_{\mathrm{RX}} = lN_{\mathrm{T}} + mY_{\mathrm{X}} + c \qquad (2)$$

where k and k_0 are the specific rates of solvolysis of a substrate RX in a given solvent and 80% ethanol respectively, l is the sensitivity to changes in the solvent nucleophilicity N_T,[11] m is the sensitivity to changes in the solvent ionizing power Y_X (for a leaving group X),[12] and c is a constant (residual) term.

It is found, however, that Y^+ values, established[13] using the 1-adamantyldimethylsulfonium ion containing a neutral molecule leaving group, vary only slightly from zero,[12,13] and, for this type of $\mathrm{R{-}X^+}$ substrate, the analysis can be carried out with omission of the mY_X term.[14] An analysis in this manner of six data points obtained by Knier and Jencks[5] led[11,14] to an l value of 0.46 and correlation coefficient r of 0.983. With omission of the point for 100% 2,2,2-trifluoroethanol (TFE; above the correlation line), the l value became 0.55 ($r = 0.992$).

The alkoxymethyl derivatives can be considered as prototypes for glucopyranosyl derivatives, and the

---

Correspondence to: D. N. Kevill, Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115-2862, USA.

[†] Dedicated to Dr John Shorter on the occasion of his 75th birthday and in recognition of his many contributions to physical organic chemistry.

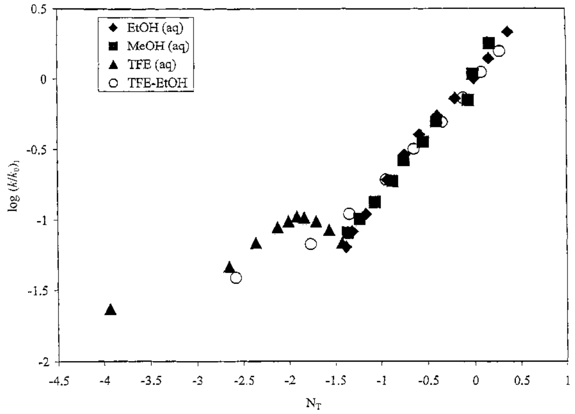


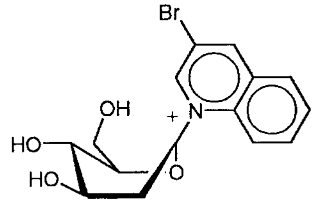
Figure 1. Plot of log(k/k_0) for solvolysis of the 2-deoxy-α-D-glucopyranosyl-4′-bromoisoquinolinium ion (**1**) against N_T values

appreciable nucleophilic assistance indicated by the l value of about 0.5 also suggests the need to consider the possibility of this type of solvent assistance during solvolyses of appropriately substituted carbohydrate derivatives.

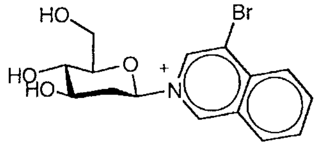
Banait and Jencks[15] observed a second-order reaction of α-D-glucopyranosyl fluoride with anionic nucleophiles in water, accompanied by a complete inversion of configuration. Under identical conditions, no reaction was found with neutral nucleophiles. An enforced concerted mechanism was proposed, and it was also suggested that *solvolyses* in water or TFE–ethanol mixtures involved an intermediate glucosyl oxocarbenium ion. However, the observation of general-base catalysis to the hydrolysis[16] requires that the *catalyzed* reaction be either concerted or with attack on an ion-pair that readily reverts to reactant. Sinnott and coworkers[6] suggested, on the basis of calculations and multiple kinetic isotope effects, that the α-fluoride hydrolyzed by an S_N2 pathway with an 'exploded' transition state and the β-fluoride was more S_N1-like in its hydrolysis, consistent with the known greater reluctance of equatorial groups toward being displaced in an S_N2 process.[17]

RESULTS AND DISCUSSION

A logical extension to the studies with the fluoride would be to replace the fluoride by a neutral-molecule leaving group. Recently, our interest in this area was rekindled by the publication of a very thorough study[18] of both the kinetics and product formation for the solvolyses, at 65.0 °C in a wide variety of solvent compositions, of the 2-deoxy-α- and -β-D-glucopyranosyl-4′-bromoisoquinolinium ions (**1** and **2**). Compound **1** reacts the faster; for example, by factors of 3.9 in 100% ethanol, 6.6 in 100% water, and 14.5 in 100% TFE. The authors analyzed the measured specific rates in terms of Grunwald–Winstein plots against Y^+ values. As we pointed out earlier, Y^+ does not change appreciably with solvent composition and the moderate changes in specific rates led to reasonably good plots, but with extremely large negative slopes (m values of −3.64 for **1** and −4.78 for **2**). Our prior experience with this type of plot strongly suggested that negative slopes of this magnitude are indicative of a pronounced dependence on solvent nucleophilicity. Accordingly, we have reanalyzed the data with use of N_T values rather than Y^+ values (Figs 1 and 2).



1



2

The values obtained from these plots of log(k/k_0) against N_T are reported in Table 1. For all 40 solvents, moderately good correlations are obtained, with slopes (l values) of 0.51 ± 0.03 for **1** ($r = 0.934$) and a slightly higher value of 0.65 ± 0.03 for **2** ($r = 0.964$). For the previously studied **3** in 13 solvents at 25.0 °C,[5] a similar value of 0.48 ± 0.04 ($r = 0.967$) was obtained. An examination of Figs 1 and 2 shows, in each case, an

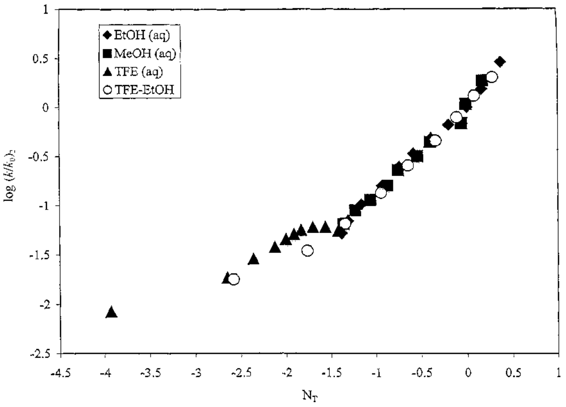


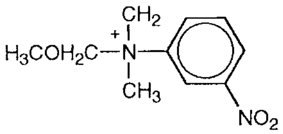
Figure 2. Plot of log(k/k_0) for solvolysis of the 2-deoxy-β-D-glucopyranosyl-4′-bromoisoquinolinium ion (**2**) against N_T values

Table 1. Correlation of the specific rates of solvolysis of **1, 2**, and **3**[a] using the N_T solvent nucleophilicity parameter

Compound	n^b	l^c	c^d	r^e	F^f
1	40^g	0.51 ± 0.03	-0.13 ± 0.19	0.9342	261
2	40^g	0.65 ± 0.03	-0.10 ± 0.17	0.9641	501
3	$13^{g,h}$	0.48 ± 0.04	-0.07 ± 0.16	0.9665	156
1	28^i	0.81 ± 0.02	0.01 ± 0.05	0.9938	2076
2	28^i	0.92 ± 0.02	0.03 ± 0.05	0.9960	3254
1	11^j	0.26 ± 0.05	-0.59 ± 0.11	0.8660	27
2	11^j	0.38 ± 0.04	-0.62 ± 0.08	0.9640	118

[a] Unless otherwise indicated, data from Ref. 18.
[b] Number of solvents.
[c] Sensitivity to changes in solvent nucleophilicity (with associated standard error).
[d] Constant term (accompanied by the standard error of the estimate).
[e] Correlation coefficient.
[f] F-test value.
[g] All available.
[h] From Ref. 5.
[i] N_T values more positive than -1.4 (see text for more detail).
[j] N_T values more negative than -1.4 (see text for more detail).

outstanding linear correlation for the more nucleophilic solvents (aqueous ethanol, aqueous methanol, and TFE–ethanol mixtures with at least 30% ethanol content). A plot for this region (28 solvents) gave surprisingly high l values of 0.81 ± 0.02 ($r = 0.9938$) for **1** and of 0.92 ± 0.02 ($r = 0.9960$) for **2**. These values are only slightly below the value of unity (by definition) for S_N2 solvolyses at the methyl carbon of the *S*-methyldibenzothiophenium ion.[14] The study of **3** in only 13 solvents prevents any attempt to analyze these solvolyses in terms of two possible distinct mechanistic regions.



3

The l values obtained from analyses of solvolyses of **1** and **2** in 11 of the 12 remaining solvents (the borderline 80% TFE–20% ethanol was omitted) are much lower (Table 1), and with a considerably inferior correlation. The inferior correlation is to be expected because of the hump that is present for the data in TFE–water mixtures for both of the plots. The origin of this hump is unknown. It does not appear to be due to interaction of solvent with the extra functionalities present, because the $\log(k/k_0)$ values for **3** can be placed very well onto the plot for **1**. One can use the data for solvolyses in TFE and 90% TFE–10% ethanol to get an extreme value for l of 0.16 for solvolyses of **1** and 0.24 for solvolyses of **2**. These values are within the range one would expect for a rather weak nucleophilic solvation of a developing carbocation.[11,19] It should be mentioned that, although they are somewhat obscured by the larger scatter of points, all of the deviations and curvatures for solvolyses in the solvents of low nucleophilicity, as seen in plots against N_T, are also evident in the earlier plots[18] against Y^+.

For the aqueous TFE solvents, the low l values are consistent both with the claim that **1** and **2** solvolyze *via* dissociative transition states, and with the formation by internal nucleophilic attack of a bicyclic acetal, in yields as high as 36–44% in pure TFE.[18]

In aqueous ethanol, aqueous methanol, and TFE–ethanol solvents with appreciable ethanol content, the arguments presented[18,20,21] supporting the operation of dissociative mechanisms, including statements that even nucleophilic solvation will be unimportant for the solvolyses of **1** and **2** in these solvents, are contrary to the present demonstration of a large sensitivity of the specific rates of reaction toward changes in solvent nucleophilicity.

For **2**, stereochemical studies indicate 87–95% formation of the ether product with inverted configuration in aqueous ethanol and aqueous methanol, but there is considerably less inversion for **1**. It is surprising that the very large sensitivity toward changes in solvent nucleophilicity in the more nucleophilic solvents, suggestive of a pathway involving a mechanism that is close to a classical S_N2, is accompanied for the majority of these solvolyses by considerably less than complete inversion of configuration in the ether products. Further studies on these and related systems, including an extension to additional mixed solvent systems, would be worthwhile.

EXPERIMENTAL

The regression analyses were carried out using the

ABSTAT statistical package (Anderson–Bell, Arvada, CO, USA).

REFERENCES

1. Streitwieser Jr A. *Solvolytic Displacement Reactions*. McGraw-Hill: New York, 1962; 103.
2. Lowry TH, Richardson KS. *Mechanism and Theory in Organic Chemistry*, 3rd edn. Harper and Row: New York, 1987; 391.
3. Ballinger P, de la Mare PBD, Kohnstam G, Prestt BM. *J. Chem. Soc.* 1955; 3641.
4. Jones TC, Thornton ER. *J. Am. Chem. Soc.* 1967; **89**: 4863.
5. Knier BL, Jencks WP. *J. Am. Chem. Soc.* 1980; **102**: 6789.
6. Zhang Y, Bommuswamy J, Sinnott ML. *J. Am. Chem. Soc.* 1994; **116**: 7557.
7. Craze G-A, Kirby AJ, Osborne R. *J. Chem. Soc., Perkin Trans. 2* 1978; 357.
8. Rhind-Tutt AJ, Vernon CA. *J. Chem. Soc.* 1960; 4637.
9. Kevill DN, Lin GML. *J. Am. Chem. Soc.* 1979; **101**: 3916.
10. Winstein S, Grunwald E, Jones HW. *J. Am. Chem. Soc.* 1951; **73**: 2700.
11. Kevill DN. In *Advances in Quantitative Structure–Property Relationships*, vol. 1, Charton M (ed.). Jai Press: Greenwich, CT, 1996; 81–115.
12. Bentley TW, Llewellyn G. *Prog. Phys. Org. Chem.* 1990; **17**: 121.
13. Kevill DN, Anderson SW. *J. Am. Chem. Soc.* 1986; **108**: 1579.
14. Kevill DN, Anderson SW. *J. Org. Chem.* 1991; **56**: 1845.
15. Banait NS, Jencks WP. *J. Am. Chem. Soc.* 1991; **113**: 7951.
16. Banait NS, Jencks WP. *J. Am. Chem. Soc.* 1991; **113**: 7958.
17. Bennet AJ, Sinnott ML. *J. Am. Chem. Soc.* 1986; **108**: 7287.
18. Zhu J, Bennet AJ. *J. Org. Chem.* 2000; **65**: 4423, including supporting information.
19. Kevill DN, D'Souza MJ. *J. Chem. Res., Synop.* 1999; 336.
20. Huang X, Surry C, Hiebert T, Bennet AJ. *J. Am. Chem. Soc.* 1995; **117**: 10 614.
21. Zhu J, Bennet AJ. *J. Am. Chem. Soc.* 1998; **120**: 3887.