COMMUNICATION

www.rsc.org/obc

OBC

Non-steady-state kinetic study of the S_N2 reaction between *p*-nitrophenoxide ion and methyl iodide in acetonitrile

Vernon D. Parker* and Yun Lu

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322, USA

Analysis of non-steady-state kinetic data for the title reaction with tetrabutylammonium counter ions in acetonitrile in the presence and absence of sodium ions rules out the ion-pair dissociation mechanism. The reinterpretation of our data by Humeres and Bentley (*Org. Biomol. Chem.*, 2003, 1, 1969–1971) was based on a series of assumptions that are shown to be invalid by kinetic experiments.

Introduction

Recently, Humeres and Bentley[1] concluded that there is no need to consider the non-steady-state hypothesis to explain our kinetic data reported[2] for the reaction between *p*-nitrophenoxide ion (Na^{+} counter-ion) and methyl iodide in acetonitrile. Curiously, their conclusions were based on kinetic data obtained in a different solvent, acetone. They also reported that HPLC analyses of reaction mixtures of *p*-nitrophenoxide ion (0.05 mM) with methyl iodide (0.01–0.1 M) in wet acetonitrile indicated that yields of S_N2 product, $ArOCH_3$, were low at short times. The authors claimed that our data can be accounted for either by dissociation of an ion-pair followed by the single-step S_N2 reaction or by base-quenching side reactions. Here we report kinetic data for the reaction of *p*-nitrophenoxide ion in the presence of tetrabutylammonium as the counter-ion in acetonitrile without added water and show that the sodium ion introduced as $NaPF_6$ acts as a spectator ion under the kinetic conditions. The evidence presented rules out the Humeres–Bentley[1] mechanism and strongly supports our conclusions presented earlier.[2]

Results and discussion

In view of the criticism[1] of our work[2] it is necessary to give more detail of our experimental procedure than customary for a communication. In particular, our routine practice preliminary to carrying out stopped-flow kinetic measurements, consists of degassing all solutions to be used in the experiment before transferring them into the glove-box, housing the stopped-flow spectrometer, maintained under a nitrogen atmosphere. The purpose of these precautions is to minimize the possibility of including inadvertent reactants in our kinetic experiments. In our previous communication,[2] the experimental procedure was not given in detail and that led to the assumption[1] that our data were obtained without degassing reactant solutions that then remained exposed to the atmosphere during kinetic experiments.

Stopped-flow mixing of *p*-nitrophenoxide solutions with non-degassed acetonitrile solutions containing water

Humeres and Bentley proposed[1] that base consuming impurities, especially carbon dioxide present in wet acetonitrile, were responsible for the deviation of our kinetic data from that expected for the single-step S_N2 mechanism. In order to test this hypothesis we carried out stopped-flow mixing experiments

where a *p*-nitrophenoxide ion solution in acetonitrile was mixed with an equal volume of acetonitrile, with and without prior degassing, containing the concentrations of water used in our kinetic experiments. We could not detect any decay of *p*-nitrophenoxide ion during the duration of the kinetic experiments even when the aqueous acetonitrile solution had not been degassed. The results of these experiments are illustrated by the raw stopped-flow data shown in Fig. 1 for solutions containing 2, 0.6 and 0.04% water. The durations of the absorbance–time profiles were identical to those previously[2] used for our kinetic experiments. Data for degassed solutions are not shown since no significant difference was observed with and without degassing the solutions prior to the stopped-flow experiments. It had been proposed[1] that CO_2, present in wet acetonitrile in kinetically significant quantities, could account for our results. The stopped-flow traces in Fig. 1 show that any base quenching reactants present in the solvent which was not degassed react during the time of mixing and do not affect the kinetics of the subsequent reaction between *p*-nitrophenoxide ion and methyl iodide.
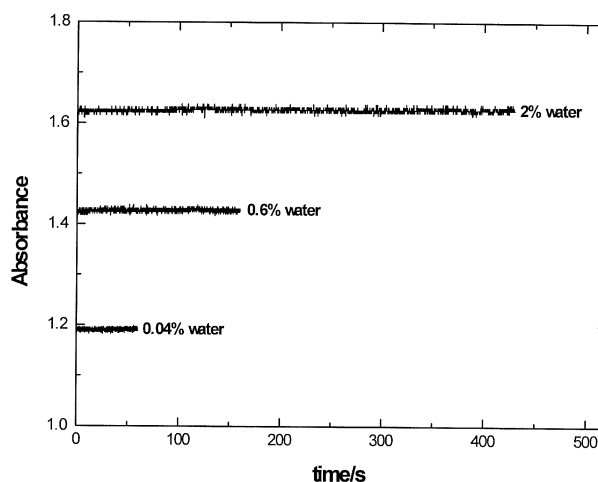

Fig. 1 Stopped-flow traces (420 nm) recorded after mixing solutions containing sodium *p*-nitrophenoxide (0.00012 M) with an equal volume of acetonitrile containing 4, 1.2 and 0.08% water, respectively.

It was further suggested[1] that photosolvolysis of methyl iodide may explain low yields of $ArOCH_3$ observed during their HPLC analyses. To test this hypothesis, we prepared degassed methyl iodide solutions, immediately before use, and kept them in dark brown bottles prior to loading the stopped-flow syringes. Kinetic runs were then carried out on the reaction between tetrabutylammonium *p*-nitrophenoxide (0.000025 M) and methyl iodide (1.0 M). The stopped-flow results from solutions kept in the dark could not be differentiated between those obtained with solutions exposed to light for short times. Thus, photosolvolysis of methyl iodide does not appear to be a problem in the kinetic investigations.
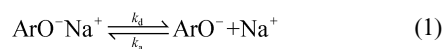
Table 1 Effect of sodium ion[a] concentration on the kinetics of the reaction of tetrabutylammonium p-nitrophenoxide (0.0025 mM) with methyl iodide (1.0 M) in acetonitrile at 298 K

[NaPF$_6$]/mM	k_{init}/s^{-1}	k_{pfo}/s^{-1}	k_{init}/k_{pfo}[a,b]
0.00	0.0109 (0.0009)	0.00799 (0.0002)	1.36 (0.09)
0.05	0.00935 (0.0009)	0.00787 (0.0003)	1.19 (0.07)
0.10	0.00930 (0.0010)	0.00775 (0.0003)	1.20 (0.10)
0.00	0.0085 (0.0006)[c]	0.00706 (0.00013)[c]	1.20 (0.08)[c]

[a] Ratio of the initial rate constant (0–0.05 extent of reaction) to that at longer times (0.05–0.50 extent of reaction). [b] Numbers in parentheses are the standard deviations from >60 absorbance–time profiles. [c] From reference 2 for the reaction between sodium p-nitrophenoxide (0.06 mM) with methyl iodide (1.0 M) in acetonitrile containing 0.04% water.

Evaluation of the 2-step, ion-pair dissociation followed by a S$_N$2 substitution, mechanism to explain previously reported[2] kinetic data

This mechanism is of the same type, reversible consecutive second-order, as we proposed for the reaction[2] and could

$$ArO^-Na^+ \underset{k_a}{\overset{k_d}{\rightleftharpoons}} ArO^- + Na^+ \qquad (1)$$

$$ArO^- + CH_3I \xrightarrow{k_{SN2}} ArOCH_3 + I^- \qquad (2)$$

give rise to extent of reaction–time profiles similar to those observed.[2] But since ion-pair formation is expected to be nearly diffusion controlled, k_a is expected to be of the order of 2×10^{10} M^{-1} s^{-1} in acetonitrile which is about 12 orders of magnitude greater than observed[2] for k_p (equivalent to k_{SN2}[MeI] in this mechanism). Thus, assuming equilibrium for step (1) leads to rate eqn. (3) to describe this mechanism ($K_1 = k_d/k_a$).[1]

$$-d[(ArO^-)_{total}]/dt = \{k_{SN2}K_1/([Na^+ + K_1])\} [(ArO^-)_{total}][CH_3I] \qquad (3)$$

We had considered this mechanism before submitting our communication[2] but rejected it because we had observed that the rates of the reaction were insignificantly affected by the presence of [NaI] in the range from 0 to 0.00024 M. Sodium iodide is completely dissociated in acetonitrile (dielectric constant equals 36) while it has an ion association constant of 160 M^{-1} in acetone (dielectric constant equals 20).[3] The kinetic data suggest that ion-pairing does not significantly affect the rate of the reaction when Na$^+$ (0.00006 M) is the counter ion in acetonitrile. The expected effect of [NaI] on the dissociation of the ion-pair (eqn. 1) is to shift the equilibrium to the left and significantly inhibit the reaction. The preliminary kinetic data obtained in the presence of NaI suggests that sodium p-nitrophenoxide (0.00006 M) is not significantly ion-paired in acetonitrile. The kinetic data in Table 1 were obtained using tetrabutylammonium p-nitrophenoxide with and without added NaPF$_6$, both of which are expected to be completely dissociated in acetonitrile.[4] The results of these experiments support our earlier work[2] indicating that k_{init}/k_{pfo} (the ratio of pseudo first-order rate constants measured in the extent of reaction range from 0 to 0.05 and 0.05 to 0.50, respectively) is significantly greater than unity and suggests that Na$^+$ acts as a spectator ion under these conditions. No water was intentionally added to these solutions. For comparison, the bottom row in Table 1 gives the data reported[2] for the reaction of the sodium salt in acetonitrile containing 0.04% water. The rate constants
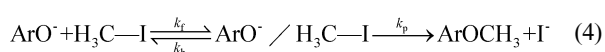
are about 25% lower in the latter case, again reflecting the effect of water on the reaction rates.

Comments on the use of conventional spectrophotometry for kinetic analysis

In their reinterpretation of our kinetic results, Humeres and Bentley[1] referred to work published in the 1960's on the precision capabilities during kinetic measurements.[5,6] Although the use of those techniques, most of which were developed in the first half of the 20th century, is still acceptable for kinetic measurements on reactions for which the mechanism is known with certainty, they have shortcomings. These methods, which do not take advantage of the data processing capabilities made possible by the digital revolution that has taken place over the past three decades, are not suitable in the 21st century for attempts to detect the subtle nuances of reaction mechanisms.

To illustrate the point made in the previous paragraph, attention is called to Fig. 2. This figure illustrates theoretical data, in the time period before steady-state is achieved, calculated for the reversible consecutive second-order mechanism of p-nitrophenoxide ion (0.00006 M) with methyl iodide (1.0 M) (eqn. 4). The rate constants used to calculate the extent of reaction–time profile are those obtained by a best-fit procedure[2] of our experimental data for the reaction carried out in acetonitrile containing 0.04% water. This plot, which on the surface is equivalent to a first-order kinetic plot, appears to represent a reasonable fit to first-order kinetics. Now, if we imagine superimposing experimental data of the quality shown in Figs 1 and 2 of reference 1 over this line, it is obvious that scatter in the data would mask any deviation from linearity of the line in Fig. 2 of this paper.
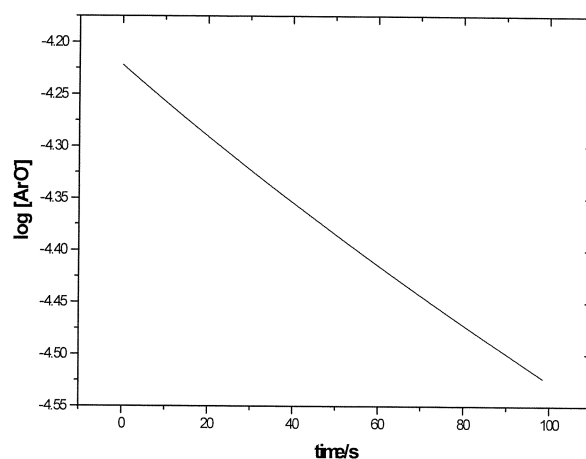

Fig. 2 Plot of log [ArO$^-$] vs. time for theoretical data calculated for the reaction between p-nitrophenoxide ion (0.00006 M) with methyl iodide (1 M) in acetonitrile containing water (0.04%) according to the mechanism illustrated in eqn. 4. The rate constants used were those reported for this reaction at 298 K (k_f = 0.00819 M^{-1} s^{-1}, k_b = 0.00408 s^{-1} and k_p = 0.0150 s^{-1}).[2]

On the other hand, Fig. 3 represents our experimental to theoretical fit of the data. In this case, the experimental extent of the reaction–time profile (solid squares) gives an excellent correspondence to the theoretical data (solid line) illustrated (previous paragraph) in Fig. 2. The solid circles with accompanying line represent theoretical data for the single-step S$_N$2 mechanism and deviate significantly from the experimental extent of reaction–time profile.

Our case for the application of the non-steady-state kinetic treatment made in previous paragraphs is corroborated by the data illustrated in Fig. 4. A first-order plot over three half-lives of the raw ln (absorbance) vs. time data for the reaction between p-nitrophenoxide ion (0.00006 M) with methyl iodide
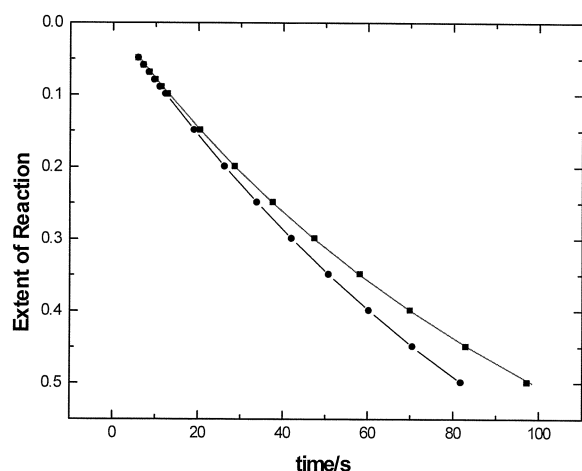
$$ArO^- + H_3C-I \underset{k_b}{\overset{k_f}{\rightleftharpoons}} ArO^- \diagup H_3C-I \xrightarrow{k_p} ArOCH_3 + I^- \qquad (4)$$

Fig. 3 Extent of reaction–time profiles for the reaction of *p*-nitrophenoxide ion (0.00006 M) with methyl iodide (1.0 M) in acetonitrile containing water (0.04%). Solid squares (experimental data) and line (theoretical data for mechanism illustrated in eqn. 4), solid circles and line (simple 1-step S_n2 mechanism).
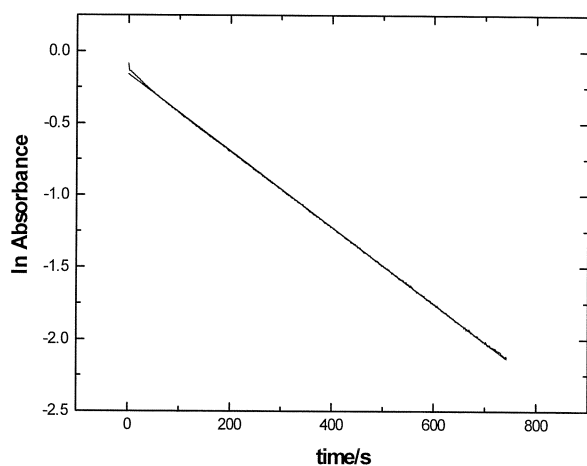

Fig. 4 Plot of ln absorbance *vs.* time (3.0 half-lives) for the reaction between *p*-nitrophenoxide ion (0.0006 M) with methyl iodide (1.0 M) in acetonitrile containing water (0.6%) at 298 K. There are 2 lines in this figure; one is for experimental data (2000 points) and the other is the linear least squares fit of the data (solid line). The two lines can only be distinguished at very short times.

(1.0 M) in acetonitrile at 298 K can only be distinguished from the linear least squares fit of the data at very short times. The non-steady-state treatment of the data corresponding to the first half-life gives results similar to those illustrated in Fig. 3.

The data in Fig.4 serves a further purpose. Humeres and Bentley[1] suggested that diffusion of unreacted reagents into the spectrophotometer cell at long times could affect our kinetic results. Other than the deviation from first-order kinetics at short times, excellent first-order kinetics over three half-lives are illustrated by Fig. 4.

Comments on the validity of the HPLC[1] experiments to determine yield of product during kinetic measurements at short time intervals after mixing

We agree that the yield of $ArOCH_3$ in the presence, depending upon concentration, of any inadvertent base-quenching reactants will be lowered when measured at short times after mixing. Under those conditions, some ArO^- is consumed in rapid acid–base reactions giving rise to decreased yields at short times. These reactions take place during the time of mixing. Our data handling procedure ignores the first seven data points (out of

2000) and then extrapolates the next 100 points (ln absorbance *vs.* time) to obtain the effective absorbance at zero time. This procedure avoids the effect of any side-reactions that take place during mixing and shortly after. We tested this procedure by replacing the methyl iodide with low concentrations of acetic acid (one of the proposed base-consuming impurities[1]) and found that the acid–base reaction was complete during the time of mixing. However, this and other possible side-reactions would cause the yields of product measured by the HPLC technique[1] to appear low at short times. On the other hand, our kinetic results are not influenced by these rapid reactions.

Conclusions

All of the data reported in our previous communication,[2] as well as that presented here, strongly support our conclusions that the S_N2 reaction between *p*-nitrophenoxide ion (0.000025–0.00006 M) and methyl iodide (0.5–2.0 M) in acetonitrile, in the presence and the absence of intentionally added water, follows the reversible consecutive second-order mechanism represented in eqn. 4. The reaction does not reach the steady-state before late in the first half-life. Application of our recently developed non-steady-state kinetic method,[7] facilitates the resolution of the apparent rate constants into the microscopic rate constants for the individual steps. Conventional kinetic analysis as proposed by others[1] is not suitable for the elucidation of subtle mechanistic nuances. The criticism of our work[2] by Humeres and Bentley does not appear to be justified.[1]

The results of a molecular dynamics study of the reactions of methyl chloride with chloride ion in the gas phase, in aqueous solution, and in DMF solution led to the conclusion by Jorgensen[8] that in DMF the reaction proceeds in two steps involving the intermediate formation of an ion–dipole complex. Bordwell[9] found no direct relationship between the size of Brönsted β_{Nu} and the extent of bond making or bond breaking in the transition states for several S_N2 reactions in DMSO and suggested the two stage mechanism involving an ion–dipole complex for these reactions. These studies[8,9] provide additional support for the reversible consecutive mechanism (eqn. 4) for the reaction between *p*-nitrophenoxide ion and methyl iodide in acetonitrile.

Acknowledgements

References

1 E. Humeres and T. W. Bentley, *Org. Biomol. Chem.*, 2003, **1**, 1969–1971.

2 Y. Lu, K. L. Handoo and V. D. Parker, *Org. Biomol. Chem.*, 2003, **1**, 36–38.

3 G. J. Janz and M. J. Tait, *Can. J. Chem.*, 1967, **45**, 1101–1107.

4 R. Fernandez-Prini, in *Physical Chemistry of Organic Solvent Systems*, A. K. Covington and T. Dickenson, eds., Plenum Press, London, ch. 5, Part 1, 1973 .

5 B. L. Murr, Jr. and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, 1962, **84**, 4672–4677.

6 R. E. Roberson, *Prog. Phys. Org. Chem.*, 1967, **4**, 213–280.

7 Y. Zhao, Y. Lu and V. D. Parker, *J. Am. Chem. Soc.*, 2001, **123**, 1579–1586; Y. Lu, Y. Zhao and V. D. Parker, *J. Am. Chem. Soc.*, 2001, **123**, 5900–5907; Y. Zhao, Y. Lu and V. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1481–1487; V. D. Parker and Y. Zhao, *J. Phys. Org. Chem.*, 2001, **14**, 604–611.

8 J. Chandrasekhar and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1985, **107**, 2974–2975; W. L. Jorgensen, *Acc. Chem. Res.*, 1989, **22**, 184–189.

9 F. C. Bordwell and D. L. Hughes, *J. Am. Chem. Soc.*, 1986, **108**, 7300–7309.