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Reinterpretation of the kinetic data and the non-steady state hypothesis (two-step mechanism) for the S_N2 reaction between *p*-nitrophenoxide and methyl iodide in aprotic solvents containing water

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Kinetic data obtained by conventional spectrophotometry for reaction of sodium *p*-nitrophenoxide with methyl iodide in degassed acetone are reported. The rate constants obtained from the first 10% of reaction do not differ significantly from those obtained over longer reaction times (*e.g.* 50% reaction)—the main criteria of Parker *et al.* (*Org. Biomol. Chem.*, 2003, **1**, 36–38) for a non-steady state two-step mechanism. Reactions are accelerated by crown ether, suggesting a mechanism *via* a free ion pair. Product studies by high performance liquid chromatography of reactions in aqueous acetonitrile (used by Parker *et al.*) show that the yield of methylated product is strongly affected by at least two base-neutralising side reactions.

Introduction

It has recently been suggested that the extents of reaction–time profiles for reactions of *p*-nitrophenoxide (ArO^-) with methyl iodide (CH_3I), obtained by stopped-flow spectrophotometry in acetonitrile containing varying small amounts of water, deviate significantly from those expected for the classical single-step displacement of iodide; a non-steady state, two-step mechanism was proposed to explain the observations that rate constants obtained from the first 10% of reaction (*i.e.* the initial rate constants) were slightly greater (1.1–1.7-fold) than corresponding rate constants obtained from 50% of reaction.[1] One of us has recently reported conventional spectrophotometric kinetic studies of the reaction of sodium *p*-nitrophenoxide with CH_3I in acetone and in aqueous mixtures,[2] and Kondo *et al.* have reported rate constants (obtained by titration of quenched extracts) for reaction of tetramethylammonium *p*-nitrophenoxide with CH_3I in dry acetonitrile.[3] We now report additional details of the spectrophotometric kinetic data, product studies by high performance liquid chromatography (HPLC) of reactions in aqueous acetonitrile, and a critical re-evaluation of the non-steady state mechanism.[1]

Results

The disappearance of *p*-nitrophenoxide ion can readily be monitored spectrophotometrically (λ = 420 nm, a wavelength specific to the *p*-nitrophenoxide) at concentrations of about 10^{-5} M.[1,2] Although pseudo-first order reactions could be attained with concentrations of CH_3I as low as 10^{-3} M, concentrations between 0.5 and 2 M were used for the stopped-flow studies;[1] even with this vast excess of CH_3I, reaction times for 50% reaction were rather long (50–1600 s)[1] for a method based on rapid-mixing (ms range)—over relatively long reaction times, diffusion of unreacted reagents into the spectrophotometer cell could also occur. Our kinetic results (Table 1) were obtained by conventional spectrophotometric measurements in sealed, thermally-equilibrated cuvettes. with a 10-fold smaller excess of CH_3I (0.05–0.2 M).

Reactions of *p*-nitrophenoxide with excess CH_3I in acetone were monitored spectrophotometrically for at least three half-lives (Table 1), whereas no more than 50% of reaction was monitored by stopped-flow.[1] Good first order kinetics were not observed unless the solvent was degassed, and if the solvent was not degassed the initial rate constant was higher than the average rate constant. Other results (see below) provide a possible explanation. Typical pseudo-first order rate constants are summarised in Table 1; rate constants obtained from the initial 10% of reaction did not differ significantly (considering the larger uncertainties) from those obtained by monitoring reactions for longer times, even in the presence of water (Figs. 1 and 2). Addition of dicyclohexano-[18]-crown 6 increased reaction rates—*e.g.*, 0.1 M crown ether accelerated the reaction over 5-fold (Table 1).

Table 1 Pseudo-first order rate constants obtained from slopes of plots of −ln Absorbance against time for reaction of sodium *p*-nitrophenoxide with an excess of methyl iodide in acetone at 30.0 °C[a]

MeI/M	Crown ether/M	$10^3\ k_{obs}/s^{-1}$
0.054	0.000	1.15
0.107	0.000	2.28
0.187	0.000	4.00
0.107	0.104	11.7
0.107	0.230	27.3

[a] Followed by the disappearance of *p*-nitrophenoxide at 420 nm; good linear fits to first order kinetics were observed over at least two half-lives in acetone, and deviations disappeared after addition of crown ether; sodium *p*-nitrophenoxide concentration *ca.* 10^{-5} M; average standard deviation ± 3.3%.

The feasibility of monitoring reactions by HPLC analyses of quenched aliquots was initially investigated using 5×10^{-5} M *p*-nitrophenoxide solutions and a smaller excess of CH_3I (10^{-2} M); after several days at 25.0 °C the yellow solutions had turned colourless. Similar results were obtained using more CH_3I (10^{-1} M) in a few hours of reaction at room temperature (*ca.* 20 °C), and importantly, it was established by scanning UV spectroscopy that after many half-lives the absorbance at λ = 420 nm was zero (and also that the product solutions absorbed strongly at 310 nm).

Initially, yields of methyl ether product ($ArOCH_3$) were low (*ca.* 10%), and unreacted CH_3I and *p*-nitrophenol were the only other HPLC signals detected at 310 nm. Yields were increased

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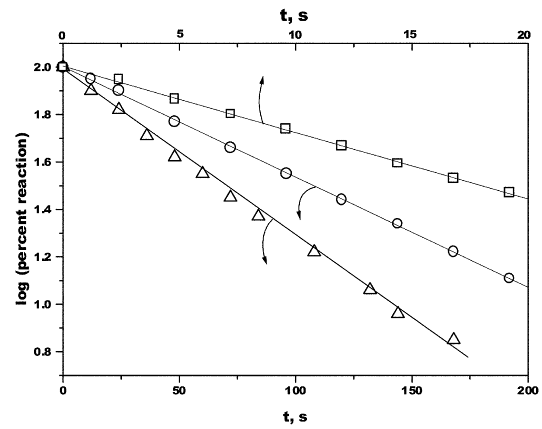


Fig. 1 Pseudo-first order kinetics of the disappearance at 420 nm of sodium *p*-nitrophenoxide, 10^{-5} M, at 30 °C in acetone, MeI 0.107 M, in the presence of dicyclohexano-[18]-crown-6: ○, 43 mM; Δ, 71 mM; □, 230 mM.

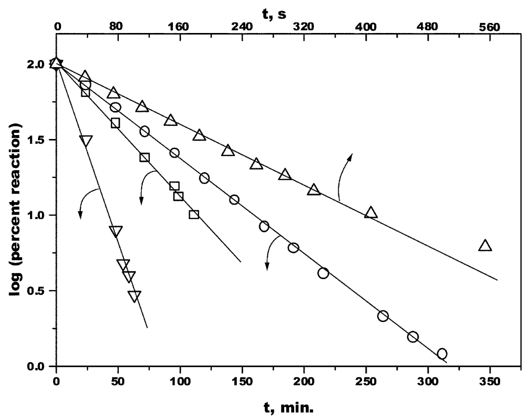


Fig. 2 Pseudo-first order kinetics of the disappearance at 420 nm of sodium *p*-nitrophenoxide, 10^{-5} M, at 30 °C, MeI 0.107 M, in various acetone–water mixtures. Acetone molar fraction: Δ, 1.0; ○, 0.60; □, 0.35; ∇, 0.10.

when extra aliquots of base were added; also, when the reaction mixture was protected from light, yields of $ArOCH_3$ were > 95%, indicating the possibility of acid production by photosolvolysis of CH_3I. No other products were detected, even when the reverse-phase HPLC column was sequentially eluted with less polar eluents, including 100% methanol.

After 10^{-2} M aqueous sodium hydroxide solution was added to 5×10^{-5} M *p*-nitrophenol in acetonitrile until a maximum absorbance was achieved, the absorbance at 420 nm was stable over a period of at least 20 minutes. However, partially neutralised solutions gave a lower absorbance even when transferred quickly (in the open air) from a cuvette to a flask and then back to the cuvette. The solubility of carbon dioxide in acetonitrile at 25 °C is 0.28 M,[4] so even though the partial pressure of CO_2 in air is only *ca.* 3×10^{-4} atmospheres, kinetically-significant amounts of CO_2 could dissolve in the acetonitrile. Both 10^{-2} M sodium hydrogen carbonate and sodium carbonate also deprotonate *p*-nitrophenol, at least partially (as reaction of CO_2 with base gives HCO_3^-, base-quenching by CO_2 will therefore be incomplete).

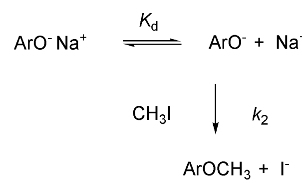
Discussion

Rates of reactions are usually reproducible to a precision of a few %, and it is difficult to achieve a precision of < 1%.[5,6] Initial rates of reactions are more susceptible to errors, but the reliability of the data for disappearance of *p*-nitrophenoxide ion is improved because the absorbance at infinite time (A_∞) is known to be zero (see above). Consequently, the rate constant can be obtained from the slope of a plot of $-\ln A$ against time, optimisation of A_∞ as in the LSKIN program[7] is not required, and the error in the rate constant is reduced if the reaction is monitored for longer times (Table 1).

The significance of degassing the solutions appears to be to prevent partial quenching of the reaction by carbon dioxide. In our spectrophotometric studies, all reagents (acetone, CH_3I and water) were degassed and protected from CO_2. The absence of secondary products and the stable absorbances in the presence of excess base indicate that oxygen does not interfere with the reaction (*e.g.* by phenolate oxidation) under our experimental conditions. We also added iodine to reaction mixtures, but no additional product was detected—iodine does react with *p*-nitrophenol in aqueous solutions at 50 °C.[8]

Good pseudo-first order kinetics, for at least three half-lives, were obtained for S_N2 reactions of sodium *p*-nitrophenoxide with an excess of CH_3I in degassed dry acetone (Table 1, Fig. 1), and good pseudo-first order kinetics were reported for similar reactions of tetramethylammonium *p*-nitrophenoxide in dry acetonitrile.[3] *It does not seem likely that reactions in acetonitrile containing small amounts of water (0.04 to 2.0, v/v—as used by Parker et al.*[1]) will proceed by a different mechanism. More likely, the presence of small amounts of water may introduce competing base-quenching side reactions such as: (i) prior presence or ingress of CO_2, followed by a relatively slow hydration to give carbonic acid;[9] (ii) photosolvolysis of CH_3I (see above), which could occur in the solution reservoirs or possibly within the UV cell of a stopped-flow apparatus; (iii) prior presence of acetic acid, formed on heating acetonitrile during purification;[10] (iv) possibly also hydrolysis of CH_3I by hydroxide, which may be present due to salt hydrolysis, depending on *K* values and the water content of the solvent. As base-quenching leads to the neutral phenol (ArOH), equilibria involving homoconjugate complexes [ArOH. . .ArO$^-$] or [(ArOH)$_2$. . .ArO$^-$][11] may be significant. Also, the reactions are influenced by ion pairing, which affects UV absorptions,[12] and mechanistic interpretations (see below).

Rate enhancements in the presence of crown ether (Table 1) are consistent with prior dissociation of *p*-nitrophenoxide to a free anion, followed by reaction with CH_3I, as suggested independently for reactions in sulfolane at 40 °C.[13] Also, the fit to first order kinetics covers a greater extent of reaction when crown ether is present (Table 1). The proposed mechanism is shown in Scheme 1,[2] where K_d is the equilibrium constant for dissociation of the contact ion pair and k_2 is the second order rate constant for reaction between CH_3I and the free anion.



Scheme 1 Ion pair dissociation followed by nucleophilic attack.

The observed second order rate constant (k_2') is then given by eqn. (1), where [Na$^+$] is the concentration of free sodium ions.[2]

$$k_2' = k_2K_d/([Na^+] + K_d) \quad (1)$$

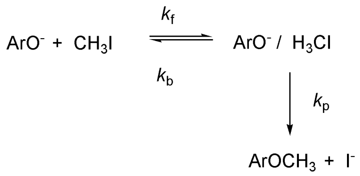
The mechanism proposed by Parker *et al.* is a reversible second order process (Scheme 2)

Under steady state conditions the apparent second order rate constant (k_{app}), corresponding to k_2',[2] is given by eqn. (2):[1]

$$k_{app} = k_fk_p/(k_p + k_b) \quad (2)$$

Schemes 1 and 2 have three similar steps, and substituting into eqn. (1), $K_d = k_f/k_b$ and $k_2 = k_p$ gives eqn. (3):

$$k_2' = k_fk_p/([Na^+]k_b + k_f) \quad (3)$$



Scheme 2 Mechanism of Parker *et al.*[1]

Eqn. (3) is the same form as eqn. (2), and according to eqn. (3), the observed rate constant could vary slightly as the reaction proceeds, because the term $[Na^+]k_b$ varies slightly during the reaction as one electrolyte (NaOAr) is replaced by another (NaI). Consequently, there is no requirement for a non-steady state hypothesis, such as that based on Scheme 2.[1] Furthermore, ion pairing was not considered in the recent study of non-steady state elimination of HBr from 2-(*p*-nitrophenyl)-ethyl bromide in alcohol–alkoxide,[14] including a relatively high concentration (0.3 M) of NaOEt in ethanol, solutions known from conductimetric studies to involve substantial ion-pairing.[15]

Conclusions

Reaction of *p*-nitrophenoxide with an excess of CH_3I in dry, degassed acetone (Table 1) or dry acetonitrile[3] shows good pseudo-first order kinetics. Small deviations from first order kinetics during the initial stages (*ca*. 10%) of reactions in very dilute solutions ($< 10^{-4}$ M) in the presence of small amounts of water, leading to a recent suggestion of 'the generality of the two-step S_N2 mechanism in solution',[1] can be interpreted either by preferential reaction *via* a free anion (Scheme 1) and/or by base-quenching side reactions.

Experimental

Materials and details of kinetic studies (Table 1) were as described earlier.[2] Product studies by HPLC were made using Fisher HPLC grade solvents (acetonitrile,[10] methanol and water), and a Waters Nova-Pak C_{18} reverse phase column usually eluted with 50% v/v methanol–water.

Product studies were performed starting with a stock solution of *p*-nitrophenol (0.0138 g) in acetonitrile (10 ml) *i.e.* 9.9×10^{-3} M; and 50 µL aliquots of the stock solution were diluted to 10 mL in a volumetric flask to give a 5×10^{-5} M solution, which was neutralised by addition of aqueous sodium hydroxide (10^{-1} or 10^{-2} M); methyl iodide (up to 60 µL) was then added, and aliquots (20 µL) were analysed by HPLC at 310 nm (absorbance range 0.05).

Acknowledgements

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