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Effect of solvent on reactivity and basicity: aminolyses of *p*-nitrophenyl acetate in H_2O and in DMSO†

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ABSTRACT: Second-order rate constants (k_N) have been measured spectrophotometrically for the reactions of *p*-nitrophenyl acetate with a series of alicyclic secondary amines in H_2O and in DMSO at 25.0 ± 0.1 °C. The solvent change from H_2O to DMSO resulted in rate enhancements. The effect of solvent on reactivity was found to be most significant for the reaction with piperazinium ion and least significant for the reaction with piperidine. The pK_a values of the conjugate amines studied were also determined in DMSO. It was found that piperazinium ion is more basic in DMSO than in H_2O by 1.04 pK_a units while piperidine is less basic in DMSO by 0.50 pK_a units. The Brønsted-type plot was linear with a large slope (β_{nuc} = 0.76–0.82) for both reactions run in H_2O and in DMSO, indicating that the aminolyses proceed through rate-determining breakdown of the addition intermediate. The difference in pK_a values determined in DMSO and in H_2O (ΔpK_a = pK_a in DMSO − pK_a in H_2O) showed a linear correlation with the difference in the second-order rate constants determined in DMSO and in H_2O ($\Delta \log k_N$ = log k_N in DMSO − log k_N in H_2O) with a slope close to unity, suggesting that ΔpK_a is fully responsible for the rate enhancement in DMSO. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: *p*-nitrophenyl acetate; aminolysis; reactivity; basicity; solvent effect

INTRODUCTION

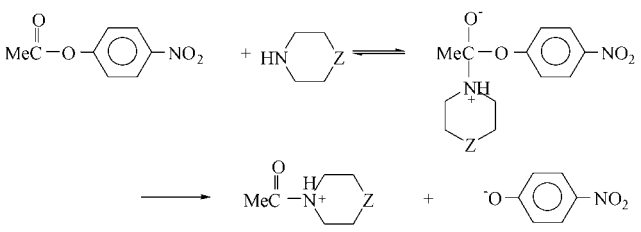
Aminolyses of carboxylic esters have been intensively investigated owing to their interest in chemistry and biochemistry.[1–6] However, most studies have been carried out in H_2O and reactions in dipolar aprotic solvents have not been performed systematically. The main reason for this is considered to be a lack of pK_a data for amines in such solvents. There have been several reports of kinetic studies for ester aminolyses in CH_3CN.[4–6] However, the pK_a data in CH_3CN for the amines studied have not been reported.

It is known that a solvent change from H_2O to dipolar aprotic solvents significantly influences not only reaction rates but also basicities.[7–11] The effect of solvent on rates has been suggested to be highly dependent on the nature of the reactants, e.g., nucleophilic substitution reactions with anionic nucleophiles undergo significant rate acceleration, whereas those between neutral molecules passing through a partially charged transition state exhibit a rate retardation upon solvent change from H_2O to dipolar aprotic solvents.[7–9] Similarly, the effect of solvent on basicity has been suggested to be dependent on the type of bases, i.e. anionic bases versus neutral bases.[10,11] Therefore, pK_a data in organic solvents are essential to correlate with reactivity in organic solvents.

We have performed kinetic studies for the reactions of *p*-nitrophenyl acetate (PNPA) with a series of alicyclic secondary amines in H_2O and in DMSO (Scheme 1), and measured the pK_a values of these amines in DMSO. Here the effect of the solvent change from H_2O to DMSO on the reactivity and basicity of amines is discussed.

RESULTS

Pseudo-first-order rate constants (k_{obs}) were measured spectrophotometrically for the reactions of PNPA with the alicyclic secondary amines in H_2O and in DMSO at



Z = CH_2, NH, NCH_2CH_2OH, O, NCHO, NH_2^+.

Scheme 1

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Table 1. Summary of second-order rate constants (k_N) for the reactions of PNPA with alicyclic secondary amines in H_2O and in DMSO 25.0 ± 0.1 °C

Amine (Z)	k_N (l mol^{-1} s^{-1}) In H_2O	k_N (l mol^{-1} s^{-1}) In DMSO
Piperazinium ion (NH_2^+)	0.00216	0.119
1-Formylpiperazine (NCHO)	0.0579	1.10
Morpholine (O)	0.485	5.80
1-(β-Hydroxyethyl) piperazine (NCH_2CH_2OH)	1.00	15.0
Piperazine (NH)	5.73	70.0
Piperidine (CH_2)	41.2	48.0

25.0 ± 0.1 °C. All the kinetic reactions in the present study obeyed pseudo-first-order kinetics. The k_{obs} values were determined from the equation $\ln (A_\infty - A_t) = -k_{obs}t + C$. The plots of k_{obs} versus amine concentration were linear for all the amines studied for reactions run in H_2O and in DMSO. Generally five different concentrations of amine solutions were used to calculate the second-order rate constants (k_N) from the slope of the linear plot of k_{obs} versus amine concentration. It is estimated from the replicate runs that the uncertainty in any particular measured rate constant is less than ±3%. The second-order rate constants obtained in this way are summarized in Table 1.

The pK_a values in DMSO were measured for all the amines studied using the equations

$$\mathrm{ArOH} + \mathrm{NH} \rightleftharpoons \mathrm{ArO^-} + \mathrm{NH_2^+} \quad (1)$$

$$K_{eq} = [\mathrm{ArO^-}][\mathrm{NH_2^+}]/[\mathrm{ArOH}][\mathrm{NH}] = [\mathrm{ArO^-}]^2/[\mathrm{ArOH}][\mathrm{NH}] = K_a^{\mathrm{ArOH}}/K_a^{\mathrm{NH_2^+}} \quad (2)$$

$$[\mathrm{NH}] = [\mathrm{NH}]_0 - [\mathrm{ArO^-}] \quad (3)$$

$$[\mathrm{ArOH}] = [\mathrm{ArOH}]_0 - [\mathrm{ArO^-}] \quad (4)$$

where $[NH]_0$ and $[ArOH]_0$ are the initial concentrations of amine and the reference acid, *p*-nitrophenol, and [NH], $[NH_2^+]$, [ArOH] and $[ArO^-]$ are the concentrations of amine, the conjugate acid of amine, *p*-nitrophenol and *p*-nitrophenoxide ion, respectively. $[ArO^-]$ can be measured spectrophotometrically using the relationship $A = \epsilon bc$, where $\epsilon = 3.53 \times 10^4$ at 435 nm and $b = 0.100$ cm. Since the pK_a value of *p*-nitrophenol in DMSO has been reported to be 11.0,[11] one can calculate the K_a values of all the amines ($K_a^{NH_2^+}$) used in the present study by measuring $[ArO^-]$. The pK_a data measured in DMSO are summarized in Table 2.

DISCUSSION

Solvent effect on reactivity

Table 1 demonstrates that the solvent change from H_2O to DMSO results in rate enhancements for the reactions of PNPA with the secondary amines. The rate enhancement is most significant for the reaction with piperazinium ion and least significant for that with piperidine, e.g., the second-order rate constant increases from 0.00216 to 0.119 l mol^{-1} s^{-1} and from 41.2 to 48.0 l mol^{-1} s^{-1} with solvent change from H_2O to DMSO for the reaction of PNPA with piperazinium ion and with piperidine, respectively. Significant rate enhancements have often been reported for nucleophilic substitution reactions with anionic nucleophiles upon solvent change from H_2O to aprotic dipolar solvents such as DMSO and CH_3CN.[7,8,13] Destabilization of the ground state (GS) of anionic nucleophiles or stabilization of the transition state (TS) has been suggested to be responsible for the rate enhancement upon such a solvent change.[7,8] However, based on the Hughes and Ingold theory,[9] one might expect that nucleophilic displacement reactions between neutral molecules as in the present aminolyses would exhibit rate retardations upon solvent change from H_2O to dipolar aprotic solvents. In fact, the reaction of PNPA with the alicyclic secondary amines has been reported to exhibit rate retardations upon solvent change from H_2O to MeCN.[14] Therefore, the present result showing rate enhancements in DMSO is unexpected.

Table 2. pK_a values for alicyclic secondary amines in H_2O and in DMSO at 25.0 ± 0.1 °C[a]

Amines (Z)	pK_a In H_2O[b]	pK_a In DMSO	$\Delta pK_a (= pK_a^{DMSO} - pK_a^{H_2O})$
Piperazinium ion (NH_2^+)	5.68	6.72	1.04
1-Formylpiperazine (NCHO)	7.98	8.28	0.30
Morpholine (O)	8.36	8.94	0.58
1-(β-Hydroxyethyl) piperazine (NCH_2CH_2OH)	9.38	9.60	0.22
Piperazine (NH)	9.82	10.50	0.68
Piperidine (CH_2)	11.22	10.70	−0.52

[a] The uncertainty in the pK_a values in DMSO is estimated to be ±0.1 pK_a unit.
[b] pK_a data were taken from Ref. 16.

In order to investigate the effect of the basicity of amines on reactivity for the present aminolysis reactions, Brønsted-type plots were constructed. As shown in Fig. 1, the Brønsted-type plot for the reactions run in H_2O is linear, whereas that for the corresponding reactions in DMSO is non-linear. Linear Brønsted-type plots have generally been obtained for aminolyses of esters with a poor leaving group.[1–4] However, aminolyses of esters with a good leaving group have often resulted in a break or a curvature in the Brønsted-type plot from a large slope (0.8 ± 0.2) to a small one (0.3 ± 0.2) as the amine becomes more basic than the leaving group by 4–5 pK_a units.[1–4] Such a break or a curvature has been attributed to a change in the rate-determining step (RDS).[1–4] Therefore, one might attribute the non-linear Brønsted-type plot shown in Fig. 1 to a change in the RDS. However, the pK_a values used in the Brønsted-type plots are those measured in H_2O but not in DMSO. Since the solvent change from H_2O to DMSO would affect not only the reactivity but also the basicity of amines,[7–11] the non-linear Brønsted-type plot shown in Fig. 1 is not necessarily due to a change in the RDS. Therefore, the pK_a values of the amines in DMSO are needed in order to elucidate the reaction mechanism in DMSO.

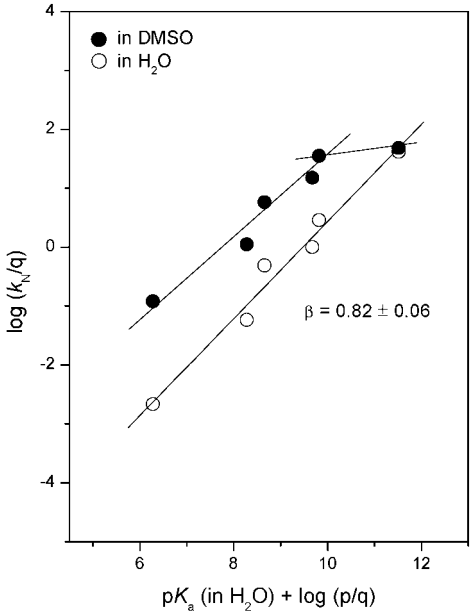

Figure 1. Brønsted-type plots for the reactions of PNPA with alicyclic secondary amines in H_2O and in DMSO at 25.0 ± 0.1 °C. The plots are statistically corrected by using p and q, i.e. $p = 2$ (except $p = 4$ for piperazinium ion) and $q = 1$ (except $q = 2$ for piperazine). See Ref. 12

Solvent effect on basicity

The pK_a values in DMSO are not available for the present amines except piperidine. Therefore, we measured the basicity of all the amines studied in the present system using *p*-nitrophenol as a reference acid whose pK_a value is known in DMSO. In Table 2 are summarized the pK_a values determined in DMSO for all the amines studied together with the pK_a data in H_2O for comparison. It is well known that the acidity of carboxylic acids and phenols decreases significantly upon solvent change from H_2O to DMSO. For example, benzoic acid and phenol are reported to be less acidic in DMSO than in H_2O by 6.9 and 8.1 pK_a units, respectively.[10,11] Such a large decrease in the acidity of the oxygen acids in DMSO has been attributed to the strong repulsion between the oxy anion (the conjugate base of oxygen acid) and the negative dipole end of DMSO.[10,11]

As shown in Table 2, amines are generally more basic in DMSO than in H_2O. However, the difference in pK_a determined in DMSO and in H_2O for the conjugate acid of these amines ($\Delta pK_a = pK_a$ in DMSO $- pK_a$ in H_2O) is only 0.30–1.04 pK_a units, which is small compared with that for the oxy anions. Furthermore, piperidine appears to be less basic in DMSO than in H_2O by 0.50 pK_a units. The basicity of amines has been shown to be significantly dependent on the type of amines.[11] It has been reported that NH_3 and $EtNH_2$ are more basic in DMSO than in H_2O by 1.3 and 0.4 pK_a units, respectively, while Et_2NH and Et_3N are less basic in DMSO than in H_2O by 0.5 and 1.7 pK_a units, respectively.[11] It is clear that the number of alkyl groups or H atoms influences the magnitude of ΔpK_a values. The NH_4^+ ion shows the largest ΔpK_a among the acyclic amines. Similarly, the conjugate acid of piperazinium ion exhibits the largest ΔpK_a among the cyclic amines studied. Both of them have four H atoms which can be deprotonated. The conjugate acids of the other amines studied have only two H atoms which can be deprotonated and show smaller ΔpK_a values. Since only

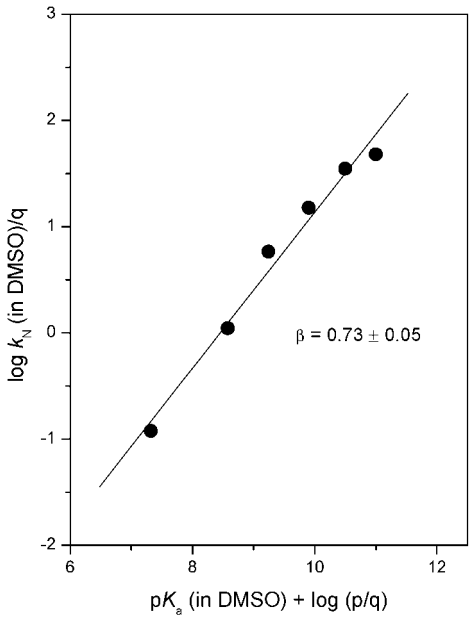

Figure 2. A Brønsted-type plot for the reactions of PNPA with alicyclic secondary amines in DMSO at 25.0 ± 0.1 °C

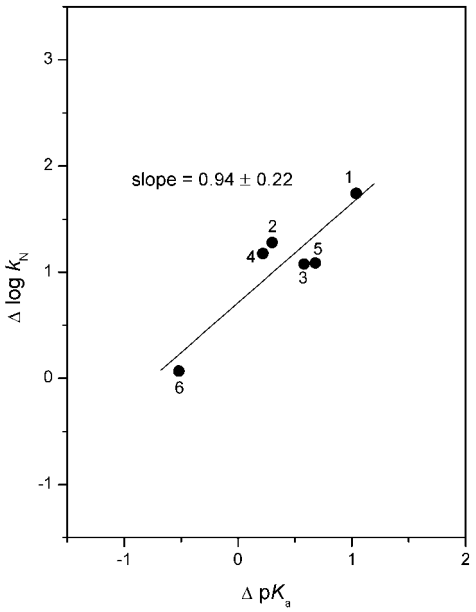

Figure 3. A plot of $\Delta\log k_N$ (= log k_N in DMSO − log k_N in H_2O) vs ΔpK_a (= pK_a in DMSO − pK_a in H_2O) for the reactions of PNPA with alicyclic secondary amines at 25.0 ± 0.1 °C. The numbers refer the amines in Table 1

the Z moiety of the amines studied in the present system is different (e.g. Z = NH_2^+, NCHO, O, NCH_2CH_2OH, NH and CH_2), one can attribute the difference in the ΔpK_a value to the difference in the Z moiety. The ΔpK_a values for the amines used in this study are considered to be consistent with those reported in the literature.[11] Furthers, the pK_a value of piperidine in DMSO was measured to be 10.70 in the present study, which is identical with the reported pK_a value of piperidine in DMSO.[15] Therefore, the pK_a values determined in the present study are considered to be reliable.

Solvent effect on reaction mechanism

Figure 2 shows a linear Brønsted-type plot for the reactions of PNPA with the alicyclic amines performed in DMSO. The pK_a values used for the Brønsted-type plot are those determined in DMSO. The linear Brønsted-type plot shown in Fig. 2 indicates that no change in RDS occurs in the present aminolysis reactions. It follows, therefore, that the non-linear Brønsted plot shown in Fig. 1 for the reactions run in DMSO is not due to a change in the RDS but to the use of improper pK_a values.

One can obtain useful information about the reaction mechanism from the magnitude of the β_{nuc} value for aminolysis reactions. It has generally been reported that a small β_{nuc} value (0.3 ± 0.1) is obtained when the aminolysis reaction proceeds through a rate-determining formation of an addition intermediate, but a large β_{nuc} value (0.8 ± 0.1) for aminolysis in which the RDS is rate-determining breakdown of the addition intermediate.[1–4] The β_{nuc} value for the reactions run in DMSO (Fig. 2) was calculated to be 0.73 ± 0.05, which is almost identical with that determined for the corresponding reactions run in H_2O (β_{nuc} = 0.82 ± 0.06 in Fig. 1). Therefore, it is plausible that the present aminolysis reactions both in H_2O and in DMSO proceed through a rate-determining breakdown of the addition intermediate, based on the large β_{nuc} values.

As mentioned in the preceding section, the change in solvent from H_2O to DMSO affected both the reactivity and basicity of the amines studied. In order to correlate the effect of solvent on reactivity and on basicity, a plot of ΔpK_a vs $\Delta\log k_N$ (= log k_N in DMSO − log k_N in H_2O) was constructed. As shown in Fig. 3, $\Delta\log k_N$ increases with increasing ΔpK_a, indicating that the increase in the basicity of the amine is responsible for the increase in the reactivity of the amine. The slope of the plot was calculated to be 0.94 ± 0.22. Therefore, it appears that the increase in basicity is almost fully reflected in the increase in reactivity of the amine upon the solvent change from H_2O to DMSO. This argument can explain the fact that piperazinium ion, which exhibits the largest increase in basicity, results in the largest increase in reactivity, whereas piperidine shows a decrease in basicity with the least rate enhancement upon the solvent change from H_2O to DMSO.

EXPERIMENTAL

Kinetics

Kinetic studies were performed with a Scinco S-2100 UV–visible spectrophotometer for slow reactions ($t_{1/2}$ ≥10 s) and with an Applied Photophysics SX-17MV stopped-flow spectrophotometer for fast reactions ($t_{1/2}$ <10 s) equipped with a Neslab RTE-110 constant-temperature circulating bath to keep the temperature in the reaction cell at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of the leaving *p*-nitrophenoxide ion (or *p*-nitrophenol for the reaction with piperazinium ion). All the reactions were carried out under pseudo-first-order conditions in which the amine concentrations were generally 20 times, but at least 10 times, greater than that of the substrate PNPA. Amine stock solutions of ca. 0.2 M were prepared in a 25.0 ml volumetric flask under a nitrogen atmosphere. DMSO and the amines used were purchased from Aldrich and distilled or recrystalized before use. All the solutions were transferred by Hamilton gas-tight syringes. Other details of kinetic methods have been reported previously.[3]

Basicity measurements

The basicity of amine in DMSO was also determined

spectrophotometrically. *p*-Nitrophenol was chosen as a reference acid. The basicity of the amines studied was determined by measuring the absorbance of *p*-nitrophenoxide ion which is at an equilibrium with the conjugate acid of the amines at five different pH values using the same UV–visible spectrophotometer as used for the kinetic study. Standard 0.10 cm quartz cells (Helma) closed at the top with a rubber septum were used. Hamilton gas-tight syringes were used to transfer solutions. All the solutions were prepared in 25.0 ml volumetric flasks closed at the top with a rubber septum just before use under a nitrogen atmosphere. Other details of basicity measurements are similar to those in the literature.[13]

CONCLUSIONS

The change in solvent from H_2O to DMSO influences not only the reactivity but also the basicity of amines. Amines are more reactive in DMSO than in H_2O, and more basic in the organic solvent with the exception of piperidine. The present aminolysis reactions proceed through a rate-determining breakdown of the addition intermediate, based on the linear Brønsted-type plot obtained with a large β_{nuc} value for both reactions run in H_2O and in DMSO. The linear plot of $\Delta\log k_N$ vs ΔpK_a with a slope close to unity implies that the effect of solvent on basicity is nearly fully reflected in reactivity.

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