The Effect of Solvent on Reaction Rates and Equilibria for the Reactions of p-Nitrophenyl Acetate with Alicyclic Secondary Amines in H₂O and DMSO

**Ik-Hwan Um,* Young-Min Park, and Eun-Hee Shin**

Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
Received November 25, 1998

The effect of solvent on reaction rates has been intensively studied.[1-5] A change in solvent from a polar solvent to a non-polar solvent has been suggested to increase or decrease reaction rates depending on the type of reactions.[1] It has generally been reported that reactions with anionic nucleophiles cause significant rate acceleration, while the ones between neutral molecules passing through a partially charged transition state structure exhibit rate retardation upon solvent change from H_2O to DMSO.[1] The first theory to explain solvent effect on reaction rates was proposed by Hughes and Ingold in 1935.[6] The qualitative theory could account for a number of solvent effect on reaction rates.

Aminolysis of carboxylic esters has been widely investigated due to importance in biochemical processes as well as in synthetic chemistry, and the reaction mechanism has been fairly well known.[7-10] However, most studies have been carried out in H_2O. Reactions in organic solvents such as DMSO or MeCN have not been much performed.[9-11] The main reason for this is considered to be lack of pK_a data of amines in such organic solvents. It is well known that solvent change from H_2O to a dipolar aprotic solvent would influence not only reaction rates but also basicity of amines.[12,13] Therefore, the pK_a data of amines in the organic solvent is essential to correlate their reactivity in the organic solvent.

We have performed a systematic study for the aminolysis of p-nitrophenyl acetate (PNPA) with a series of secondary alicyclic amines in H_2O and in DMSO containing 10 mole % H_2O (97.5 w/w % DMSO), and measured pK_a values of these amines in pure DMSO.
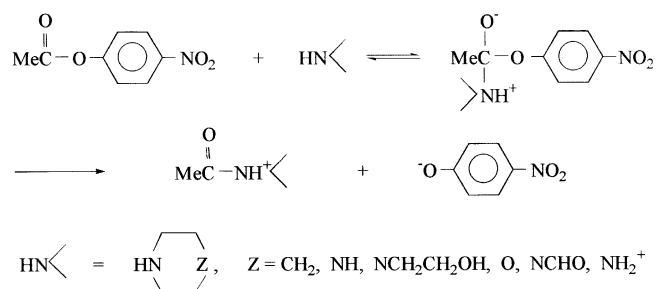
As shown in Table 1, the solvent change from H_2O to DMSO results in rate enhancements for the reactions of PNPA with the secondary amines. The rate enhancement is most significant for the reaction with piperazinium ion, and nearly negligible for the one with piperidine. Based on the Hughes and Ingold theory, one might expect rate retardation for the present aminolysis upon solvent change from a

Table 1. Summary of second-order rate constants for the reactions of PNPA with alicyclic secondary amines in H_2O and in DMSO containing 2.5% H_2O at 25 °C

amines (Z)	k_2, M⁻¹s⁻¹	
	in H_2O	in 97.5 w/w % DMSO
1. piperazinium ion(NH₂⁺)	0.00216	0.121
2. 1-formylpiperazine(NCHO)	0.0579	0.748
3. morpholine(O)	0.485	5.00
4. 1-(β-hydroxyethyl)-piperazine(NCH₂CH₂OH)	1.00	13.2
5. piperazine(NH)	5.73	81.9
6. piperidine(CH₂)	41.2	57.2

strongly polar solvent (H_2O) to a less polar solvent (DMSO). In fact, we recently found that the rate for the same reactions decreases upon solvent change from H_2O to MeCN.[14] Thus, the present result would be unexpected.

In order to investigate the effect of the basicity of amines on reactivity for the present aminolysis, Brønsted-type plots have been constructed. As shown in Figure 1, one can see a linear Brønsted-type plot for the reactions run in H_2O, while
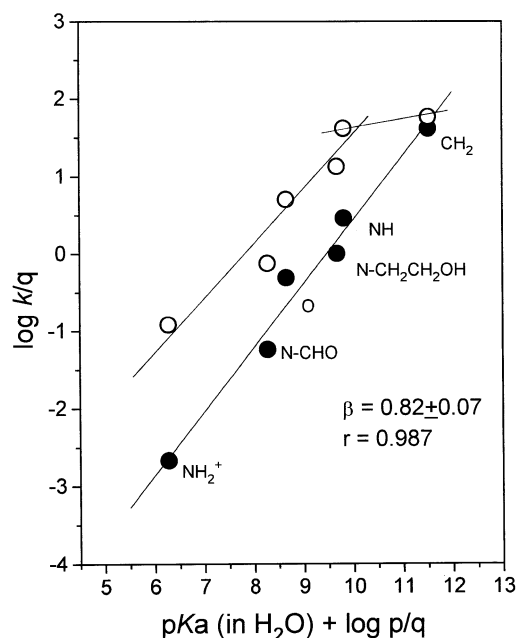

Figure 1. Brønsted-type plots for the reactions of PNPA with alicyclic secondary amines in H_2O (●) and in 97.5 w/w % DMSO (○) at 25.0±0.1 °C. The plots are statistically corrected by using p and q. *i.e.*, p=2 (except p=4 for piperazinium ion) and q=1 (except q=2 for piperazine). See reference 16.

a curved one with highly scattered points for the corresponding reactions run in DMSO. Such a curvature in a Brønsted-type plot has often been observed for aminolysis of carboxylic esters with a good leaving group, e.g., from a large β_{nuc} value (0.8+0.1) for weakly basic amines to a small β_{nuc} value (0.2+0.1) for highly basic amines.[7-10] A break or curvature in a Brønsted-type plot has been suggested to be evidence of a change in reaction mechanism or rate-determining step (RDS).[7-10] Therefore, one might attribute the nonlinear Brønsted-type plot shown in Figure 1 to a change in RDS. However, the pKa values used in the Brønsted-type plot are measured in H_2O but not in DMSO. Since the solvent change from H_2O to DMSO would affect the basicity of amines, the pKa values in DMSO are essential to construct a reliable Brønsted-type plot.

The pKa values in DMSO are not available for the present amines except piperidine. Therefore, we have measured acid dissociation constants of the conjugate acid of all the amines studied using equations (1)-(4). $[NH]_o$ and $[ArOH]_o$ are the initial concentration of amine and the reference acid, p-nitrophenol. [NH], $[NH_2^+]$, [ArOH] and [ArO] are the concentration of amine, the conjugate acid of amine, p-nitrophenol and p-nitrophenoxide ion, respectively. [ArO] can be measured spectrophotometrically using the relationship, $A = \varepsilon bc$, where $\varepsilon = 3.53 \times 10^4$ at 435 nm and $b = 0.100$ cm. Since the pKa value of p-nitrophenol in DMSO has been reported to be 11.0,[15] one can calculate Ka values of all the amines used in the present study from eqn (2) by measuring [ArO].
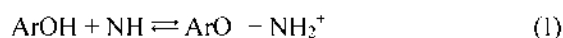
$$ArOH + NH \rightleftharpoons ArO - NH_2^+ \tag{1}$$
$$K_{eq} = [ArO][NH_2^-] / [ArOH][NH]$$
$$= [ArO]^2 / [ArOH][NH]$$
$$= Ka^{ArOH} / Ka^{NH_2^+} \tag{2}$$
$$[NH] = [NH]_o - [ArO] \tag{3}$$
$$[ArOH] = [ArOH]_o - [ArO] \tag{4}$$

The pKa values measured in this way are summarized in Table 2 together with the data measured in H_2O for a comparison purpose. The pKa value for oxygen acids has been reported to be significantly higher in DMSO than in H_2O. For example, benzoic acid and phenol are known to be less acidic in DMSO than in H_2O by 6.9 and 8.1 pKa units, respectively.[12,13] Such a large decrease in the acidity of oxy-

gen acids in DMSO is due to the strong repulsion between the oxy anion (the conjugate base of oxygen acids) and the negative dipole end of DMSO. As shown in Table 2, one can see that the amines are generally more basic in DMSO than in H_2O. However, the difference in basicity is only 0.30-1.04 pKa units, which is quite small compared with that of oxy anions. Furthermore, piperidine appears to be less basic in DMSO than in H_2O by 0.5 pKa unit. The interesting pKa trend is not limited to the cyclic amines but appears to be similar to other amines, i.e., the difference in pKa value (ΔpKa = pKa in DMSO - pKa in H_2O) has been reported to be +1.3, +0.4 and -0.5 for NH_3, $EtNH_2$ and Et_2NH, respectively.[15] Besides, the pKa value of piperidine in DMSO has been measured to be 10.70 in the present study, which is identical to the reported pKa value of piperidine in DMSO.[15] Therefore, the pKa values and the method used to measure them in the present study are considered to be reliable.

In Figure 2 is demonstrated a Brønsted-type plot for the reaction of PNPA with the cyclic amines run in DMSO. The pKa values used are the ones obtained in DMSO. One can see a linear Brønsted-type plot, indicating that the RDS change does not occur in the present aminolysis. The slope (β_{nuc}) in Figure 2 is calculated to be 0.77+0.05, which is practically identical to the one obtained from the corresponding reaction run in H_2O ($\beta_{nuc} = 0.82+0.07$ in Figure 1). The magnitude of β_{nuc} value has been suggested to be a measure of the effective charge developed on the N atom of the amine in the transition state (TS).[7-10] Therefore, one can expect that the TS structure would be similar for the reactions run in H_2O and in DMSO.

Table 2. pKa values for alicyclic secondary amines in H_2O and in DMSO at 25 °C

amine	pKa		ΔpKa(pKa^{DMSO}- pKa^{H_2O})
	in H_2O^a	in DMSO^b	
1. piperazinium ion	5.68	6.72	1.04
2. 1-formylpiperazine	7.98	8.28	0.30
3. morpholine	8.36	8.94	0.58
4. 1-(β-hydroxyethyl)-piperazine	9.38	9.60	0.22
5. piperazine	9.82	10.50	0.68
6. piperidine	11.22	10.70	-0.52

^{a}pKa values taken from ref. 17. ^{b}pKa values measured in this study.
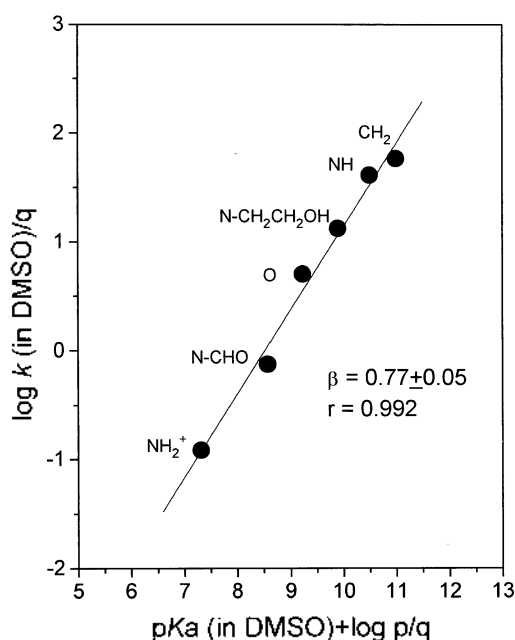

Figure 2. A Brønsted-type plot for the reactions of PNPA with alicyclic secondary amines in DMSO at 25.0±0.1 °C. The plot is statistically corrected by using p and q, i.e., p=2 (except p=4 for piperazinium ion) and q=1 (except q=2 for piperazine). See reference 16.
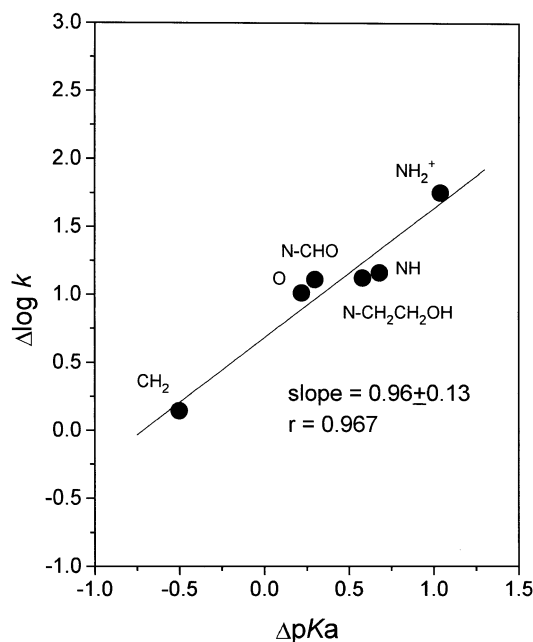
Figure 3. A plot of $\Delta\log k$ ($\log k$ in DMSO - $\log k$ in H_2O) vs ΔpKa (pKa in DMSO - pKa in H_2O) for the reactions of PNPA with alicyclic secondary amines at 25.0±0.1 °C.

In order to evaluate the effect of solvent on rates and equilibria, a plot of ΔpKa vs $\Delta\log k$ ($^-\log k$ in DMSO - $\log k$ in H_2O) has been constructed. As shown in Figure 3, $\Delta\log k$ increases with increasing ΔpKa, and a good linearity is observed in the plot. It is evident that the largest ΔpKa for piperazinium ion is responsible for the largest $\Delta\log k$ for it. The slope of this plot has been calculated to be 0.96+0.13, indicating that the effect of solvent on basicity is fully reflected in rates.

Therefore, the nonlinear Brφnsted-type plot shown in Figure 1 for the reactions run in DMSO is not due to a change in the RDS but due to the use of improper pKa values. More systematic studies are currently underway.

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