Kinetics and Mechanism of the Aminolysis of Anilino Thioethers with Benzylamines in Acetonitrile

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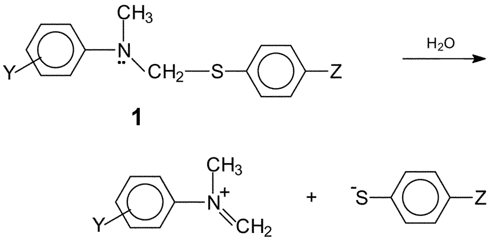
The aminolyses of anilinothioethers ($C_6H_5N(CH_3)CH_2SC_6H_4Z$) in acetonitrile with benzylamines ($XC_6H_4CH_2NH_2$) have been investigated. The rates are much lower in acetonitrile than in methanol (with aniline). The Brönsted β_X values are similar but β_Z values are smaller compared to those for the reactions in MeOH with anilines. The large negative ρ_{XZ} ($\cong$ -0.8, after correction for fall-off) value is interpreted to indicate a frontside attack S_N2 mechanism, in which the two oppositely changed reaction centers in the TS, $-N^{\delta+}\cdots S^{\delta-}-$, are in close vicinity increasing the interaction between nucleophile and leaving group. The inverse secondary kinetic isotope effects ($k_H/k_D < 1.0$) are observed with deuterated benzylamines ($XC_6H_4CH_2ND_2$).

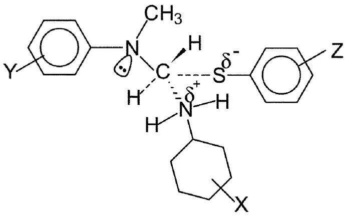
Key Words : Anilinothioether, Frontside-attack, S_N2, Inverse secondary isotope effect

Introduction

Iminium ions, $=C=N^+=$, are intermediates formed in many chemical and enzyme-catalyzed reactions, but are known to be highly unstable in aqueous solution with a lifetime of 10^{-7}-10^{-8} s. The iminium cations (**I**) are generated in aqueous solution from the solvolysis of anilinothioethers, **1**, eq. (1). The solvolysis reaction is sensitive to the basicity of the electron-donating nitrogen atom of the aniline (a Brönsted slope, β_X, for log k_{solv} *vs* the pK_a of the protonated N,N-dimethylaniline being *ca.* 0.79),[1a] because the lone-pair electrons on N are donated to the antibonding orbital of the cleaving bond, σ^*_{C-S}, by a vicinal charge transfer interaction, $n_N \rightarrow \sigma_{C-S}$. However, in the presence of a nucleophile, a concerted nucleophilic displacement (S_N2) takes place due to the extremely short lifetime of an iminium cation that is in contact with nucleophiles.



I (1)



II

The reactions of **1** with aniline nucleophiles ($XC_6H_4NH_2$) in methanol[2] were found to exhibit large ρ_X (β_X = 0.44-1.00) and ρ_Z (= 1.6-2.5) values with large negative cross-interaction constant,[3] ρ_{XZ} = -1.7, which has been interpreted to indicate a frontside nucleophilic attack in the rate-limiting step with a transition state (TS) structure, **II**. In this TS the partially charged functional centers of (positive) nucleophile, $N^{\delta+}$, and negative leaving group, $S^{\delta-}$, form nearest neighbors leading to a strong interaction. In view of this interesting mechanistic possibility, we delve further to throw more light for the mechanism of the nucleophilic substitution reaction of anilinothioethers. In the present work, the aminolysis of anilinothioethers with benzylamines ($XC_6H_4CH_2NH_2$) in acetonitrile have been investigated, eq. (2a).

$$C_6H_5N(CH_3)CH_2SC_6H_4Z + 2XRNH_2$$
$$\rightarrow C_6H_5N(CH_3)CH_2NHRX + {}^-SC_6H_4Z + XRNH_3^+ \qquad (2)$$

(a) $R = C_6H_4CH_2$; MeCN ; 50.0 °C
(b) $R = C_6H_4$; MeOH ; 45.0 °C

Results and Discussion

The rate law followed by the present reaction is given by eqs. (3) and (4), where [S] and [BA] are the concentrations of the substrate, **1**, and nucleophile, benzylamine, respectively. The second-order rate constants, k_2, were obtained as the slopes of eq. (3).

$$d\,[ArS^-]/dt = k_{obs}\,[S] \qquad (3)$$

$$k_{obs} = k_2\,[BA] \qquad (4)$$

The k_2 values together with the Hammett (ρ_X, ρ_Z) and

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Table 1. The Second Order Rate Constants, $k_N \times 10^5$ dm^3 mol^{-1} s^{-1} for the Reactions of Anilino Thioethers with X-Benzylamines in Acetonitrile at 50.0 °C

X	Z					$\rho_Z{}^a$	$\beta_Z{}^b$
	p-Me	H	*p*-Cl	*p*-Br	*P*-NO$_2$		
p-OMe	1.01	1.59	3.30	4.68	18.3	1.35 ± 0.10	-0.35
	0.655^c			3.15			
	0.429^d			2.17			
p-Me	0.832	1.30	2.63	3.71	14.5	1.33 ± 0.10	-0.33
H	0.674	1.00	2.00	2.86	10.9	1.30 ± 0.10	-0.32
p-Cl	0.495	0.741	1.45	1.86	6.56	1.20 ± 0.08	-0.31
	0.330			1.25			
	0.217			0.829			
$\rho_X{}^e$	-0.60 ± 0.03	-0.66 ± 0.04	-0.71 ± 0.03	-0.79 ± 0.03	-0.88 ± 0.04	$\rho_{XZ}{}^f$ = -0.30	
$\beta_X{}^g$	0.57 ± 0.01	0.63 ± 0.03	0.68 ± 0.03	0.75 ± 0.03	0.84 ± 0.03		

[a] The σ values were taken from Dean, J. A. *Handbook of organic Chemistry,* McGraw-Hill, New York, 1987, Table 7-1. Correlation coefficients were better than 0.991 in all cases. [b] See text: Correlation coefficients were better than 0.999 in all cases. [c] At 40 °C. [d] At 30 °C. [e] The σ values were taken from McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420. Correlation coefficients were better than 0.996 in all cases. [f] Correlation coefficients was 0.992. [g] The p*K*a values were taken from Fischer, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588. Correlation coefficients were better than 0.998 in all cases. X = *p*-CH$_3$O were excluded from the Brönsted plot for β_X (benzylamine) due to an unreliable pK_a value listed.

Brönsted (β_X, β_Z) coefficients are summarized in Table 1. The cross-interaction constant, ρ_{XZ}[3], determined using eq. (5) is ρ_{XZ} = -0.3, which corresponds to $\rho_{XZ} \cong -0.8$ if the fall-off by a factor of 2.4-2.8[4] due to an extra intervening CH$_2$ group in benzylamine is taken into account. The β_X values

$$\log (k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \qquad (5a)$$

$$\rho_{XZ} = \partial\rho_X/\partial\sigma_Z = \partial\rho_Z/\partial\sigma_X \qquad (5b)$$

were determined by the plots of log k_2 (MeCN) versus pK_a (H$_2$O) of benzylamines. This procedure was found to be reliable, since the pK_a (MeCN) varies in parallel with the pK_a (H$_2$O) with a reasonably constant difference of ΔpK_a (= pK_a (MeCN) - pK_a (H$_2$O)) $\cong$ 7.5 for a structurally similar series of amines.[5] The β_Z values in MeCN were estimated by applying a factor of 0.62 (β_Z by pK_a (MeCN)/β_Z by pK_a (H$_2$O)) to the β_Z values obtained from the slopes of the plots log k_2 (MeCN) against pK_a (H$_2$O).[6]

The rate of the aminolysis of anilinothioethers with X=Y=Z=H is slower by a factor of 10^2 for the reaction in acetonitrile with benzylamine, eq. (2a) (1.00×10^{-5} dm^3 mol^{-1} s^{-1} at 50.0 °C) than that in methanol with aniline, eq. (2b) (1.70×10^{-3} dm^3 mol^{-1} s^{-1} at 45.0 °C).[2] The magnitude of β_X (=β_{nuc}) is similar in the two aminolysis reactions; β_X = 0.57-0.84 and 0.44-1.00[2] for eq. (2a) and (2b) respectively. However, the -β_Z (= -β_{eg}) values are smaller ($\cong$ 0.3-0.4) than those for eq. (2b)[2] ($\cong$ 1.1-0.7 assuming pK_a values for the anilines in H$_2$O varies in parallel[5a,b] (or similar) in MeOH). Considering these Brönsted values, the TS in acetonitrile is somewhat tighter than that in methanol. In contrast, however, the cross-interaction constant, ρ_{XZ}, is much smaller in the present work ($\cong$ -0.8) compared to that in methanol, (ρ_{XZ} = -1.7),[2] albeit the value obtained in this work is itself quite large relative to those for other backside S$_N$2 reactions with positive ρ_{XZ} ($\rho_{XZ} > 0$).[3,7] Since electrostatic interaction between the two partially charged functional centers, N$^{\delta+}$ and S$^{\delta-}$, should be much reduced in an aprotic solvent, *e.g.* MeCN, than in a protic solvent, *e.g.* MeOH, the reduced interaction between the two reaction centers in MeCN seems to result in a smaller magnitude of ρ_{XZ} than in MeOH. The large negative ρ_{XZ} obtained in the present work is comparable to those for the reactions for which a frontside nucleophilic attack has been proposed. According to the high level (G2(+)) *ab initio* MO studies on the frontside S$_N$2 reactions,[8] elongation of the bond between the reaction center carbon and the leaving group is considered to be a significant factor in decreasing the unfavorable nature of the frontside S$_N$2 reaction with retention of configuration. Since the S atom is a 2nd raw element, the bond length linking to S in the thioether is relatively long, and also the bond cleavage in the TS is facilitated by the strong $n_N \rightarrow \sigma^*_{C\text{-}S}$ vicinal charge transfer interactions due to the relatively low $\sigma^*_{C\text{-}S}$ level.[9] Secondary the two oppositely charged centers, N$^{\delta+}\cdots$ S$^{\delta-}$, in close vicinity in the TS should increase the interaction (electrostatically) between the two groups, nucleophile (X) and leaving group (Z) which is reflected in the relatively large ρ_{XZ} values. The closely located two reaction centers may also facilitate electron transfer from the nucleophile to the leaving group in the TS, which should result in a large avoided crossing energy[10] and lower the activation barrier.

Table 2. The Secondary Kinetic Isotope Effects for the Reactions of Anilino Thioethers with Deuterated X-Benzylamines in Acetonitrile at 50.0 °C

X	Z	$k_H \times 10^5$ (M^{-1}s^{-1})	$k_D \times 10^5$ (M^{-1}s^{-1})	k_H/k_D
p-OMe	*p*-Me	1.01 (± 0.02)	1.12 (± 0.03)	0.90 ± 0.03^a
p-OMe	H	1.59 (± 0.03)	1.81 (± 0.04)	0.88 ± 0.03
p-OMe	*p*-Cl	3.30 (± 0.06)	3.88 (± 0.07)	0.85 ± 0.02
p-OMe	*p*-Br	4.68 (± 0.08)	5.63 (± 0.09)	0.83 ± 0.02
p-Cl	*p*-Me	0.495 (± 0.005)	0.538 (± 0.007)	0.92 ± 0.02
p-Cl	H	0.741 (± 0.008)	0.832 (± 0.01)	0.89 ± 0.01
p-Cl	*p*-Cl	1.45 (± 0.02)	1.68 (± 0.03)	0.86 ± 0.02
p-Cl	*p*-Br	1.86 (± 0.05)	2.18 (± 0.05)	0.85 ± 0.03

[a] Standard deviations.

Table 3. Activation Parameters[a] for the Reactions of Anilino Thioethers with X-benzylamines in Acetonitrile

X	Z	$\Delta H^{\neq}$/kcal mol^{-1}	-$\Delta S^{\neq}$/cal mol^{-1} K^{-1}
p-OMe	*p*-Me	7.7	58
p-OMe	*p*-Br	6.8	57
p-Cl	*p*-Me	7.3	60
p-Cl	*p*-Br	7.2	58

[a] Calculated by the Eyring equation. The maximum errors calculated (by the method of Wiberg, K. B. *Physical Organic Chemistry*, Wiley, New York, 1964, p 378) are ± 0.5 kcal mol^{-1} and ± 2 e.u. for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, respectively. The levels of confidence are better than 95%. Temperature range is 30.0-50.0 °C.

The secondary kinetic isotope effects ($k_H/k_D < 1.0$) determined with deuterated benzylamines[7] ($XC_6H_4CH_2ND_2$) in MeCN (Table 2) are similar to those with deuterated anilines ($XC_6H_4ND_2$)[2] in MeOH. This is consistent with the fact that the degree of bond formation in the TS, as judged by the magnitude of b_X values, is similar in the two reaction series. The inverse secondary kinetic isotope effect with $k_H/k_D < 1.0$ results from an increased N-H (N-D) vibration due to steric compression experienced by the approach of the nucleophile (amines) toward the reaction center carbon.[7]

The activation parameters, $\Delta H^{\neq}$ and $\Delta S^{\neq}$, are summarized in Table 3. The $\Delta H^{\neq}$ values are somewhat higher ($\cong$ 7-8 kcal mol^{-1}) than those for the reactions in MeOH with anilines ($\Delta H^{\neq} \cong$ 4-5 kcal mol^{-1}). This may be also be due to the effect of aprotic solvent, MeCN, which has much smaller ionizing power (no solvolysis in pure MeCN) than the protic solvent, MeOH (ionizing power scale,Y = -1.09),[11] as evident from the lower degree of bond cleavage in MeCN (smaller -β_Z value) than in MeOH (larger -β_Z value).

Experimental Section

Materials. Merk GR acetonitrile was used after three distillations. The benzylamine nucleophiles, Aldrich GR, were used without further purification.

Substrates. Preparations and analytical data are reported elsewhere.[2]

Kinetic Measurement. Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method with large excess of benzylamine (BA). Second order rate constants, k_2, were obtained from the slope of a plot of k_{obs} *vs* [BA] with more than five concentrations of benzylamine. The k_2 values in Table 1 are the averages of more than three runs and were reproducible to within ±3%.

Product Analysis. Substrate, N-methyl-N-[(4-bromophenylthio)methyl]-aniline (0.05 mole) was reacted with excess 4-methoxybenzylamine (0.5 mole) with stirring for more than 15 half-lives at 50.0 °C in acetonitrile. The reaction mixture was extracted with ether and the solvent was removed by distillation under reduced pressure. Anilide was separated by column chromatography (silicagel, 10% ethylacetate-n-hexane). The spectral data are as follows.

3-$NO_2C_6H_4N(CH_3)CH_2NHCH_2C_6H_4$-4-OMe: liquid, IR (KBr), 3363 (C-H), 3160 (N-H), 1608, 1475 (C=C, aromatic), 1355 (N=O), 821 (C-H, aromatic); ^{1}H NMR (400 MHz, $CDCl_3$), 2.92 (3H, s, N-CH_3), 3.75 (3H, s, -OCH_3), 4.12 (1H, broad, NH), 4.89 (2H, s, CH_2), 6.95-7.65 (8H, m, aromatic ring); ^{13}C NMR (100.4 MHz, $CDCl_3$), 160.5, 148.2, 145.6, 133.3, 131.2, 128.7, 121.4, 118.2, 111.8, 75.5, 60.4, 52.3, 37.5; mass, *m/z* 300 (M^+). Anal. Calcd for $C_{16}H_{18}N_3O_3$; C, 64.0; H, 6.01. Found: C, 64.2; H, 6.03: MS *m/z* 301 (M^+), Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.8; H, 6.41. Found: C, 63.6; H, 6.43.

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References

1. (a) Eldin, S.; Jencks, W. P. *J. Am. Chem. Soc*. **1995**, *117*, 4851. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Daver: New York, 1987. (c) Bohme, H.; Haake, M. In *Iminium Salts in Organic Chemistry*; Taylor, E. C., Ed.; Wiley: New York, 1976; p 145.
2. (a) Oh, H. K.; Yang, J. H.; Lee, H. W.; Lee, I. *New J. Chem*. **2000**, *24*, 213. (b) Song, H. B.; Oh, H. K.; Choi, M. H.; Koo, I. S.; Lee, I. *Bull. Korean Chem. Soc*. **2003**, *24*, 91.
3. (a) Lee, I. *Chem. Soc. Rev*. **1990**, *19*, 317. (b) Lee, I. *Adv. Phys. Org. Chem*. **1992**, *27*, 59.
4. (a) Siggel, M. R. F.; Streitwieser, A.; Thomas, T. D. *J. Am. Chem. Soc*. **1988**, *110*, 8022. (b) Charton, M. *Prog. Phys. Org. Chem*. **1981**, *13*, 119.
5. (a) Ritchie, C. D. In *Solute-Solvent Interactions*; Coetzee, J. F.; Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; Ch. 4. (b) Coetzie, J. F. *Prog. Phys. Org. Chem*. **1967**, *4*, 54. (c) Spillane, W. J.; Hogan, G.; McGrath, P.; King, J.; Brack, C. *J. Chem. Soc. Perkin Trans. 2* **1996**, 2099. (d) Lee, I.; Kim, C. K.; Han, I. S.; Lee, H. W.; Kim, W. K.; Kim, Y. B. *J. Phys. Chem. B* **1999**, *103*, 7302.
6. (a) Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874. (b) Koh, H. J.; Han, K. L.; Lee, H. W.; Lee, I. *Bull. Korean Chem. Soc*. **2002**, *23*, 715.
7. Lee, I. *Chem. Soc. Rev*. **1995**, *24*, 223.
8. Glukhovtsev, M. W.; Pross, A.; Schlegel, H. B.; Bach, R. D.; Radom, L. *J. Am. Chem. Soc*. **1996**, *118*, 11258.
9. Epiotiz, N. D.; Cherry, W. R.; Shaik, S.; Yates, Y.; Bernardi, F. *Structural Theory of Organic Chemistry*; Springer-Verlag: Berlin, 1977; Part I.
10. Xing, Y.-M.; Xu, X.-F.; Chen, L.; Cai, Z.-S.; Zhae, X.-Z.; Cheng, J.-P. *Phys. Chem. Chem. Phys*. **2002**, *4*, 4669.
11. Reichart, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: Weinheim, 1988; p 351.