Kinetics and Mechanism of the Aminolysis of Aryl *N*-Cyclohexyl Thiocarbamates in Acetonitrile

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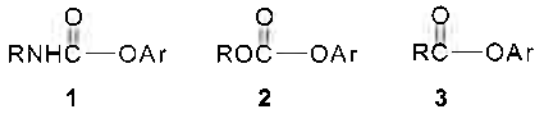
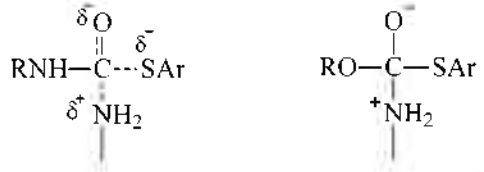
The mechanism for aminolysis of carbamates, **1** has been reported to be quite similar to that for the corresponding reactions of aryl carbonates, **2** and aryl esters, **3**.[1-3] The mechanism for the reactions of benzylamines with **1** and **2** have been suggested to change from a stepwise mechanism with a tetrahedral intermediate, $T^{\pm}$, to a concerted one upon

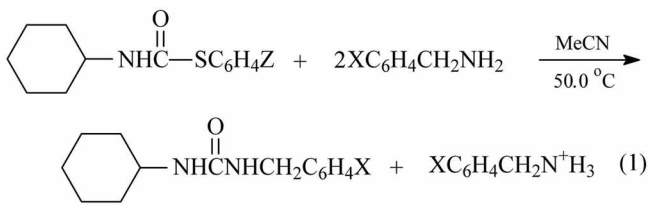


changing the leaving group from phenoxides to thiophenoxides. This suggests that the strength of push provided by PhNH to expel the leaving group from $T^{\pm}$ is similar to that by EtO, and the destabilization of $T^{\pm}$ due to this push is strong enough for $^{-}$SAr but is too weak for $^{-}$OAr to lead the aminolysis to a concerted process.



TS : for **1** $T^{\pm}$: intermediate for **2**

In order to pursue further the mechanistic similarities between carbamates and carbonates, we carried out kinetic studies on the aminolysis of aryl *N*-cyclohexylthiocarbamates (ACTC: c-$C_6H_{11}NHC(=O)SC_6H_4Z$) with benzylamines in acetonitrile, eq. (1). The primary purpose of this work is



(1)

to establish the aminolysis mechanism for eq. (1) and to examine the effect of the nonleaving group, c-$C_6H_{11}NH$-, on the mechanism. We varied substituents in the nucleophile (X) and leaving group (Z) and the rate constants, k_2, are subjected to a multiple regression analysis to determine the cross-interaction constant,[4] ρ_{XZ} in eq. (2). For a concerted mechanism the sign of ρ_{XZ} was found to be negative[4] and the reactivity-selectivity principle (RSP) failed.[5]

$$\log(k_{XZ}/k_{HH}) = \rho_X\sigma_X + \rho_Z\sigma_Z + \rho_{XZ}\sigma_X\sigma_Z \quad (2a)$$

$$\rho_{XZ} = \partial\rho_Z/\partial\sigma_X = \partial\rho_Y/\partial\sigma_Z \quad (2b)$$

Experimental Section

Materials. GR grade acetonitrile was used after three distillations. GR grade benzylamine nucleophiles were used after distillation or recrystallization.

Substrates.

Phenyl *N*-cyclohexyl thiocarbamate: A solution of thiophenol (0.01 mol) in dry toluene (10 mL) was added to a solution of cyclohexyl isocyanate (0.01 mol). A catalytic quantity (0.5 mL) of pyridine was added and the solution refluxed for 2 h. On evaporation of the solvent *in vacuo*, the thiocarbamate precipitated and was recrystallized from chloroform-pentane. The other substituted phenyl *N*-cyclohexyl thiocarbamates were prepared in an analogous manner and recrystallized from chloroform-pentane. The substrates synthesized were confirmed by spectral and elemental analysis as follows.

$C_6H_{11}NHC(=O)SC_6H_4$-*p*-CH_3: m.p. 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.95 (11H, m, C_6H_{11}), 2.43 (3H, s, CH_3), 6.22 (1H, s, NH), 7.19 (2H, d, J = 8.30 MHz, meta H), 7.46 (2H, d, J = 8.30 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 165.3, 139.8, 135.3, 130.2, 125.3, 50.4, 32.8, 25.4, 24.6, 21.4; ν_{max} (KBr), 3306 (NH), 2834 (CH, aromatic), 1646 (C=O), 746 (C-S); MS *m*/*z* 249 (M^-). Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.4; H, 7.71. Found: C, 67.6; H, 7.72.

$C_6H_{11}NHC(=O)SC_6H_5$: m.p. 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.99 (11H, m, C_6H_{11}), 6.25 (1H, s, NH), 7.36-7.60 (5H, m, C_6H_5); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 164.7, 135.2, 129.3, 129.2, 128.7, 50.4, 32.8, 25.4, 24.6; ν_{max} (KBr), 3284 (NH), 2831 (CH, aromatic), 1655 (C=O), 742 (C-S); MS *m*/*z* 235 (M^+). Anal. Calcd $C_{13}H_{17}NOS$: C, 66.3; H, 7.30. Found: C, 66.4; H, 7.32.

$C_6H_{11}NHC(=O)SC_6H_4$-*p*-Cl: m.p. 138-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.01 (11H, m, C_6H_{11}), 6.20 (1H, s, NH), 7.42 (2H, d, J = 8.78 MHz, meta H), 7.50 (2H, d, J = 8.78 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 163.8, 136.3, 135.6, 129.3, 127.1, 50.8, 32.9, 25.4, 24.6; ν_{max} (KBr), 3307 (NH), 2832 (CH, aromatic), 1685 (C=O), 744

(C-S); MS *m*/z 277 (M^+). Anal. Calcd $C_{13}H_{16}ClNOS$: C, 57.9; H, 6.01. Found: C, 57.8; H, 6.03.

$C_6H_{11}NHC(=O)SC_6H_4$-*p*-Br: m.p. 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.98 (11H, m, C_6H_{11}), 6.21 (1H, s, NH), 7.36 (2H, d, J = 8.35 MHz, meta H), 7.55 (2H, d, J= 8.35 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 163.7, 136.5, 132.2, 127.7, 123.9, 50.8, 32.9, 25.4, 24.6; ν_{max} (KBr), 3318 (NH), 2836 (CH, aromatic), 1654 (C=O), 745 (C-S); MS *m*/z 314 (M^-). Anal. Calcd $C_{13}H_{16}BrNOS$: C, 49.7; H, 5.11. Found: C, 49.9; H, 5.10.

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_{obsd}, were determined by the Guggenheim method[6] with large excess of benzylamine. The plots of k_{obsd} *vs* [benzylamine] were linear with more than five different concentrations and the second-order rate constants, k_2, have been determined from the slope of the linear plots. The k_2 values in Table 1 are the averages of more than three runs and were reproducible to within ± 3%.

Product Analysis. The substrate phenyl *N*-cyclohexyl thiocabamate (0.01 mole) was reacted with excess *p*-methoxybenzylamine (0.1 mole) with stirring for more than 15 half-lives at 50.0 °C in acetonitrile (*ca.* 200 mL) and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was subjected to column chromatography (silica gel, 20% ethyl acetate-*n*-hexane). Analysis of the product gave the following results.

$C_6H_{11}NHC(=O)NHCH_2C_6H_4$-*p*-$OCH_3$: m.p. 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$), δ 2.01 (11H, m, C_6H_{11}), 3.93 (3H, s, OCH_3), 4.32 (2H, d, CH_2), 4.84 (1H, s, NH), 6.80 (2H, d, J = 8.78 MHz, meta H), 7.25 (2H, d, J = 8.30 MHz, ortho H); ^{13}C NMR (100.4 MHz, $CDCl_3$), δ 158.7, 157.3, 137.2, 128.7, 113.9, 55.3, 49.1, 44.0, 33.9, 25.6, 24.9; ν_{max} (KBr), 3327 (NH), 2925 (CH, aliphatic), 2850 (CH, aromatic), 1624 (C=O), 1514 (N-C), 1249 (C-O); MS *m*/z 262 (M^-). Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.7; H, 8.51. Found; C, 68.9; H, 8.50.

Results and Discussion

The reactions of aryl *N*-cyclohexylthiocarbamates (ACTC; c-$C_6H_{11}NHC(=O)SC_6H_4Z$) with benzylamines (BA) follow a clean second-order kinetics, eq. (3). Unlike in the aminolysis of aryl *N*-phenylcarbamate (APC), no base catalysis by the amine was noted.

$$\text{Rate} = k_{obs}\,[\text{Substrate}] \quad (3a)$$

$$k_{obs} = k_2\,[\text{BA}] \quad (3b)$$

The rate constants, k_2, determined are summarized in Table 1 together with the selectivity parameters, ρ_X, β_X, ρ_Z, and β_Z. For the determination of β_X (β_{nuc}), the pK_a values of benzylamines in H_2O are used. This procedure was found to be reliable since the pK_a values in MeCN and in H_2O varies in parallel, albeit the absolute values are different.[7] For the β_Z (β_{eq}) values, a factor of 0.62 was multiplied to all the β_Z values determined using the pK_a(H_2O) values.[8] The rates are substantially slower for the aminolysis of ACTC than for the corresponding reactions of aryl *N*-phenylthiocarbamates (APTC).[1b] This slower rate found with *N*-cyclohexyl (ACTC) relative to *N*-phenyl (APTC) analog can be attributed to the weaker push provided by the cyclohexylamino (c-$C_6H_{11}N$) than phenylamino (PhNH) group to expel the leaving group from a tetrahedral structure[8] which may be either an intermediate $T^{\pm}$ or a transition state, $T^{=}$ (TS).

Further important mechanistic criteria for the concerted with ACTC rather than the stepwise (as with APC) is that the sign of cross-interaction constant ρ_{XZ} is negative for ACTC (rather than positive as with APC) and the RSP fails with ACTC.[5,7] The stepwise mechanism is not favored for the present reactions, since for the stepwise aminolysis of esters, carbonates and carbamates, the sign of ρ_{XZ} (and ρ_{XY}) is positive and the RSP holds.[5,7]

The magnitude of β_X is, however, large ($\beta_X \cong$ 0.9-1.4) which is normally considered to indicate a stepwise reaction.[11] For concerted aminolysis reactions, the β_X values were found to range from 0.4-0.8.[12] It is, however, well

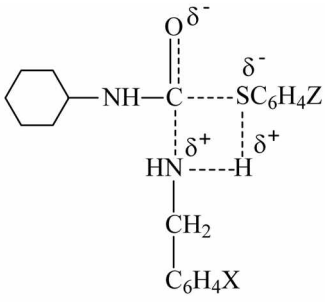
Table 1. The Second Order Rate Constants, k_2 (10^3 dm^3 mol^{-1} s^{-1}) for the Reactions of Z-Aryl *N*-Cyclohexyl Thiocarbamates with X-Benzylamines in Acetonitrile at 50.0 °C

X	Z				ρ_Z[a]	β_Z[b]
	p-Me	H	*p*-Cl	*p*-Br		
p-OMe	2.72[c]	9.17	96.9	170[c]	4.43 ± 0.04	−1.85 ± 0.08
	1.85			114		
	1.27[d]			77.5[d]		
p-Me	1.57	7.85	67.8	78.9	4.19 ± 0.02	−1.75 ± 0.11
H	1.11	5.18	39.8	40.9	3.90 ± 0.05	−1.66 ± 0.10
p-Cl	1.02[c]	2.98	19.6	33.2[c]	3.70 ± 0.02	−1.55 ± 0.10
	0.701			22.6		
	0.476[d]			15.1[d]		
m-Cl	0.501	2.02	12.4	14.1	3.57 ± 0.02	−1.49 ± 0.09
ρ_X[e]	−0.90 ± 0.01	−1.04 ± 0.17	−1.38 ± 0.01	−1.40 ± 0.03	ρ_{XZ}[e] =	−1.29 ± 0.02
β_X[f]	0.90 ± 0.01	1.05 ± 0.02	1.40 ± 0.01	1.41 ± 0.04		

[a]The σ values were taken from ref. 9. Correlation coefficients were better than 0.997 in all cases. [b]The pKa values were taken from A. Albert and E. P. Serjeant, "*The Determination of Ionization Constants*" 3rd Ed., Chapman and Hall, London, p 145. Correlation coefficients were better than 0.995 in all cases. [c]At 60°C. [d]At 40 °C. [e]Calculated by a multiple regression analysis using eq. (2a), r = 0.999, n = 20 and F_{calc} = 1410 (F_{tab} = 10.66 at the 99.9% confidence level). [f]The pKa values were taken from ref. 10. Correlation coefficients were better than 0.996 in all cases. For X = *p*-CH_3O an extrapolated value of pK_a = 9.64 was used.

known that the large magnitude of the Brönsted slope alone is not sufficient to decide the aminolysis mechanism as stepwise. Jencks and coworkers reported concerted acyl transfer reactions with large β_X values. β_X = 0.6-0.9 for the reactions of phenyl formates with substituted O-chlorophenolate anions[13] and β_X = 0.7-1.0 for the reactions of a series of nucleophilic reagents with substituted *N*-acetylpyridinium ions.[14] Williams and coworkers[15] reported even larger β_X values (β_X = 1, 3, and 1.6) for the concerted acyl transfer reactions. Thus the large β_X values observed in the present work may be taken as an indicative of a stepwise mechanism, but can not provide a conclusive evidence for a stepwise mechanism.

The kinetic isotope effects (Table 2) involving deuterated nucleophile, $XC_6H_4CH_2ND_2$, are normal (k_H/k_D > 1.0) suggesting a possibility of forming hydrogen-bonded four-center type TS (**4**)[16] as has often been proposed. Since no base catalysis was found (the rate law is first order with respect to [BA], eq. (3)), the proton transfer occurs concurrently with the rate-limiting expulsion of ArO^- in the TS but not catalyzed by benzylamine. The consumption of proton by the excess benzylamine should therefore take place in a subsequent rapid step.



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The low activation enthalpies, $\Delta H^{\neq}$, and highly negative activation entropies, $\Delta S^{\neq}$, (Table 3) are also in line with the proposed TS. Especially, the $\Delta H^{\neq}$ values are somewhat lower and the $\Delta S^{\neq}$ values are higher negative values than other aminolysis systems.[13] The expulsion of ArO^- anion in the rate determining step (an endoergic process) is assisted by the hydrogen-bonding with an amino hydrogen of the benzylammonium ion within the intermediate, $T^{\pm}$. This will lower the $\Delta H^{\neq}$ value, but the TS becomes structured and rigid (low entropy process) which should lead to a large negative.

Table 2. The Kinetic Isotope Effects for the Reactions of Z-phenyl *N*-cyclohexyl Thiocarbamates with X-Benzylamines in Acetonitrile at 50.0 °C

X	Z	$k_H/10^3$ $M^{-1}s^{-1}$	$k_H/10^3$ $M^{-1}s^{-1}$	k_H/k_D
p-OMe	*p*-Me	1.85(±0.03)	1.41(±0.02)	1.31 ± 0.02[a]
p-OMe	H	9.17(±0.08)	6.64(±0.06)	1.38 ± 0.02
p-OMe	*p*-Cl	96.9(±1.5)	66.8(±1.1)	1.45 ± 0.04
P-OMe	*p*-Br	114(±2.0)	75.0(±1.3)	1.52 ± 0.03
p-Cl	*p*-Me	0.701(±0.006)	0.519(±0.004)	1.35 ± 0.02
p-Cl	H	2.98(±0.03)	2.09(±0.02)	1.42 ± 0.02
p-Cl	*p*-Cl	19.6(±0.2)	13.1(±0.09)	1.50 ± 0.03
p-Cl	*p*-Br	22.6(±0.4)	14.3(±0.1)	1.58 ± 0.02

[a]Standard deviations.

Table 3. Activation Parameters[a] for the Reactions of Z-Pphenyl *N*-Cyclohexyl Thiocarbamates 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	7.4	48
p-OMe	*p*-Br	4.6	40
p-Cl	*p*-Me	7.2	50
p-Cl	*p*-Br	4.6	43

[a]Calculated by the Eyring equation. The maximum errors calculated (by the method of K. B. Wiberg, *Physical Organic Chemistry*, Wiley, New York, **1964**, p 378) are = 0.6 kcal mol^{-1} and = 2 e.u. for ΔH and ΔS, respectively.

In summary, we propose a concerted mechanism with a hydrogen bonded cyclic transition state for the aminolysis of aryl *N*-cyclohexyl thiocarbamates with benzylamines in acetonitrile. The evidences to support our proposal are a negative cross-interaction constant, failure of RSP, a strong push provided to expel ArS^- by the nonleaving group, c-$C_6H_{11}N$, the kinetic isotope effects greater than unity and relatively low $\Delta H^{\neq}$ with large negative $\Delta S^{\neq}$ values.

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