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

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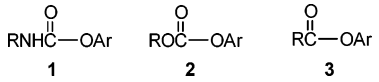
The aminolysis of aryl *N*-ethyl thiocarbamates (EtNHC(=O)SC_6H_4Z) with benzylamines ($XC_6H_4CN_2NH_2$) in acetonitrile at 30.0 °C is investigated. The rates are faster than the corresponding values for aryl *N*-phenyl thiocarbamates (PhNHC(=O)SC_6H_4Z), reflecting a stronger push to expel the leaving group by EtNH than the PhNH nonleaving group in a concerted process. The negative ρ_{XZ} (−0.86) and failure of the reactivity−selectivity principle found are consistent with the concerted mechanism. The kinetic isotope effects involving deuterated nucleophiles (k_H/k_D = 1.5−1.7) and low $\Delta H^{\ddagger}$ with large negative $\Delta S^{\ddagger}$ values suggest a hydrogen bond cyclic transition state.

Introduction

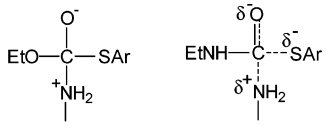
Although there is abundant literature on the kinetics and mechanism of the aminolysis of aryl carbonates[1] and esters,[2] the aminolysis reactions of aryl carbamates[3] have been less studied kinetically. The mechanism of the aminolysis of substituted diphenyl carbonates has been studied, and structure−reactivity relationships have been examined in detail by Gresser and Jencks.[1a]. Castro and co-workers have reported a number of mechanistic studies on the aminolysis of aryl carbonates[1c−f] and esters.[2h−l] These and other studies showed that most of the aminolysis of aryl carbonates and esters proceed by either a stepwise mechanism through a zwitterionic tetrahedral intermediate, $T^{\pm}$, or concertedly, depending on the amine, substrate, and solvent involved.

The aminolysis mechanism of aryl carbamates **1** is quite similar to that of aryl carbonates **2** and aryl esters **3**. A change in the mechanism of the aminolysis with



1 **2** **3**

benzylamines in acetonitrile has been observed from stepwise through a tetrahedral intermediate, $T^{\pm}$, to concerted for the carbamates[3a,b] **1** (with R = Ph) as well as for the carbonates[4] **2** (with R = Et) when the leaving group is changed from phenoxide (**a**, $^-$OAr) to thiophenoxide (**b**, $^-$SAr). This suggests that the strength of



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

push provided to expel the leaving group from $T^{\pm}$ by PhNH 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.

To pursue further the mechanistic similarities between carbamates and carbonates, we carried out kinetic studies on the aminolysis of aryl *N*-ethyl thiocarbamates (AETC, EtNHC(=O)SC_6H_4Z) with benzylamines in acetonitrile, eq 1. The primary purpose of this

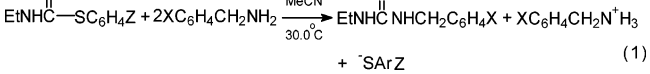


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TABLE 1. Second-Order Rate Constants, k_2 (10^3 dm^3 mol^{-1} s^{-1}) for the Reactions of Z-Phenyl *N*-Ethyl Thiocarbamates with X-Benzylamines in Acetonitrile at 30.0 °C

X	Z = *p*-Me	Z = H	Z = *p*-Cl	Z = *p*-Br	ρ_Z[a]	β_Z[b]
p-OMe	10.1[c]			41.0[c]		
	6.96	11.2	26.3	39.4	1.53 ± 0.08	−0.45 ± 0.06
	4.94[d]			20.6[d]		
p-Me	5.99	9.79	19.9	22.2	1.38 ± 0.07	−0.35 ± 0.02
H	4.77	7.36	13.9	15.7	1.24 ± 0.08	−0.32 ± 0.02
p-Cl	4.21[c]			11.1[c]		
	3.06	4.23	7.51	7.74	1.01 ± 0.05	−0.26 ± 0.02
	2.17[d]			5.34[d]		
m-Cl	2.39	3.31	5.66	6.01	0.98 ± 0.05	−0.25 ± 0.02
ρ_X[e]	−0.73 ± 0.03	−0.88 ± 0.03	−1.05 ± 0.03	−1.10 ± 0.05	ρ_{XZ}[f] = −0.86	
β_X[g]	0.74 ± 0.03	0.87 ± 0.04	1.06 ± 0.02	1.25 ± 0.11		

[a] The σ values were taken from ref 8.Correlation coefficients were better than 0.997 in all cases. [b] The pK_a values were taken from Buckingham, J., Ed.. *Dictionary of Organic Chemistry*, 5th ed.; Chapman and Hall: New York, 1982. These values of β_Z (in MeCN) are estimated by multiplying β_Z (in H_2O) by 0.62: See footnote 13 of Oh, H. K.; Ku, M. H.; Lee, H. W.; Lee, I. *J. Org. Chem*. **2002**, *67*, 3874. Correlation coefficients were better than 0.983 in all cases. [c] At 40 °C. [d] At 20 °C. [e] The σ values were taken from ref 6. Correlation coefficients were better than 0.996 in all cases. [f] The correlation coefficient was 0.997. [g] The pK_a values were taken from Fischer, A.; Galloway,W. J.; Vaughan, J. *J. Chem. Soc*. **1964**, 3588. Correlation coefficients were better than 0.989 in all cases. For X = *p*-CH_3O an extrapolared value of 9.64 was used.

work is to establish the aminolysis mechanism for eq 1 and to examine the effect of the nonleaving group, EtNH−, on the mechanism. It is of much interest to examine whether the concerted mechanism observed for the aminolysis of aryl *N*-phenyl thiocarbamates (APTC, PhNHC(=O)SC_6H_4Z) with benzylamines in acetonitrile[3b] also applies to the corresponding reactions of AETC, which has a stronger electron donor group, EtNH. 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,[5] ρ_{XZ}, in eq 2. For a concerted mechanism, the sign of ρ_{XZ} was found to be negative[5,6] and the reactivity−selectivity principle (RSP) failed.[6]

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

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

Results and Discussion

The reactions of Z-phenyl *N*-ethyl thiocarbamates with X-benzylamines in acetonitrile at 30.0 °C obey a clean second-order rate law, eqs 3 and 4, where [AETC] and [BA] are the concentrations of aryl *N*-ethyl thiocarbamate and benzylamine, respectively. The second-order rate constants, k_2, summarized in Table 1 are obtained from a straight line plot of k_{obs} vs [BA].

$$\text{rate} = k_{obs}[\text{AETC}] \quad (3)$$

$$k_{obs} = k_2[\text{BA}] \quad (4)$$

The rates are ca. 2−8 times faster than the corresponding aminolysis values for the APTCs.[3b] This rate enhancement found with *N*-ethyl (AETC) relative to *N*-phenyl (APTC) analogues can be attributed to the lower steric effect and the stronger push provided by the ethylamino (EtNH) than phenylamino (PhNH) group to expel the leaving group from a tetrahedral structure,[7] which may be either an intermediate $T^{\pm}$ or a transition state (TS). Electron donor abilities ($\sigma < 0$) of the RO and RNH groups are compared in Table 2. Since the lone pair electrons on O (n_O) and N (n_N) atoms are donated to the lowest unoccupied MO (LUMO) of the C−S bond orbital (σ^*_{C-S}) by $n_O \rightarrow \sigma^*_{C-S}$ and $n_N \rightarrow \sigma^*_{C-S}$ type vicinal charge-transfer interactions within the $T^{\pm}$ structures,[6,9] the higher the nonbonding orbital ($\epsilon_{n_O} < \epsilon_{n_N}$) (and the lower the σ^*_{C-S} level) the stronger the charge-transfer interaction, ΔE, in eq 5, where $\Delta\epsilon = \epsilon_{\sigma^*} - \epsilon_n$ and $F_{n\sigma^*}$ is the Fock

TABLE 2. Substituent Constants for RO and RNH (R = Me, Et, and Ph) Groups[6]

	σ_m	σ_p	σ_p^+
MeO	0.12	−0.27	−0.78
EtO	0.10	−0.24	−0.81
PhO	0.25	−0.03	−0.50
MeNH	−0.21	−0.70	−1.81
EtNH	−0.24	−0.61	(∼−1.8)
PhNH	−0.02	−0.56	−1.40

$$\Delta E = -2F_{n\sigma^*}{}^2/\Delta\epsilon \quad (5)$$

matrix element which is proportional to the overlap integral between the two interacting orbitals, $S_{n\sigma^*}$, and hence the stronger will become the push provided by the RNH than the RO group to expel the leaving group. The resonance electron donor ability (σ_p^+) listed[8] in Table 2 should roughly parallel ΔE in eq 5, since the lone pair electrons on N or O are delocalized through the π^* orbital of the benzene ring by $n \rightarrow \pi^*$ interaction with the electron-deficient functional center on the σ_p^+ scale.[9] We note that in general RNH groups are stronger electron donors than the corresponding RO groups, and the two alkyl groups (R = Me and Et) have similar electron-releasing effects, which are stronger than that for the phenyl (R = Ph) group. The order of increasing electron donor ability can be given as shown in eq 6.

$$\text{PhO} < \text{MeO} \cong \text{EtO} \ll \text{PhNH} < \text{MeNH} \cong \text{EtNH} \quad (6)$$

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The stronger electron donor ability of the EtNH than the PhNH group is thus reflected in the faster aminolysis rates for AETC than for the corresponding reactions of APTC. The alkyl and phenyl groups (R = alkyl and Ph in **3** lack lone pair electrons) are weak electron donors compared to RNH and RO in **1** and **2**. Thus, the push to expel the leaving group from $T^{\pm}$ by them (**3**) should be much weaker than those by RNH (**1**) and RO (**2**), and the aminolyses were found to proceed by the stepwise mechanism with rate-limiting breakdown of $T^{\pm}$.[10] The electron donor ability of a phenoxy group (R = Ph in **2**) is stronger than that of R = alkyl and phenyl in **3**, but is lower than that of EtO (R = Et in **2**), and is much lower than that of PhNH and/or EtNH in **1**. The results of Gresser and Jencks[1a] show that the aminolysis of aryl phenyl carbonates, R = Ph in **2**, with quinuclidines in water proceeds by a stepwise mechanism. No corresponding aminolysis data with benzylamines are available for the diaryl carbonate series, R = Ph in **2**, in water nor in acetonitrile.

Interestingly, as we move up to the stronger electron-donating groups in the sequence shown in eq 6, EtO and PhNH, a mechanistic change occurs from stepwise with phenoxide (**a**, $^{-}$OAr)[3a,4a] to concerted with thiophenoxide (**b**, $^{-}$SAr)[3b,4b] leaving groups. This is because the thiophenoxides are better leaving groups than phenoxides, since the σ^*_{C-S} orbital is lower than the σ^*_{C-O} level and hence is a better electron acceptor, $\Delta\epsilon$ in eq 5 is smaller,[9a] and is readily broken compared to the C−O bond. For example, the aminolysis of *O*-ethyl aryl carbonates (R = Et in **2a**) with benzylamines[4a] in MeCN is stepwise with rate-limiting breakdown of $T^{\pm}$ ($\beta_X = 2.4$ for Z = 4-NO_2, and $\rho_{XZ} = 1.35$), but the corresponding reaction of *O*-ethyl aryl thiolcarbonate[4b] (R = Et in **2b**) is concerted ($\beta_X = 0.6$ for Z = 4-NO_2 and $\rho_{XZ} = -0.47$). Likewise, the aminolysis of *N*-phenyl aryl carbamates (R = Ph in **1a**) with benzylamines[3a] in MeCN is stepwise ($\beta_X = 1.3$, $\rho_{XZ} = +1.10$), but that of thiocarbamate[3b] analogues (R = Ph in **1b**) proceeds by a concerted mechanism ($\beta_X = 1.3$, $\rho_{XZ} = -0.63$).

Mechanistic changes are often observed for the aminolysis of carbonates from stepwise in water to concerted in acetonitrile.[11,12] For example, the aminolyses of aryl chloroformates in water (with secondary alicyclic amines) are stepwise,[11c] whereas the corresponding reactions in acetonitrile (with anilines) are concerted.[11b] Likewise, the aminolysis of 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates is stepwise[13] (biphasic Brønsted plot) in water, but is concerted ($\beta_X = 0.53$) in a less polar solvent (44 wt % aqueous ethanol).[14] The change of solvent from water to a less polar solvent *de*stabilizes the zwitterionic intermediate, resulting in an increase in the rate of expulsion of the amines from $T^{\pm}$, and rendering the intermediate more unstable kinetically.[11c,14]

TABLE 3. Kinetic Isotope Effects Involving Deuterated Benzylamines ($XC_6H_4CH_2ND_2$) for the Reactions of Z-Phenyl *N*-Ethyl Thiocarbamates with X-Benzylamines in Acetonitrile at 30.0 °C

X	Z	k_H (10^3 M^{-1} s^{-1})	k_D (10^3 M^{-1} s^{-1})	k_H/k_D
p-OMe	*p*-Me	6.70 (±0.06)	4.70 (±0.05)	1.48 ± 0.02[a]
p-OMe	H	11.2 (±0.1)	7.32 (±0.04)	1.53 ± 0.02
p-OMe	*p*-Cl	26.3 (±0.5)	16.6 (±0.2)	1.58 ± 0.04
p-OMe	*p*-Br	29.4 (±0.6)	17.7 (±0.2)	1.66 ± 0.04
p-Cl	*p*-Me	3.06 (±0.02)	2.00 (±0.02)	1.53 ± 0.02
p-Cl	H	4.23 (±0.04)	2.63 (±0.04)	1.61 ± 0.03
p-Cl	*p*-Cl	7.51 (±0.08)	4.49 (±0.05)	1.67 ± 0.03
p-Cl	*p*-Br	7.74 (±0.06)	4.45 (±0.04)	1.74 ± 0.02

[a] Standard deviations.

It is also known that the *carbonyl* group (C=O) has a greater proclivity for the concerted mechanism than the *thiocarbonyl* group (C=S)[15] due to a narrower energy gap between the π^* and σ^* levels, $\Delta\epsilon = \epsilon(\pi^*_{C=O}) - \epsilon(\sigma^*_{C-S}) < \Delta\epsilon = \epsilon(\pi^*_{C=S}) - \epsilon(\sigma^*_{C-S})$, enabling efficient mixing of the two orbitals.[6,16] For example, concerted mechanisms are found for the aminolyses of *S*-(2,4-dinitrophenyl)[15] and *S*-(2,4,6-trinitrophenyl)[18] *O*-ethyl thiocarbonates in contrast to the stepwise mechanisms for the corresponding dithiocarbonates.[13]

Benzylamines are reported to strongly destabilize the intermediate,[6] $T^{\pm}$, due to their powerful nucleofugality from $T^{\pm}$, as the order of the increasing rate of expulsion shows:[6,19] pyridines < anilines < secondary alicyclic amines < quinuclidines < benzylamines. These three factors, the less polar solvent, MeCN, than water, a carbonyl rather than a thiocarbonyl compound, and benzylamines used in the present work, are all conducive to the concerted mechanism.

Note that the sign of ρ_{XZ} is invariably positive for stepwise but is negative for concerted reactions.[6] Since the aminolysis of *N*-ethyl aryl thiocarbamates involves a still stronger electron donor (PhNH < EtNH in Table 2) than in the corresponding concerted aminolysis reactions of *N*-phenyl aryl thiocarbamates, it is reasonable to expect a concerted mechanism for the present series of reactions. Further support for the concerted mechanism is provided by the negative ρ_{XZ} (−0.86) obtained,[5,6] and failure of the RSP.[6] The selectivities (the magnitudes of ρ, β, and k_H/k_D values in Tables 1 and 3) are greater for the faster reactions.This type of anti-RSP is considered another criterion for the concerted aminolysis.[6] Examination of Table 1 shows that the β_X values are 0.7−1.,3 which are rather larger than the values normally

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TABLE 4. Activation Parameters[a] for the Reactions of Z-Phenyl *N*-Ethyl Thiocarbamates with X-Benzylamines in Acetonitrile

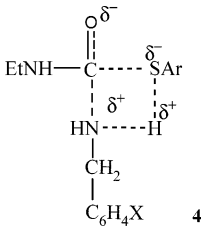
X	Z	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$-\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
p-OMe	*p*-Me	5.8	49
p-OMe	*p*-Br	5.6	47
p-Cl	*p*-Me	5.4	52
p-Cl	*p*-Br	5.8	48

[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 ±1.0 kcal mol^{-1} and ±4 eu for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively.

expected for the concerted aminolysis reactions, $\beta_X = 0.4-0.7$.[17,20] However, β_X values smaller than 0.4[21] and larger than 0.7[22] have also been obtained for the concerted aminolysis reactions. Especially in solvents less polar than water, larger β_X values (1.3−1.6) are often obtained for the concerted processes.[23] Thus, the large β_X values in the present work may be due to the less polar solvent used, MeCN. The relatively large β_X values are however consistent with the rather tight TS structure with a tighter bond formation. The β_Z values in Table 1 are within the range of values that are expected for a concerted aminolysis reaction.[20b,24]

The kinetic isotope effects, k_H/k_D, involving deuterated benzylamines[25] ($XC_6H_4CH_2ND_2$) in

Table 3 are larger than 1.0 (1.5−1.7), suggesting a proton transfer in the TS, which in turn suggests a hydrogen-bonded cyclic TS structure, **4**.



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The relatively small $\Delta H^{\ddagger}$ values with large negative $\Delta S^{\ddagger}$ values in Table 4 are consistent with this proposed TS structure. The $\Delta H^{\ddagger}$ values are small due to a larger energy gain in C−N bond formation relative to energy loss in C−S bond cleavage in the TS and the assistance in the C−S bond cleavage by the hydrogen bonding, and the $\Delta S^{\ddagger}$ values are large negative due to the strained hydrogen-bonded four-membered cyclic TS structure.

In summary, we propose a concerted mechanism with a hydrogen-bonded cyclic transition state for the aminolysis of aryl *N*-ethyl thiocarbamates with benzylamines in acetonitrile on the basis of the negative cross-interaction constant, failure of RSP, kinetic isotope effects greater than unity, and relatively low $\Delta H^{\ddagger}$ values with large negative $\Delta S^{\ddagger}$ values. The five conducive factors for the concerted aminolysis mechanism for the present reaction series are (i) a strong (strongest) push provided to expel ArS^- by the nonleaving group, EtNH, (ii) destabilization of the intermediate, $T^{\pm}$, by a powerful expulsion rate of the benzylamine from $T^{\pm}$, (iii) the greater leaving ability of ^-SAr than ^-OAr due to the greater electron acceptor ability of the σ^*_{C-S} than the σ^*_{C-O} bond orbital, (iv) the instability of the intermediate, $T^{\pm}$, in a less polar solvent, MeCN, than in water due to the ionic nature of $T^{\pm}$, and (v) the greater proclivity of the carbonyl (C=O) than the thiocarbonyl (C=S) group for the concerted mechanism due to a relatively narrow energy gap between the $\pi^*_{C=O}$ and σ^*_{C-S} orbitals, $\Delta\epsilon = \epsilon_{\pi^*} - \epsilon_{\sigma^*}$ = small.

Experimental Section

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

Substrates. Phenyl *N*-Ethyl Thiocarbamate. A solution of thiophenol (0.01 mol) in dry toluene (10 mL) was added to a solution of ethyl isocyanate (0.01 mol). A catalytic quantity (0.5 mL) of pyridine was added and the solution refluxed for 1 h. On evaporation of the solvent in vacuo, the thiocarbamate precipitated and was recrystallized from chloroform−pentane. The other substituted phenyl *N*-ethyl thiocarbamates were prepared in an analogous manner and recrystallized from chloroform−pentane. The substrates synthesized were confirmed by spectral and elemental analysis (Supporting Information).

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.[26] Pseudo-first-order rate constants, k_{obs}, were determined by the Guggenheim method[27] with a large excess of benzylamine. 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. The substrate phenyl *N*-ethyl thiocarbamate (0.01 mol) was reacted with excess *p*-chlorobenzylamine (0.1 mol) with stirring for more than 15 half-lives at 30.0 °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*-hexene). Analysis of the product gave the results shown in the Supporting Information.

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Supporting Information Available: Spectral, melting point, and elemental analysis data for substrates and product analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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