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# Aminolysis of Aryl *N*-Ethyl Thionocarbamates: Cooperative Effects of Atom Pairs O and S on the Reactivity and Mechanism

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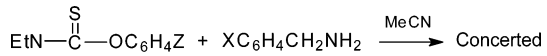
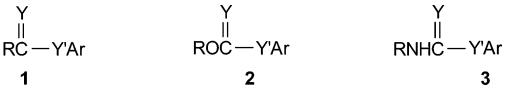



The aminolysis reactions of aryl *N*-ethyl thionocarbamates (ETNC/EtHN-C(=S)-$OC_6H_4Z$) with benzylamines ($XC_6H_4CH_2NH_2$) in acetonitrile are investigated at 30.0 °C. The rate of ETNC is slower by a factor of ca. 3 than the corresponding aminolysis of aryl *N*-ethyl thiocarbamate (AETC/EtHN-(C=O)-$SC_6H_4Z$), which has been interpreted in terms of cooperative effects of atom pairs O and S on the reactivity and mechanism. For concerted processes, these effects predict a rate sequence, −C(=S)−S− < −C(=S)−O− < −C−(=O)−S− < −C−(=O)−O−, and the present results are consistent with this order. The negative cross-interaction constant, $\rho_{XZ} = -0.87$, the magnitude of $\beta_Z$ (= 0.36−0.50) and failure of the RSP are in accord with the concerted mechanism. The normal kinetic isotope effects, $k_H/k_D = 1.52-1.78$, involving deuterated benzylamines suggest a hydrogen-bonded cyclic transition state. Other factors influencing the mechanism are also discussed.

## Introduction

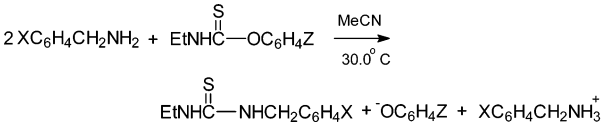
Despite the large amount of research that has been carried out, there are still many facets of the aminolysis of aryl esters,[1] carbonates,[2] carbamates,[3] and their thio analogues, **1**−**3**, that are not well understood. These include the effects of the nonleaving group R, RO, or RNH and the combined or cooperative effects of the atom pairs Y and Y′ on the aminolysis reactivity and mechanism of **1**−**3**.




R = alkyl, aryl or arylalkyl group

Y, Y' = O or S

In an attempt to clarify some of these problems, we have undertaken an examination of the effects of atom pairs Y, Y′ on the reactivity which is reflected in the mechanism. In this work, we carried out kinetic studies of the aminolysis of aryl *N*-ethyl thionocarbamates (ETNC/**3** with R = Et, Y = S, and Y′ = O) with benzylamines (BAs) in acetonitrile, eq 1. We varied




(1)

substituents in the nucleophile (X) and leaving group (Z), and the rate constants,[4] $k_2$, are subjected to a multiple regression analysis to determine the cross-interaction

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

| | Z | | | | | |
|---|---|---|---|---|---|---|
| X | *p*-Me | H | *p*-Cl | *p*-Br | $\rho_Z$ [a] | $\beta_Z$ [b] |
| | 2.63 | | | 14.3 | | |
| *p*-OMe | 2.08[c] | 4.65 | 12.6 | 11.4[c] | 1.81 ± 0.02 | −0.50 ± 0.02 |
| | 1.62[d] | | | 9.01[d] | | |
| *p*-Me | 2.06 | 3.46 | 9.26 | 10.0 | 1.71 ± 0.04 | −0.47 ± 0.01 |
| H | 1.40 | 2.32 | 5.60 | 6.09 | 1.58 ± 0.03 | −0.43 ± 0.02 |
| | 0.968 | | | 3.60 | | |
| *p*-Cl | 0.755[c] | 1.45 | 2.97 | 2.84[c] | 1.44 ± 0.03 | −0.40 ± 0.02 |
| | 0.596[d] | | | 2.22[d] | | |
| *m*-Cl | 0.701 | 1.00 | 1.95 | 2.35 | 1.30 ± 0.03 | −0.36 ± 0.02 |
| $\rho_X$ [a] | −0.88 ± 0.02 | −0.98 ± 0.02 | −1.17 ± 0.02 | −1.18 ± 0.03 | | |
| | | | | | $\rho_{XZ}$[e] = | −0.87 ± 0.18 |
| $\beta_X$ [f] | 0.88 ± 0.02 | 0.98 ± 0.02 | 1.18 ± 0.02 | 1.19 ± 0.03 | | |

[a] The $\sigma$ values were taken from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev*. **1991**, *91*, 166. Correlation coefficients were better than 0.995 in all cases. [b] The p$K_a$ values were taken from: Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants,* 3rd ed.; Chapman and Hall: London, p 145. Correlation coefficients were better than 0.999 in all cases. [c] At 20 °C. [d] At 10 °C. [e] Calculated by a multiple regression analysis using eq 2a. $r = 0.997$, $n = 20$, and $F_{calc} = 1410$ ($F_{tab} = 10.66$ at the 99.9% confidence level). [f] 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 0.997 in all cases. For X = *p*-$CH_3O$ an extrapolated value of p$K_a$ = 9.64 was used.

constant, $\rho_{XZ}$, in eq 2a,b. It has been shown that for a concerted reaction series the sign of $\rho_{XZ}$ is negative and the reactivity−selectivity principle (RSP) fails.[5]

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

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

## Results and Discussion

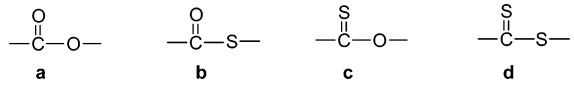
The reactions of aryl *N*-ethyl thionocarbamates (ETNC) with benzylamines (BAs) in acetonitrile follow clean, second-order kinetics given by eqs 3 and 4, where $k_{obs}$ is the pseudo-first-order rate constant and $k_2$ is the second-order rate constant for the aminolysis of the substrate. The $k_2$ values are summarized in Table 1 together with selectivity parameters $\rho_X$, $\beta_X$, $\rho_Z$, and $\beta_Z$. The $\beta_X$ ($\beta_{nuc}$) values are obtained by using the p$K_a$ ($H_2O$) values, which are considered to be reliable since the p$K_a$ values in MeCN and in $H_2O$ vary in parallel.[6] The $\beta_Z$ ($\beta_{lg}$) values are obtained by multiplying a factor of 0.62 to all the $\beta_Z$ values determined using the p$K_a$ ($H_2O$) values.[3d,7]

$$\text{rate} = k_{obs}[\text{ETNC}] \qquad (3)$$

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

The rate ($k_2 = 2.32 \times 10^{-3}$ s$^{-1}$ M$^{-1}$ for X = Z = H at 30.0 °C) is slower than that for the corresponding reaction of aryl *N*-ethyl thiocarbamate ($k_2 = 7.36 \times 10^{-3}$ s$^{-1}$ M$^{-1}$)[8] approximately by a factor of 3. This rate sequence is an indication of the concerted mechanism as corroborated below.

There are four kinds of structures (**a**−**d**) according to different combinations of atom pairs Y and Y′ (= O and S) in **1**−**3**. For a given nonleaving group (R, RO, or RNH)




and aromatic ring structure (Ar), the strength of positive charge on the functional center (carbonyl carbon), $C_\alpha$, will depend on the sum of electronegativity of O and S atom pairs. The electronegativity of O (3.41) is larger than that of S (2.58),[9] and since an electron is transferred from an ether oxygen (Y′ = O) to a carbonyl oxygen (Y = O),[10] the carbonyl oxygen is more electronegative than the ether oxygen (and similarly with Y = S and Y′ = S), and hence, the positive charge on $C_\alpha$ will increase in the order shown in eq 5

$$\mathbf{d} < \mathbf{c} < \mathbf{b} < \mathbf{a} \qquad (5)$$

Since in the concerted aminolysis (or in the stepwise reaction with rate-limiting formation of a zwitterionic tetrahedral intermediate, $T^{\pm}$) the rate is faster for the substrate with a greater electrophilic character, i.e., with a greater positive charge, of the carbonyl carbon, $C_\alpha$, the rate sequence predicted by sequence 5 is

$$\text{ETNC } (\mathbf{c}) < \text{AETC } (\mathbf{b})$$

which is indeed the sequence found experimentally. One might also argue that (i) the stability of putative tetrahedral intermediate ($T^{\pm}$) is the most stable with ETNC (**c**) but is the least stable with AETC (**b**) (vide infra) and (ii) the nucleofugality of the leaving group is greater in AETC (**b**) than that in ENTC (**c**) so that the rate of the concerted reaction with AETC should be faster than with ETNC on these accounts. However, the concerted reaction series of **2** and **3** in general follow the rate sequence 5.

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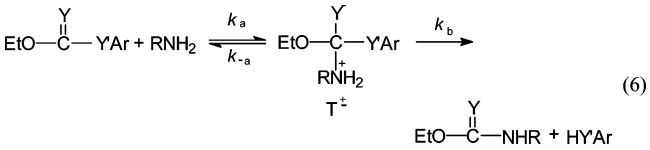
(10) (a) McKinnon, D. M.; Queen, A. *Can. J. Chem*. **1972**, *50*, 1401. (b) Ruff, F.; Csizmadia, I. G. *Organic Reactions. Equilibria, Kinetics, and Mechanism*; Elsevier: Amsterdam, 1994; p 330.

The rate order for the solvolysis (in aqueous solution)[10a] and aminolysis (in water[11] and acetonitrile[12]) of phenyl chloroformate and its thio analogues is correctly represented by the sequence 5. These compounds have the same leaving group, $Cl^-$, so that the rate order is determined solely by the combined or cooperative effects of atom pairs O and S. The mechanisms predicted for these reactions are either concerted[12] or rate-limiting formation of the intermediate.[10a,11]

Stepwise aminolysis reactions proceed through a zwitterionic tetrahedral intermediate, $T^{\pm}$, with either rate-limiting formation ($k_a$) of $T^{\pm}$ or expulsion of leaving group ($k_b$) from $T^{\pm}$, eq 6 (for *O*-ethyl series).



(6)

Application of steady-state approximation leads to eq 7

$$k_2 = k_a k_b/(k_{-a} + k_b) \tag{7}$$

For the rate-limiting expulsion of the leaving group from $T^{\pm}$, $k_{-a} \gg k_b$, and

$$k_2 = k_a k_b/(k_{-a} + k_b) \cong (k_a/k_{-a})k_b = Kk_b \tag{8}$$

For the rate-limiting formation of $T^{\pm}$, $k_b \gg k_{-a}$, and

$$k_2 \cong k_a \tag{9}$$

Thus, in the former case, eq 8, the rate depends on both the stability of $T^{\pm}$, $K$, and the expulsion rate of the leaving group from $T^{\pm}$, $k_b$.

Thus, the variation of reactivity, $\Delta k_2$, is given as eq 10.

$$\Delta k_2 = (\partial k_2/\partial \mathrm{K})\Delta \mathrm{K} + (\partial k_2/\partial k_b)\Delta k_b \tag{10}$$

However, when the rate of leaving group expulsion is enhanced ($\Delta k_b > 0$) by the nonleaving group, such as RO, the intermediate, $T^{\pm}$, will be destabilized ($\Delta K < 0$) to an approximately similar extent, $|\Delta K| \cong |\Delta k_b|$. In such cases, $\Delta k_2$ in eq 10 will depend on the ratio of the partial derivatives, which is approximately equal to $(k_b/K)$[13] (eq 11) since partial derivatives of $k_2 \cong Kk_b$ (eq 8) with respect to $K$ and $k_b$ are $k_b$ and $K$, respectively.

$$|(\partial k_2/\partial K)/(\partial k_2/\partial k_b)| \cong (k_b/K) \tag{11}$$

In the case of the enhanced expulsion rate from $T^{\pm}$ by the nonleaving group, the stability of $T^{\pm}$ decreases due to the increase in the expulsion rate, $k_b$, so that

$$(k_b/K) > 1 \tag{12}$$

which implies, according to eq 11, that the variation of $K$ (the stability of $T^{\pm}$) will set the pattern of the variation of reactivity, $\Delta k_2$.

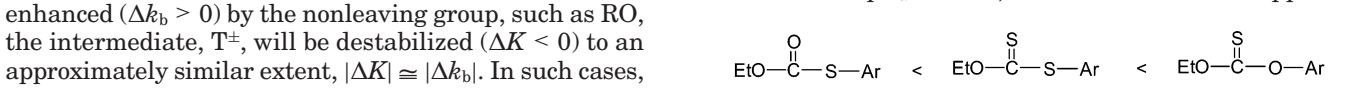
This means that the sequence of $K$ values becomes important in determining the rate ($k_2$) order. In such cases, the stability of the intermediate, $T^{\pm}$, will be important (vide infra) and the rate sequence will follow the sequence of $T^{\pm}$ stability, order 13, which is quite different from

$$\mathbf{b} < \mathbf{a} < \mathbf{d} < \mathbf{c} \tag{13}$$

order 5 for the concerted mechanism. The stability of $T^{\pm}$ is determined (i) by the acceptor ability of C=Y and (ii) by the donor ability of −Y′− in **1**−**3**. It has been shown that the acceptor ability of C=S is stronger than that of C=O[14] and the donor ability of −O− is stronger than that of −S−[15] leading to the $T^{\pm}$ stability sequence given as order 13. According to this sequence, the rate of ETNC (**c**) is predicted to be faster than that of AETC (**b**), **b** < **c**, which is the reverse of the order experimentally found so that the present reaction series is unlikely to proceed by a stepwise mechanism.

An example of such stepwise aminolysis reaction series which is consistent with rate order 13 is found in the pyridinolysis of 2,4-dinitrophenyl *O*-ethyl carbonates.[2d,i,14a] These reactions are reported to exhibit biphasic Bronsted plots. The steeper linear part ($\beta_X \geq 0.9$) for the less basic pyridines (with stronger electron acceptor or weaker donor substituents, $\delta\sigma_X > 0$) changes to the smaller Bronsted slope ($\beta_X \cong 0.2$) for the basic pyridines (with stronger electron donor, or weaker acceptor substituents, $\delta\sigma_X < 0$), which has been interpreted to indicate a change in the rate-limiting step from expulsion of the leaving group from $T^{\pm}$ ($k_b$) to formation of $T^{\pm}$ ($k_a$). However, it is now apparent that the rate-limiting step actually changes from the intermediate ($T^{\pm}$) stability ($K$), but not from $k_b$ in $Kk_b$ (in eq 8), to formation of $T^{\pm}$ ($k_a$). In accordance with this change, the rate order also changes from sequence 13 to sequence 5.

For X = H ($pK_a = 5.37$), the rate ($k_2$) order 13 applies.




For X = *p*-$NMe_2$ ($pK_a = 9.87$), the rate order 5 applies.

$$\mathbf{d}\ (k_2 = 13\ \mathrm{s^{-1}M^{-1}})^{2d} < \mathbf{c}\ (k_2 = 20\ \mathrm{s^{-1}M^{-1}})^{14a} < \mathbf{b}\ (k_2 = 31\ \mathrm{s^{-1}M^{-1}})^{2i}$$

We note that these rate orders are not influenced by the nucleofugality of the leaving group, since the rates of those (**b** and **d**) with the stronger nucleofuge, −SAr, are slower than that (**c**) of the weaker nucleofuge, −OAr, in the former rate sequence, 13.

(11) (a) Castro, E. A.; Ruiz, M. G.; Salinas, S.; Santos, J. G. *J. Org. Chem*. **1999**, *64*, 4817. (b) Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem*. **1997**, *62*, 4395. (c) Castro, E. A.; Ruiz, M. G.; Santos, J. G. *Int. J. Chem. Kinet*. **2001**, *33*, 281.

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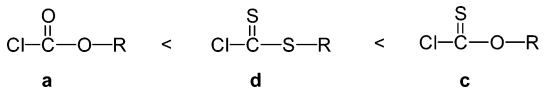
(14) (a) Castro, E. A.; Cubillos, M.; Santos, J. G.; Tellez, J. *J. Org. Chem*. **1997**, *62*, 2512. (b) Castro, E. A.; Ibanez, F.; Santos, J. G.; Ureta, C. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1919. (c) Lee, I.; Kim, C. K.; Li, H. G.; Sohn, C. K.; Kim, C.K.; Lee, H. W.; Lee, B.-S. *J. Am. Chem. Soc*. **2000**, *122*, 11162.

(15) Reference 13, p 19.

The less basic amines have a stronger leaving ability from $T^{\pm}$ ($k_{-a}$ = large)[5] but provide a weaker push to expel the leaving group from $T^{\pm}$ ($k_b$ = small) and hence $k_{-a} \gg k_b$. In contrast, basic amines are weaker nucleofuges from $T^{\pm}$ ($k_{-a}$ = small)[5] but provide a stronger push to expel the leaving group from $T^{\pm}$ ($k_b$ = large) so that $k_b \gg k_{-a}$. Thus, for the weakly basic amines $k_2 \cong Kk_b$ (eq 8), while for the basic amines $k_2 \cong k_a$ (eq 9), in agreement with the experimental observation of a change in the rate-limiting step from expulsion of the leaving group to formation of the intermediate. As one might have expected, the rate order for the amines with the p$K_a$ range between these two [e.g., for X = *p*-$NH_2$; p$K_a$ = 9.37: **d** (4.8 $s^{-1}M^{-1}$) < **b** (14 $s^{-1}M^{-1}$) < **c** (21 $s^{-1}M^{-1}$)][2d,i,14a] does not conform to any of the two rate sequences, 13 and 5.

Another example is the rates of solvolysis of alkyl (R = methyl, ethyl, isopropyl) chloroformates (except for Cl−C(=O)−SR[10a]), which is consistent with the sequence 13.




The solvolysis of these compounds is therefore considered to proceed by a stepwise mechanism through an intermediate, $T^{\pm}$, whose stability is the rate-determining factor. The solvolysis of Cl−(C=O)−SR was in fact the fastest,[10a] which can be rationalized by competitive departure of $Cl^-$ and $^-SR$ groups from $T^{\pm}$. The putative tetrahedral intermediate, $T^{\pm}$, for this compound may be so unstable (sequence 13) that the intermediate may not exist, and the reaction is most likely to proceed by a concerted mechanism. In such a case, the reaction cannot be compared with others in the series based on sequence 13.

In contrast, however, when the $k_b$ value is not enhanced or weakly enhanced by the nonleaving group as in esters, **1** (R = alkyl, aryl, or arylalkyl), the stability of the intermediate ($K$) increases to large values and ($k_b/K$) < 1. In this case, according to eq 11, the reactivity, $\Delta k_2$, will follow the pattern set by the leaving ability, $k_b$. As a result, the $k_b$ step becomes more important than the $K$ value in determining the rate sequence. For example, in the aminolysis of aryl 2-furoates (R = furyl in **1**) with benzylamines in MeCN, the rates are faster for **b**[16] than for **a**[17] (**a** < **b**) by ca. 70 times. Since both reactions


proceed by a stepwise mechanism with rate-limiting expulsion of leaving group from $T^{\pm}$, the rate order expected according to sequence 13 is **b** < **a**, which is the reverse of the experimental results. The experimental rate order (**a** < **b**) obviously reflects the importance of nucleofugality of the leaving group, $^-SAr$ being a better nucleofuge than $^-OAr$. Note that in this case the leaving ability is not enhanced by the 2-furoyl group. As a result the intermediate is rather stable and the $k_b$ term is relatively small so that the $k_b$ becomes more selective in determining the rate order and the sequence of $k_2$ is determined by that of $k_b$. Similar example is the aminolysis of **1** with R = cyclopropyl in MeCN.[18]

Thus, qualitatively when $K > k_b$ (as in the aminolysis of **1**) the rate sequence follows the order of $k_b$, but when $K < k_b$ (as in the aminolysis of **2**) the rate sequence is determined by the order of $K$ (stability of $T^{\pm}$). Thus, the strong stability of an intermediate (large $K$) results in weak selectivity. The situation is like the reactivity−selectivity principle (RSP),[4b,5,19] which asserts that the faster rate is less selective and the slower rate is more selective. However, it is hard to quantify these two cases, since the aminolysis mechanim of **1**−**3** depends also on the amine nature and solvent (vide infra).

Finally, when the enhancement of leaving ability is so strong (($k_b/K$) ≫ 1) that the intermediate can no longer exist (as in the aminolysis of **3**), the aminolysis proceeds by a concerted mechanism (or by the rate-limiting formation of $T^{\pm}$) and the rate order 5 applies. So there are three kinds of rate-limiting steps ($k_a$, $K$, or $k_b$) available, not two ($k_a$ or $k_b$) as has been believed to exist up to now, for the aminolysis of esters, carbonates, and carbamates, **1**−**3**.

These results show that the reactivity and mechanism of the aminolysis of esters, carbonates and carbamates (**1**−**3**) are strongly influenced by the cooperative effects of atom pairs O and S, and the amines as well as the nonleaving group in $T^{\pm}$ have significant effects on the expulsion rate of the leaving group from $T^{\pm}$.

In summary, in the aminolysis of esters, **1**, the stepwise mechanism with rate-limiting expulsion of leaving group is favored due to the strong stability of the intermediate, $T^{\pm}$, and the order of rate is determined by that of the nucleofugality of the leaving group. In contrast, however, in the aminolysis of carbonates, **2**, the push provided to expel the leaving group by the nonleaving group, RO, becomes relatively strong. As a result the stability of $T^{\pm}$ decreases and the order of $T^{\pm}$ stability, sequence 13, determines that of the overall rate. Last, in the aminolysis of carbamates, **3**, the intermediate, $T^{\pm}$, is so strongly destabilized that the reaction is enforced to a concerted mechanism, or to a rate-limiting formation of $T^{\pm}$, and the rate order follows sequence 5. Distinction between these two possibilities is possible by the magnitude of $\beta_X$ ($\beta_{nuc}$), (≅0.4−0.7 for the former and ≅0.1−0.3 for the latter).[11] We therefore think that the rate sequences 5 and 13 can be used as mechanistic criteria for the aminolysis reactions involving the O and S atom pairs in the substrates, **1**−**3**.

The concerted mechanism proposed for the aminolysis of ETNC in MeCN is supported by the negative cross-interaction constant,[5] $\rho_{XZ} = -0.87$, and failure of the reactivity-selectivity principle (RSP).[5] We note that the magnitude of selectivity parameters ($\rho_X$, $\beta_X$, $\rho_Z$, and $\beta_Z$) are greater for the faster rates indicating that the RSP does not hold (anti-RSP). The size of $\beta_Z$ is also in the range of values that are expected for a concerted ami-

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**TABLE 2. Secondary Kinetic Isotope Effects for the Reactions of Z-Aryl *N*-Ethyl Thionocarbamates with X-Benzylamines in Acetonitrile at 30.0 °C**

| X | Z | $k_H$ ($M^{-1}$ $s^{-1}$) | $k_D$ ($M^{-1}$ $s^{-1}$) | $k_H/k_D$ |
|---|---|---|---|---|
| *p*-OMe | *p*-Me | 2.63(±0.04) | 1.72(±0.03) | 1.52 ± 0.04[a] |
| *p*-OMe | H | 4.65(±0.06) | 2.94(±0.05) | 1.58 ± 0.03 |
| *p*-OMe | *p*-Cl | 12.6(±0.1) | 7.54(±0.07) | 1.67 ± 0.02 |
| *P*-OMe | *p*-Br | 14.3(±0.2) | 8.21(±0.08) | 1.74 ± 0.03 |
| *p*-Cl | *p*-Me | 0.968(±0.001) | 0.616(±0.006) | 1.57 ± 0.02 |
| *p*-Cl | H | 1.45(±0.02) | 0.901(±0.008) | 1.61 ± 0.03 |
| *p*-Cl | *p*-Cl | 2.97(±0.03) | 1.73(±0.02) | 1.71 ± 0.03 |
| *p*-Cl | *p*-Br | 3.60(±0.03) | 2.02(±0.04) | 1.78 ± 0.04 |

[a] Standard deviations.

nolysis process.[20] The $\beta_X$ values are 0.88−1.19 which are rather larger than values normally expected for the concerted aminolysis reactions, $\beta_X = 0.4-0.7$.[20a,21] However, $\beta_X$ values smaller than 0.4[22] and larger than 0.7[23] have also been reported for the concerted aminolysis reactions. The larger $\beta_X$ values are often obtained in solvents less polar than water[24] so that the large $\beta_X$ values in the present work may be due to the MeCN used.

Of the five factors that are known to influence the aminolysis mechanisms of **1**−**3**, three (i−iii) agree, but two (iv−v) disagree with the concerted mechanism for the present reactions: (i) The strong push provided by EtNH (in ETNC) to expel the leaving group destabilizes the putative tetrahedral intermediate, $T^{\pm}$, to such an extent that the $T^{\pm}$ cannot exist and results in a concerted process.[3d,f] (ii) The strong nucleofugality of benzylamine from $T^{\pm}$ provides additional destabilization of the putative intermediate, which is also in favor of the concerted mechanism. The nucleofugality of amines from $T^{\pm}$ is known to increase in the order pyridines < anilines < secondary alicyclic amines < quinuclidines < benzylamines.[5,25] (iii) The less polar (acetonitrile) solvent used in the present work is also more conducive to the concerted mechanism compared with water.[25] (iv) As stated above, the C=S group is a better acceptor of electrons from an ether (−Ö−) or thioether (−S̈−) atom than the C=O group and provides stronger stabilization to the ($T^{\pm}$) intermediate.[14] Therefore, thiocarbonyl (in ETNC) is less likely to lead to a concerted mechanism than the carbonyl group. (v) The leaving ability of $^-$OAr is weaker than that of $^-$SAr, which is in disfavor of a concerted mechanism.[21b]

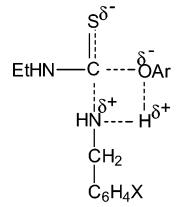
In summary, the above three factors (i−iii) together with the combined or cooperative effects of O and S atom pairs discussed above in conjunction with the rate orders 5 and 13 provide strong support for the concerted mechanism for the reactions (eq 1) studied in this work.

**TABLE 3. Activation Parameters[a] for the Reactions of Z-Aryl *N*-Ethyl Thionocarbamates 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 | 3.5 | 58 |
| *p*-OMe | *p*-Br | 3.4 | 56 |
| *p*-Cl | *p*-Me | 3.6 | 60 |
| *p*-Cl | *p*-Br | 3.6 | 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 eu for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, respectively.

The kinetic isotope effects, $k_H/k_D$, involving deuterated benzylamines[26] ($XC_6H_4CH_2ND_2$) in Table 2 are normal type, $k_H/k_D > 1.0$, indicating that a proton transfer from the benzylamine nucleophile occurs in the TS, which in turn suggests a hydrogen-bonded four-membered cyclic TS. The low $\Delta H^{\ddagger}$ with relatively large negative $\Delta S^{\ddagger}$ values in Table 3 are consistent with this proposed TS structure.




TS

The $\Delta H^{\ddagger}$ values are low due to a large energy gain in C−N bond formation relative to energy loss in C−O bond cleavage in the TS and also due to the assistance in the C−O bond cleavage by the hydrogen bonding. The $\Delta S^{\ddagger}$ values are large and negative due to the strained, cyclic, four-membered TS structure.

## Experimental Section

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

**Substrates. Phenyl *N*-Ethyl Thionocarbamate.** A solution of phenol (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 2 h. On evaporation of the solvent in vacuo, the phenyl *N*-ethyl carbamate precipitated and was recrystallized from chloroform−pentane. The phenyl *N*-ethyl carbamate was dissolved in dry toluene and refluxed with Lawesson's reagent, which is used to convert carbonyl to thiocarbonyl for 24 h. After extraction of reaction mixture with methylene chloride, the phenyl *N*-ethyl thionocarbamate precipitated and was recrystallized from petroleum ether. The other substituted phenyl *N*-ethyl thionocarbamates were prepared in an analogous manner and recrystallized from petroleum ether. The substrates synthesized were confirmed by spectral and elemental analysis as follows.

**$C_2H_5NHC(=S)OC_6H_4$-*p*-$CH_3$:** mp 116−118 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18 (3H, t, $CH_3$), 2.32 (3H, s, $CH_3$), 3.28 (2H, m, $CH_2$), 6.40 (1H, s, NH), 6.98−7.15 (4H, m, $C_6H_4$); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 154.6, 148.7, 134.6, 129.6, 121.3, 36.2, 20.1, 15.2; $\nu_{max}$ (KBr) 3350 (NH), 3072 (CH, aliphatic), 2970 (CH, aromatic), 1300 (C−O), 1264 (C=S); MS *m*/*z* 195 ($M^+$). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.5; H, 6.71. Found: C, 61.7; H, 6.69

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**$C_2H_5NHC(=S)OC_6H_5$:** mp 69−70 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.17 (3H, t, $CH_3$), 3.26 (2H, m, $CH_2$), 6.42 (1H, s, NH), 7.11−7.36 (5H, m, $C_6H_5$); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 154.4, 150.9, 129.1, 125.1, 121.5, 36.1, 15.1; $\nu_{max}$ (KBr) 3340 (NH), 3069 (CH, aliphatic), 2975 (CH, aromatic), 1262 (C−O), 1223 (C=S); MS *m/z* 181 ($M^+$). Anal. Calcd for $C_9H_{11}NOS$: C, 59.6; H, 6.11. Found: C, 59.5; H, 6.13.

**$C_2H_5NHC(=S)OC_6H_4$-*p*-Cl:** mp 108−110 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18 (3H, t, $CH_3$), 3.28 (2H, m, $CH_2$), 6.21 (1H, s, NH), 7.05−7.31 (4H, m, $C_6H_4$); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 153.9, 149.4, 130.4, 129.2, 122.8, 36.2, 15.1; $\nu_{max}$ (KBr) 3337 (NH), 3074 (CH, aliphatic), 2978 (CH, aromatic), 1299 (C−O), 1264 (C=S); MS *m/z* 215 ($M^+$). Anal. Calcd for $C_9H_{10}ClNOS$: C, 50.1; H, 4.71. Found: C, 50.3; H, 4.73.

**$C_2H_5NHC(=S)OC_6H_4$-*p*-Br:** mp 122−124 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18 (3H, t, $CH_3$), 3.26 (2H, m, $CH_2$), 6.34 (1H, s, NH), 7.01−7.46 (4H, m, $C_6H_4$); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 153.8, 149.9, 132.1, 123.3, 118.1, 36.2, 15.1; $\nu_{max}$ (KBr), 3337 (NH), 3071 (CH, aliphatic), 2982 (CH, aromatic), 1262 (C−O), 1219 (C=S); MS *m/z* 260 ($M^+$). Anal. Calcd for $C_9H_{10}BrNOS$: C, 41.6; H, 3.90. Found: C,41.4; H, 3.92.

**Kinetic Measurements.** Rates were measured conductometrically in acetonitrile. The conductivity bridge used in this work was a homemade computer-automatic A/D converter conductivity bridge.[27] Pseudo-first-order rate constants, $k_{obs}$, were determined by the Guggenheim method[28] 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 *p*-chlorophenyl *N*-ethyl thionocabamate (0.01 mole) was reacted with excess benzylamine (0.1 mole) 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*-hexane). Analysis of the product gave the following results.

**$C_2H_5NHC(=S)NHCH_2C_6H_5$:** mp 115−117 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.19 (3H, t, $CH_3$), 2.94 (2H, s, $-NHCH_2$), 3.34 (2H, q, $CH_2$), 6.32 (1H, s, NH), 7.08−7.31 (5H, m, $C_6H_5$); $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ 153.9, 149.5, 130.4, 129.2, 122.8, 50.5, 36.2, 15.2; $\nu_{max}$ (KBr) 3314 (NH), 3012 (CH, aliphatic), 2929 (CH, aromatic), 1669 (C=S); MS *m/z* 194 ($M^+$). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 61.8; H, 7.30. Found: C, 61.6; H, 7.32.

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