

# Structure–reactivity correlations in the aminolysis of aryl dithiomethyl- and dithiophenylacetates with anilines in acetonitrile

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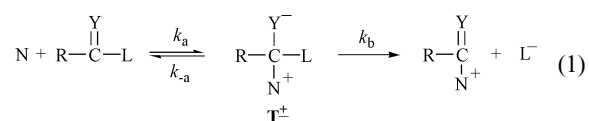
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The kinetics and mechanism of the aminolysis ( $\text{XC}_6\text{H}_4\text{NH}_2$ ) of dithio esters,  $\text{RC}(=\text{S})\text{SC}_6\text{H}_4\text{Z}$  with  $\text{R} = \text{C}_2\text{H}_5$  and  $\text{C}_6\text{H}_5\text{CH}_2$  are investigated in acetonitrile at 45.0 °C. By application of various structure–reactivity correlations, selectivity parameters  $\rho_{\text{X}}$ ,  $\beta_{\text{X}}$ ,  $\rho_{\text{Z}}$ ,  $\beta_{\text{Z}}$  and  $\rho_{\text{XZ}}$  are determined. The reactions are predicted to proceed stepwise with rate-limiting expulsion of the  $\text{ArS}^-$  group. The dithio ester with  $\text{R} = \text{C}_2\text{H}_5$  exhibits the fastest rate and the largest positive  $\rho_{\text{XZ}}$  value; this is interpreted to result from the strongest electron donating ability of the ethyl group in the intermediate and a crowded tetrahedral intermediate and transition state in which the nucleophile (X) and leaving group (Z) are in close proximity due to the bulky  $\text{C}_2\text{H}_5$  group. Much faster rates are observed for the thiocarbonyl ( $\text{C}=\text{S}$ ) rather than carbonyl ( $\text{C}=\text{O}$ ) esters in the stepwise nucleophilic substitution reactions, which may be ascribed to the lower  $\pi^*_{\text{C}=\text{S}}$  and  $\sigma^*_{\text{C}-\text{LG}}$  levels than those of the corresponding antibonding levels in the carbonyl esters. The normal kinetic isotope effects,  $k_{\text{H}}/k_{\text{D}} > 1.0$ , involving deuterated anilines suggest concurrent proton transfer with the expulsion of the  $\text{ArS}^-$  leaving group in a four-center hydrogen bonded transition state.

## Introduction

The two common mechanisms for the aminolysis of carbonyl, **I**, and thiocarbonyl, **II**, esters and carbonates are (i) concerted through a tetrahedral transition state (TS) and (ii) stepwise through a tetrahedral intermediate.<sup>1</sup> The latter reaction pathway can be described by eqn. (1), where R and L are non-



leaving and leaving groups, N represents an amine and Y is either O (**I**) or S (**II**). A nonlinear Brønsted plot results from a change in the rate-determining step, from that of  $k_b$  at low amine basicity (with  $\beta_{\text{nuc}} \geq 0.8$ ) to that of  $k_a$  at high amine basicity (with  $\beta_{\text{nuc}} \leq 0.3$ ). Applying the steady-state condition to  $\text{T}^\ddagger$  in eqn. (1), the equation  $k_{\text{N}} = k_a k_b / (k_{-a} + k_b) \cong (k_a / k_{-a}) \times k_b = K k_b$  is obtained when the second step is rate-limiting, and this accounts for the change in the rate-determining step at  $\text{p}K_{\text{a}}^\circ$  where  $k_{-a} = k_b$  applies. The aminolysis mechanisms naturally depend on Y, R, L, N in eqn. (1) and solvent. Fixing L (=  $\text{SC}_6\text{H}_4\text{Z}$ ) and solvent (acetonitrile), we recently found an interesting mechanistic changeover due to changes in Y (O or S),<sup>2</sup> N (benzylamines or anilines)<sup>2,3</sup> and R ( $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $\text{C}_6\text{H}_5\text{CH}_2$ ,  $\text{C}_6\text{H}_5$  or  $\text{C}_2\text{H}_5\text{O}$ ).<sup>2-5</sup> For example, change of Y from O to S resulted in lowering of  $\text{p}K_{\text{a}}^\circ$  for  $\text{R} = \text{CH}_3$  and  $\text{C}_6\text{H}_5$  so that the rate-limiting step of the aminolysis for carbonyl esters, **I**, with benzylamines<sup>2a,b</sup> changed from expulsion of thiolate anion,  $\text{ArS}^-$ , from  $\text{T}^\ddagger$  (with  $\beta_{\text{nuc}} = \beta_{\text{X}} = 1.36$  and 1.86, and  $\rho_{\text{XZ}} > 0$ ) to formation of  $\text{T}^\ddagger$  (with  $\beta_{\text{X}} = 0.55$  and 0.63 and  $\rho_{\text{XZ}} > 0$ ) for thiocarbonyl esters,<sup>2c,d</sup> **II**,

Table 1. The aminolysis of all the carbonyl (**I**) series, except for  $\text{R} = \text{C}_2\text{H}_5\text{O}$  (concerted, with  $\rho_{\text{XZ}} < 0$ ), in Table 1 proceeds through the stepwise path with rate-limiting expulsion of the leaving group (with  $\beta_{\text{X}} = 1.36$ –2.11 and  $\rho_{\text{XZ}} > 0$ ).

Another important aspect of the change of R is that the cross-interaction constants,  $\rho_{\text{XZ}}$  in eqns. (2)<sup>6</sup> where X and Z are

$$\log(k_{\text{XZ}}/k_{\text{HH}}) = \rho_{\text{X}}\sigma_{\text{X}} + \rho_{\text{Z}}\sigma_{\text{Z}} + \rho_{\text{XZ}}\sigma_{\text{X}}\sigma_{\text{Z}} \quad (2a)$$

$$\rho_{\text{XZ}} = \partial\rho_{\text{X}}/\partial\sigma_{\text{Z}} = \partial\rho_{\text{Z}}/\partial\sigma_{\text{X}} \quad (2b)$$

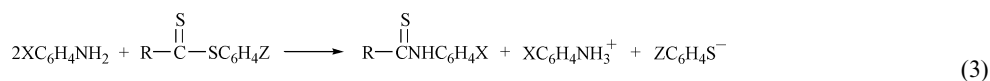
substituents in the nucleophile and leaving group, are exceptionally large with  $\text{R} = \text{C}_2\text{H}_5$  for the carbonyl<sup>5a</sup> as well as the thiocarbonyl<sup>5c</sup> series, which suggests that the interaction between nucleophile (X) and leaving group (Z) is very strong in a very tight TS structure<sup>6</sup> for both carbonyl and thiocarbonyl thio esters with  $\text{R} = \text{C}_2\text{H}_5$  only.

This surprising result prompts us to test whether the similar large  $\rho_{\text{XZ}}$  value persists with weakly basic amines (anilines) or not, and to explore the possible cause for this large  $\rho_{\text{XZ}}$  value.

In this work, we performed kinetic studies on the aminolysis of the two dithio esters with  $\text{R} = \text{C}_2\text{H}_5$  and  $\text{C}_6\text{H}_5\text{CH}_2$ , in acetonitrile at 45.0 °C, eqn. (3), and examined the aminolysis mechanism applying various structure–reactivity correlations.

## Results and discussion

The reactions studied in this work followed the rate law described by eqns. (4) and (5), where S and N represent the substrate and nucleophile, aniline, and  $k_{\text{N}}$  is the rate constant for aminolysis of the substrate. The reactions were run under pseudo-first-order conditions with a large excess of aniline



with  $\text{R} = \text{C}_2\text{H}_5$  or  $\text{C}_6\text{H}_5\text{CH}_2$ ,  $\text{X} = p\text{-OMe}$ ,  $p\text{-Me}$ ,  $\text{H}$ ,  $p\text{-Cl}$  or  $p\text{-Br}$   
and  $\text{Z} = p\text{-Me}$ ,  $\text{H}$ ,  $p\text{-Cl}$  or  $p\text{-Br}$

**Table 1** Rates ( $k_N/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ) and selectivity parameters ( $\rho_X, \beta_X, \rho_Z, \beta_Z$  and  $\rho_{XZ}$ ) for the aminolysis of thiol esters, **I** [ $\text{RC}(=\text{O})\text{SC}_6\text{H}_4\text{Z}$ ], and dithio esters, **II** [ $\text{RC}(=\text{S})\text{SC}_6\text{H}_4\text{Z}$ ], with benzylamines ( $\text{XC}_6\text{H}_4\text{CH}_2\text{NH}_2$ ) in acetonitrile

Entry	R	$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{SC}_6\text{H}_4\text{Z}$						$\text{R}-\overset{\text{S}}{\parallel}{\text{C}}-\text{SC}_6\text{H}_4\text{Z}$							
		$k_N^a$	$\rho_X^b$	$\beta_X^b$	$\rho_Z^c$	$\beta_Z^c$	$\rho_{XZ}^d$	Ref.	$k_N^a$	$\rho_X^b$	$\beta_X^b$	$\rho_Z^c$	$\beta_Z^c$	$\rho_{XZ}^d$	Ref.
1	CH <sub>3</sub>	$3.93 \times 10^{-3}$ (45.0 °C)	-1.40	1.36	5.32	-2.21	0.90	2b	0.699 (20.0 °C)	-0.56	0.55	1.19	-0.50	0.40	2d
2	C <sub>2</sub> H <sub>5</sub>	$7.32 \times 10^{-3}$ (45.0 °C)	-2.09	2.11	2.74	-1.18	2.36	5a	9.84 (35.0 °C)	-2.24	2.19	2.77	-1.15	3.51	5c
3	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	$4.94 \times 10^{-3}$ (55.0 °C)	-1.50	1.55	1.61	-1.66	0.92	5b	11.6 (25.0 °C)	-2.21	2.03	3.51	-1.38	2.05	5d
4	C <sub>6</sub> H <sub>5</sub>	$2.51 \times 10^{-3}$ (55.0 °C)	-1.88	1.86	3.84	-1.63	0.27	2a	$3.82 \times 10^{-1}$ (30.0 °C)	-0.65	0.24	0.56	-0.24	0.50	2c
5	C <sub>2</sub> H <sub>5</sub> O	$2.18 \times 10^{-2}$ (45.0 °C)	-0.63	0.63	1.51	-0.63	-0.47	4a							

<sup>a</sup> For X = Y = Z = H. <sup>b</sup> For Z = H. <sup>c</sup> For X = H. <sup>d</sup> For Y = H when Y is varied.

**Table 2** The second order rate constants,  $k_N \times 10^4/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ , for the reactions of Z-aryl dithiophenylacetates with X-anilines in acetonitrile at 45.0 °C

X	Z				$\rho_Z^a$	$\beta_Z^b$
	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br		
<i>p</i> -OMe	6.92 5.34 <sup>c</sup> 4.07 <sup>d</sup>	16.4	56.9	71.0 54.6 <sup>c</sup> 41.2 <sup>d</sup>	$2.43 \pm 0.14$	$-0.98 \pm 0.07$
<i>p</i> -Me	3.16	7.80	28.7	36.1	$2.55 \pm 0.14$	$-1.03 \pm 0.07$
H	1.06	2.76	11.2	14.1	$2.72 \pm 0.15$	$-1.10 \pm 0.07$
<i>p</i> -Cl	0.251	0.781	3.67	5.05	$3.11 \pm 0.19$	$-1.25 \pm 0.12$
<i>m</i> -Cl	0.0810 0.0610 <sup>c</sup> 0.0459 <sup>d</sup>	0.271	1.43	2.00 1.68 <sup>c</sup> 1.28 <sup>d</sup>	$3.31 \pm 0.20$	$-1.33 \pm 0.11$
$\rho_X^e$	$-2.95 \pm 0.06$	$-2.64 \pm 0.07$	$-2.42 \pm 0.07$	$-2.34 \pm 0.08$	$\rho_{XZ}^f = 1.41 \pm 0.31$	
$\beta_X^g$	$1.04 \pm 0.02$	$0.93 \pm 0.03$	$0.85 \pm 0.03$	$0.82 \pm 0.03$		

<sup>a</sup> The  $\sigma$  values were taken from ref. 17. Correlation coefficients were better than 0.996 in all cases. <sup>b</sup> The  $\text{p}K_a$  values were taken from ref. 18. Z = *p*-Br was excluded from the Brønsted plot for  $\beta_Z$  due to an unreliable  $\text{p}K_a$  value. Correlation coefficients were better than 0.996 in all cases. <sup>c</sup> At 35.0 °C. <sup>d</sup> At 25.0 °C. <sup>e</sup> The source of  $\sigma$  is the same as for footnote a. Correlation coefficients were better than 0.998 in all cases. <sup>f</sup> Correlation coefficient was 0.998. <sup>g</sup> The  $\text{p}K_a$  values were taken from ref. 19. Correlation coefficients were better than 0.998 in all cases.

**Table 3** The second order rate constants,  $k_N \times 10^3/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ , for the reactions of Z-aryl dithiomethylacetates with X-anilines in acetonitrile at 45.0 °C

X	Z				$\rho_Z^a$	$\beta_Z^b$
	<i>p</i> -Me	H	<i>p</i> -Cl	<i>p</i> -Br		
<i>p</i> -OMe	9.72 19.1 <sup>c</sup> 5.05 <sup>d</sup>	19.8	81.2	89.5 175 <sup>c</sup> 46.5 <sup>d</sup>	$2.42 \pm 0.17$	$-1.00 \pm 0.01$
<i>p</i> -Me	4.05	8.50	38.3	39.8	$2.53 \pm 0.17$	$-1.06 \pm 0.02$
H	1.25	3.19	13.2	14.6	$2.64 \pm 0.08$	$-1.10 \pm 0.06$
<i>p</i> -Cl	0.223	0.669	3.50	3.89	$3.08 \pm 0.08$	$-1.29 \pm 0.07$
<i>m</i> -Cl	0.0551 0.128 <sup>c</sup> 0.0242 <sup>d</sup>	0.180	1.38	1.83 3.97 <sup>c</sup> 0.842 <sup>d</sup>	$3.73 \pm 0.24$	$-1.51 \pm 0.03$
$\rho_X^e$	$-3.42 \pm 0.10$	$-3.08 \pm 0.12$	$-2.72 \pm 0.06$	$-2.60 \pm 0.09$	$\rho_{XZ}^f = 1.90 \pm 0.26$	
$\beta_X^g$	$1.20 \pm 0.03$	$1.09 \pm 0.04$	$0.96 \pm 0.03$	$0.91 \pm 0.04$		

<sup>a</sup> The source of  $\sigma$  is the same as that for a, Table 2. Correlation coefficients were better than 0.995 in all cases. <sup>b</sup> The source of  $\text{p}K_a$  is the same as that for footnote b, Table 2. Correlation coefficients were better than 0.998 in all cases. <sup>c</sup> At 55.0 °C. <sup>d</sup> At 35.0 °C. <sup>e</sup> The source of  $\sigma$  is the same as for footnote a. Correlation coefficients were better than 0.998 in all cases. <sup>f</sup> Correlation coefficient was 0.998. <sup>g</sup> The source of  $\text{p}K_a$  is the same as that for footnote g, Table 2.

$$\text{Rate} = k_{\text{obs}}[\text{S}] \quad (4)$$

$$k_{\text{obs}} = k_N[\text{N}] \quad (5)$$

nucleophiles. The values of  $k_N$  were obtained as the slopes of plots of  $k_{\text{obs}}$  against  $[\text{N}]$ , and are summarized in Tables 2 and 3 for aryl dithiophenyl- (R = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>) and dithiomethylacetates (R = C<sub>2</sub>H<sub>5</sub>), respectively. In these Tables, the selectivity parameters obtained as  $\sigma$  and  $\text{p}K_a$  dependence of the composite rate constant  $k_N = Kk_b, \rho_X, \beta_X, \rho_Z, \beta_Z$  and  $\rho_{XZ}$ , are also shown.

In the determination of Brønsted coefficients,  $\beta_X$  and  $\beta_Z$ , the  $\text{p}K_a$  values in water are used; the  $\text{p}K_a$  (CH<sub>3</sub>CN) values for structurally similar amines are known to change in parallel with the  $\text{p}K_a$  (H<sub>2</sub>O) values.<sup>5a,7</sup> Although the absolute  $\beta_Z$  values may not be reliable, the comparison of  $\beta_Z$  values for different series of substrates is justified since we have determined the  $\beta_Z$  values in the same reaction medium, acetonitrile. In order to facilitate comparisons of rates and selectivity parameters between different substrates, (for different R groups), we have summarized them in Table 4. First of all, the anilinolysis of *O*-ethyl *S*-aryl

**Table 4** Rates ( $k_N/\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ) and selectivity parameters ( $\rho_X$ ,  $\beta_X$ ,  $\rho_Z$ ,  $\beta_Z$ , and  $\rho_{XZ}$ ) for the aminolysis of dithioesters, **II** [ $\text{RC}(=\text{S})\text{SC}_6\text{H}_4\text{Z}$ ], with anilines ( $\text{XC}_6\text{H}_4\text{NH}_2$ ) in acetonitrile

Entry	R	$k_N^a$	$\rho_X^b$	$\beta_X^b$	$\rho_Z^c$	$\beta_Z^c$	$\rho_{XZ}^d$	Ref.
1	CH <sub>3</sub>	$9.46 \times 10^{-4}$ (50.0 °C)	-3.05	0.84	1.90	-0.81	0.58	2d
2	C <sub>2</sub> H <sub>5</sub>	$3.19 \times 10^{-3}$ (45.0 °C)	-3.08	1.09	2.64	-1.10	1.90	This work
3	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	$2.76 \times 10^{-4}$ (45.0 °C)	-2.64	0.93	2.72	-1.10	1.41	This work
4	C <sub>6</sub> H <sub>5</sub>	$2.85 \times 10^{-3}$ (55.0 °C)	-2.86	1.03	2.26	-0.76	0.60	3
5	C <sub>2</sub> H <sub>5</sub> O	$1.71 \times 10^{-2}$ (30.0 °C)	-1.46	0.54	0.45	-0.19	-0.56	4b

<sup>a</sup> For X = Y = Z = H. <sup>b</sup> For Z = H. <sup>c</sup> For X = H. <sup>d</sup> For Y = H when Y is varied.

dithiocarbonates<sup>4b</sup> (R = C<sub>2</sub>H<sub>5</sub>O) has been reported to proceed concertedly based on (i) the small magnitude of  $\beta_X$  (= 0.54) and  $\beta_Z$  (= -0.19) values relative to those reacting stepwise with large  $\beta_X$  ( $\geq 0.8$ ) and  $-\beta_Z$  ( $\leq -0.8$ )<sup>1,8</sup> and (ii) negative  $\rho_{XZ}$  (< 0).<sup>6c</sup> For the remaining Rs (entries 1–4), the same mechanism applies with positive  $\rho_{XZ}$ , large magnitude of  $\beta_X$  and  $\beta_Z$ , and adherence to the reactivity–selectivity principle (RSP),<sup>6,9</sup> *i.e.*, rate-limiting expulsion of thiolate anion (ArS<sup>-</sup>) leaving group from the tetrahedral intermediate, T<sup>‡</sup>. Reference to Table 1 reveals that the rate is the fastest ( $k_N$  is the greatest) with R = C<sub>2</sub>H<sub>5</sub> among the four stepwise reaction series (entries 1–4). This is also true for the aminolysis rates of carbonyl, **I**, and thiocarbonyl, **II**, series with benzylamines shown in Table 1. Albeit exact comparison is difficult due to the  $k_N$  values determined at different temperatures, the approximate rate order is R = C<sub>2</sub>H<sub>5</sub> ( $\sigma^* = -0.10$ ) > CH<sub>3</sub> (0.0) > C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub> (+0.22) > C<sub>6</sub>H<sub>5</sub> (+0.60), which is the order of decreasing electron donating ability of the R group represented by the Taft  $\sigma^*$  scale<sup>10</sup> as shown in parentheses. This is quite reasonable in view of the rate-limiting expulsion of the ArS<sup>-</sup> group from T<sup>‡</sup>, since in the tetrahedral structure only the inductive effect is expected to apply and the greater the electron donation by R, the greater will be the leaving ability of the ArS<sup>-</sup> group ( $k_b$ ). If the electronic effect of R were predominant in the bond formation step ( $k_a$ ), then the rate sequence should have been in the reverse order since a stronger electron acceptor R will lead to a stronger positive charge on the carbonyl carbon in the substrate.

Thus, the fastest rates for aminolyses of carbonyl as well as thiocarbonyl esters with R = C<sub>2</sub>H<sub>5</sub> are in line with the stepwise mechanism with rate-limiting expulsion of ArS<sup>-</sup>. The concerted reaction pathway predicted for R = C<sub>2</sub>H<sub>5</sub>O ( $\sigma^* = -0.18$ ) both with anilines<sup>4b</sup> (Table 4) and benzylamines<sup>4a</sup> (Table 1, entry 5) can also be explained in a similar vein: substitution of ethoxy group destabilizes the tetrahedral intermediate so much as to prevent the existence of the putative intermediate, and therefore, the mechanism changes from stepwise to enforced concerted. This destabilization is mainly due to a strong electron donating effect of the ethoxy group in the TS leading to a greater nucleofugality and faster leaving from the tetrahedral intermediate of the ArS<sup>-</sup> group.

For R = CH<sub>3</sub> and C<sub>6</sub>H<sub>5</sub> (entries 1 and 4) groups, a biphasic rate dependence on the amine basicity is observed; the aminolysis proceeds stepwise with rate-limiting expulsion of ArS<sup>-</sup> with weakly basic anilines<sup>2d,3</sup> (entries 1 and 4 in Table 4) but with rate-limiting formation of T<sup>‡</sup> with strongly basic benzylamines<sup>2c,d</sup> (entries 1 and 4 for the dithio series in Table 1). The change of the rate-determining step is apparent from (i) the change in  $\beta_X$  (and  $\beta_Z$ ) from large to smaller magnitude and (ii) positive  $\rho_{XZ}$  throughout.<sup>6c</sup> Although  $\beta_X \approx 0.6$  (entries 1 and 4 in Table 1) may be considered rather high for the rate-limiting formation of T<sup>‡</sup>, for which  $\beta_X$  values of less than 0.3 ( $\beta_X \geq 0.3$ )<sup>8</sup> are common and a concerted pathway may seem more appropriate, we nevertheless found that  $\beta_X$  values come out rather high in general for the aminolysis with benzylamines as the comparison of  $\beta_X$  values in Table 1 with those in Table 4 shows. This prediction of rate-limiting formation is also based on the positive  $\rho_{XZ}$  value,<sup>6c</sup> since in the concerted nucleophilic substitution reactions a negative  $\rho_{XZ}$

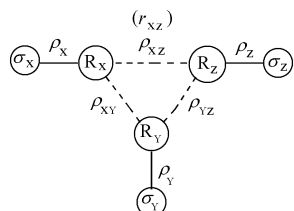
is expected as we found for R = C<sub>2</sub>H<sub>5</sub>O in Tables 1 and 4 (entry 5).

We find a mechanistic difference between the carbonyl (**I**) (Table 1) and thiocarbonyl (**II**) series (Tables 1 and 4): for the former series (**I**) the rate-limiting expulsion ( $k_b$ ) applies even up to relatively strong basic amines (benzylamines),<sup>2a,b</sup> whereas for the latter dithio series, (**II**), the rate-limiting step changes from rate-limiting expulsion of ArS<sup>-</sup> from T<sup>‡</sup> with weakly basic amines, anilines<sup>2d,3</sup> (Table 4), to rate-limiting formation with strongly basic amines, benzylamines<sup>2c,d</sup> (Table 1). This means that the center of the Brønsted curvature for the thiocarbonyl series, **II**, shifted to a lower  $\text{p}K_a$  value, *i.e.*, from  $\text{p}K_a^\circ \geq \text{p}K_a = 9.51$  (for *p*-MeO-benzylamine in H<sub>2</sub>O) for the carbonyl to  $\text{p}K_a^\circ \leq \text{p}K_a = 9.14$  (for *p*-Cl-benzylamine in H<sub>2</sub>O) for the thiocarbonyl series. The smaller  $\text{p}K_a^\circ$  value results from a smaller  $k_{-a}/k_b$  ratio (for a given amine and leaving group)<sup>11</sup> for the thiocarbonyl compared to the carbonyl compound. It has been shown that the change of carbonyl to thiocarbonyl decreases both  $k_{-a}$  and  $k_b$  but the decrease in  $k_{-a}$  is greater.<sup>11</sup> A similar effect has been found in the aminolysis of *p*-nitrophenyl benzoate and thionobenzoate in aqueous solution. The  $\text{p}K_a^\circ$  value of greater than 11 was obtained for the former reactions, whereas  $\text{p}K_a^\circ = 9.2$  was found with the latter reactions.<sup>12</sup> Again  $\text{p}K_a^\circ = 7.8$  for the pyridinolysis of methyl 2,4-dinitrophenyl carbonate shifted to  $\text{p}K_a^\circ = 6.8$  for the same reactions with ethyl 2,4-dinitrophenyl thionocarbonate in aqueous solution.<sup>11</sup>

It has been shown by MO calculation that the possibility of an acyl transfer reaction through a tetrahedral intermediate is the greater, the lower the  $\pi^*_{\text{C=O}}$  (or  $\pi^*_{\text{C=S}}$ ) level and the higher the  $\sigma^*_{\text{C-LG}}$  level, *i.e.*, the greater the level gap,  $\Delta\varepsilon = \varepsilon(\sigma^*) - \varepsilon(\pi^*)$ .<sup>13</sup> For CH<sub>3</sub>C(=O)Cl and CH<sub>3</sub>C(=S)Cl at the RHF/6-31+G\*\*//B3LYP/6-31+G\* level,<sup>14</sup> the  $\pi^*_{\text{C=S}}$  level is much lower (by *ca.* 1.9 eV) but the  $\sigma^*_{\text{C-Cl}}$  level is slightly lower (by *ca.* 0.3 eV) than the corresponding levels of the carbonyl compound so that the level gap,  $\Delta\varepsilon$ , is much greater for the thiocarbonyl transfers. This means that the thiocarbonyl transfer is more prone to proceed through a tetrahedral intermediate than the carbonyl transfers. Since both the  $\pi^*_{\text{C=S}}$  and  $\sigma^*_{\text{C-LG}}$  levels of thiocarbonyl compounds are lower than the corresponding levels of carbonyl compounds, both the initial attack on the thiocarbonyl  $\pi$  bond, C=S, by a nucleophile, *e.g.*, amines, (*i.e.*,  $k_a$  is greater) and the leaving group expulsion due to electron flow into the  $\sigma^*_{\text{C-LG}}$  orbital in a stepwise mechanism are more facile (*i.e.*,  $k_b$  is greater) for the thiocarbonyl than the carbonyl derivatives. However, since the  $\pi^*-\sigma^*$  level gap is much narrower for the carbonyl compound, the concerted carbonyl transfer will be more facile for the carbonyl than the thiocarbonyl due to greater  $\pi^*-\sigma^*$  mixing. Theoretically, the carbonyl transfer through a tetrahedral TS is found to have a lower energy barrier.<sup>14</sup>

Although predictions from MO theory are applicable strictly in the gas phase, our experimental results in acetonitrile shown in Table 1 are in excellent agreement. Indeed, the rates for the thiocarbonyl series are seen to be much faster than those for the corresponding carbonyl series (comparisons are valid only for entries 2 and 3 which have a common mechanism of the rate-limiting breakdown of T<sup>‡</sup>; for entries 1 and 4, the thiocarbonyl and carbonyl compounds have different reaction mechanisms).

An important aspect we note in Tables 1 and 4 is that the magnitude of  $\rho_{XZ}$  is unusually large for  $R = C_2H_5$  (entry 2 in both Tables). The size of  $\rho_{XZ}$  is considered to represent the intensity of interaction in the TS<sup>6</sup> between the two substituents in the nucleophile (X) and leaving group (Z), and hence the larger the  $\rho_{XZ}$ , the stronger is the interaction, *i.e.*, the closer are the two fragments, the nucleophile and leaving group, in the TS. In order to see whether this interpretation is correct or not and whether the size of  $\rho_{XZ}$  is indeed inversely related to the distance ( $r_{XZ}$  in Scheme 1) between the two, we attempted to optimize



Scheme 1

the MO theoretical structures of the intermediate, T<sup>‡</sup>, and the substrate. This was a rather difficult endeavour since the systems are so large that *ab initio* calculations, even at a relatively low level, require extremely long computational times and hence are very expensive. The intermediate structure at the RHF/6-31G\* level revealed that the amine, aniline, and the leaving group, thiolate anion, are located nearer due to the bulky ethyl group in T<sup>‡</sup>, especially when the ethyl group rotates freely around the C–C bond, so that the TS structure corresponding to the  $k_b$  step should also be crowded and the closer distance between the two fragments, nucleophile (X) and leaving group (Z), can be explained. For other R groups, *e.g.*, with  $R = CH_3$  or  $C_6H_5CH_2$ , the structures of the intermediates are less crowded, and hence the distance,  $r_{XZ}$ , is greater than that for  $R = C_2H_5$ .

The kinetic isotope effects,  $k_H/k_D$ , involving deuterated amine nucleophiles ( $XC_6H_4ND_2$ ) have been determined<sup>6b</sup> in acetonitrile as shown in Table 5. The  $k_H/k_D$  values are significantly

**Table 5** Kinetic isotope effects for the reactions of dithioesters, II [RC(=S)SC<sub>6</sub>H<sub>4</sub>Z] with deuterated X-anilines in acetonitrile at 45.0 °C

X	Z	R = C <sub>2</sub> H <sub>5</sub> $k_H/k_D$	R = C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> $k_H/k_D$
<i>p</i> -OMe	<i>p</i> -Me	1.64 ± 0.02 <sup>a</sup>	1.53 ± 0.02 <sup>a</sup>
<i>p</i> -OMe	H	1.47 ± 0.02	1.39 ± 0.02
<i>p</i> -OMe	<i>p</i> -Cl	1.30 ± 0.03	1.32 ± 0.03
<i>p</i> -OMe	<i>p</i> -Br	1.13 ± 0.03	1.19 ± 0.03
<i>p</i> -Cl	<i>p</i> -Me	1.24 ± 0.02	1.74 ± 0.02
<i>p</i> -Cl	H	1.13 ± 0.02	1.66 ± 0.03
<i>p</i> -Cl	<i>p</i> -Cl	1.08 ± 0.03	1.51 ± 0.02
<i>p</i> -Cl	<i>p</i> -Br	1.04 ± 0.02	1.42 ± 0.02

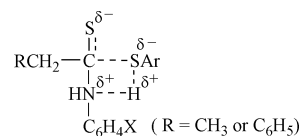
<sup>a</sup> Standard deviations.

**Table 6** Activation parameters<sup>a</sup> for the reactions of dithioesters, II [RC(=S)SC<sub>6</sub>H<sub>4</sub>Z], with X-anilines in acetonitrile

R	X	Z	$\Delta H^\ddagger/\text{kcal mol}^{-1}$	$-\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$
C <sub>2</sub> H <sub>5</sub>	<i>p</i> -OMe	<i>p</i> -Me	12.7	28
	<i>p</i> -OMe	<i>p</i> -Br	12.7	24
	<i>m</i> -Cl	<i>p</i> -Me	16.0	28
	<i>m</i> -Cl	<i>p</i> -Br	14.9	24
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	<i>p</i> -OMe	<i>p</i> -Me	4.4	59
	<i>p</i> -OMe	<i>p</i> -Br	4.5	54
	<i>m</i> -Cl	<i>p</i> -Me	4.7	67
	<i>m</i> -Cl	<i>p</i> -Br	4.0	64

<sup>a</sup> Calculated by the Eyring equation. The maximum errors calculated (by the method in ref. 20) are ±0.6 kcal mol<sup>-1</sup> and ±2 e.u. for  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ , respectively.

greater than unity, *i.e.*, primary kinetic isotope effects are operative and the amine proton shift in the TS is implicated.<sup>6b</sup> This means that deprotonation of the amine hydrogen takes place concurrently with the expulsion ( $k_b$ ) of the leaving group, ArS<sup>-</sup>. In this proposed TS structure (Scheme 2), the leaving



Scheme 2

group departure is facilitated by a partial protonation of ArS<sup>-</sup> and therefore the activation energy required for the C–S bond scission and reformation of the C=S bond may be partially lowered. Even though the proton is transferred to thiolate anion partially in the TS, the aniline, which is in large excess, will become protonated eventually and the reaction proceeds as represented by eqn. (3). The proposed TS structure (Scheme 2) should lead to relatively low activation enthalpies ( $\Delta H^\ddagger$ ) and large negative activation entropies ( $\Delta S^\ddagger$ ), as we have found for all the reactions listed in Tables 1 and 4 (except for entry 5,  $R = C_2H_5O$ ). The activation parameters determined in the present work by the Eyring equation<sup>15</sup> are shown in Table 6. We note that the  $\Delta H^\ddagger$  values for the reactions of dithio compounds with  $R = C_2H_5$  are somewhat higher than the other corresponding values. In addition the  $k_H/k_D$  values for this series tend to be somewhat smaller than the other corresponding values. This could be related to the relatively tight TS in which the nucleophile (X) and the thiophenolate leaving group (Z) are in rather close proximity, as the large magnitude of  $\rho_{XZ}$  suggested, so that the protonation (on deprotonation) has progressed very little and hydrogen bonding assistance for bond cleavage is low.

The magnitudes of the selectivity parameters in Tables 2 and 3 decrease as the rates become faster so that the reactivity–selectivity principle (RSP) holds.<sup>9</sup> This adherence to the RSP is considered another necessary condition for a stepwise acyl transfer reaction with rate-limiting breakdown of the tetrahedral intermediate.<sup>6a-c</sup>

## Conclusions

We conclude that: (i) the stepwise aminolysis reaction of carbonyl or thiocarbonyl esters or carbonates exhibits a positive  $\rho_{XZ}$ , irrespective of whether the rate-determining step is formation or breakdown of the tetrahedral intermediate, T<sup>‡</sup>. (ii) The concerted aminolysis mechanism, on the other hand, is characterized by a negative  $\rho_{XZ}$ . (iii) The stepwise mechanism is more likely to be obtained, the lower the  $\pi^*_{C=O}$  or  $\pi^*_{C=S}$  level and the higher the  $\sigma^*_{C-LG}$  level, *i.e.*, the wider the level gap  $\Delta\varepsilon = \varepsilon(\sigma^*) - \varepsilon(\pi^*)$ . (iv) Since both the  $\pi^*$  and  $\sigma^*$  levels of the thiocarbonyl (C=S) compound are lower than the corresponding levels of the carbonyl (C=O) compound, the reactivity of

the stepwise reaction is faster for the thiocarbonyl than for the carbonyl esters. (v) The reactivity order for the stepwise aminolysis follows roughly the order of the electron donating ability of the R group as represented by the Taft  $\sigma^*$  scale with the fastest rate for R = C<sub>2</sub>H<sub>5</sub>. (vi) The largest  $\rho_{XZ}$  value of R = C<sub>2</sub>H<sub>5</sub> for the stepwise aminolysis among four R groups (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> and C<sub>6</sub>H<sub>5</sub>) appears to result from the close proximity of nucleophile (X) and leaving group (Z) in the TS due to the steric crowding of the bulky C<sub>2</sub>H<sub>5</sub> group in the tetrahedral intermediate T<sup>±</sup>.

## Experimental

### Materials

Merck GR acetonitrile was used after three distillations. The Aldrich anilines were used without further purification.

### Substrates

Preparations and analytical data are reported elsewhere.<sup>5c,d</sup>

### Kinetic measurements

Rates were measured conductometrically in acetonitrile. Since the anilines were in large excess, [S]  $\approx 10^{-3}$  M and [N] = 0.02–0.45 M in eqns. (4) and (5), the proton transfer can be considered to occur to aniline, instead of thiolate anion, and the conductivity of the medium increases with the progress of the reaction as expressed by eqn. (3). The conductivity bridge used in this work was a laboratory-made computer-automatic A/D converter conductivity bridge. Pseudo-first-order rate constants,  $k_{\text{obs}}$ , were determined by the Guggenheim method.<sup>16</sup> More than 4 concentrations of aniline were used in the determination of  $k_N$  [eqn. (5)] and the  $k_N$  values reported are averages of at least two determinations with reproducibility of  $\pm 3\%$ .

### Product analysis

Substrate, phenyl dithiophenylacetate (0.05 mol) (and phenyl dithiomethylacetate (0.05 mol)), was reacted with excess aniline (0.5 mol) with stirring for more than 15 half-lives at 45.0 °C in acetonitrile, and the products were isolated by evaporating the solvent under reduced pressure. The product mixture was treated with column chromatography (silica gel, 20% ethyl acetate–*n*-hexane). Analysis of the products gave the following results. IR absorptions are given in cm<sup>-1</sup> and NMR shifts in ppm.

**C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>C(=S)NHC<sub>6</sub>H<sub>5</sub>.** Liquid, IR (KBr) 1606 (N–H), 1512 (C–C, aromatic), 1492 (C=C, aromatic), 1461 (C–H, CH<sub>2</sub>), 1209 (C=S), 705 (C–H, aromatic); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.14 (1H, s, NH), 4.14 (2H, s, CH<sub>2</sub>), 7.36–7.51 (10H, m, aromatic ring); <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>)  $\delta$  214.2 (C=S), 134.6, 132.7, 131.4, 129.0, 127.4, 126.5, 124.3, 122.7, 58.1.

**CH<sub>3</sub>CH<sub>2</sub>C(=S)NHC<sub>6</sub>H<sub>5</sub>.** Liquid, IR (KBr) 2989 (C–H, CH<sub>2</sub>), 2938 (C–H, CH<sub>3</sub>), 1607 (N–H), 1504 (C–C, aromatic), 1463 (C=C, aromatic), 1279 (C=S), 701 (C–H, aromatic); <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$  2.42 (3H, s, CH<sub>3</sub>), 3.12 (1H, s, NH), 3.17 (2H, q, CH<sub>2</sub>), 7.51–7.68 (4H, m, aromatic ring); <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>)  $\delta$  224.4 (C=S), 134.6, 133.1, 131.8, 130.2, 58.0, 44.6.

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