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Kinetics and Mechanism of the Pyridinolysis of *S*-4-Nitrophenyl 4-Substituted Thiobenzoates in Aqueous Ethanol

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The pyridinolysis of *S*-4-nitrophenyl 4-X-substituted thiobenzoates (X = H, Cl, and NO_2; **1**, **2**, and **3**, respectively) is studied kinetically in 44 wt % ethanol−water, at 25.0 °C and an ionic strength of 0.2 M (KCl). The reactions are measured spectrophotometrically (420−425 nm) by following the appearance of 4-nitrobenzenethiolate anion. Pseudo-first-order rate coefficients (k_{obsd}) are obtained throughout, under excess of amine over the substrate. Plots of k_{obsd} vs [free amine] at constant pH are linear with the slope (k_N) independent of pH. The Brønsted-type plot (log k_N vs pK_a of the conjugate acids of the pyridines) for the reactions of thiolbenzoate **1** is curved with a slope at high pK_a, $\beta_1 = 0.20$, and slope at low pK_a, $\beta_2 = 0.94$. The pK_a value for the center of the Brønsted curvature is p$K_a^0 = 9.7$. The pyridinolysis of thiolbenzoates **2** and **3** show linear Brønsted-type plots of slopes 0.94 and 1.0, respectively. These results and other evidence indicate that these reactions occur with the formation of a zwitterionic tetrahedral intermediate ($T^{\pm}$). For the pyridinolysis of thiolbenzoate **1**, breakdown of $T^{\pm}$ to products (k_2 step) is rate-limiting for weakly basic pyridines and $T^{\pm}$ formation (k_1 step) is rate-determining for very basic pyridines. The k_2 step is rate-limiting for the reactions of thiolbenzoates **2** and **3**. The smallest pK_a^0 value for the reaction of **1** is due to the weakest electron withdrawal of H (relative to Cl and NO_2) in the acyl group, which results in the smallest k_{-1}/k_2 ratio. The pK_a^0 values for the title reactions are smaller than those for the reactions of secondary alicyclic amines with thiolbenzoates **1**−**3**. This is attributed to a lower leaving ability from the $T^{\pm}$ of pyridines than isobasic alicyclic amines. The lower pK_a^0 value found for the pyridinolysis of 2,4-dinitrophenyl benzoate (p$K_a^0 = 9.5$), compared with that for the pyridinolysis of **1**, is explained by the greater nucleofugality from $T^{\pm}$ of 2,4-dinitrophenoxide than 4-nitrobenzenethiolate, which renders the k_{-1}/k_2 ratio smaller for the reactions of the benzoate relative to thiolbenzoate **1**. The title reactions are also compared with the aminolysis of similar thiolbenzoates in other solvents to assess the solvent effect.

Introduction

We have been interested lately in the mechanisms of the aminolysis of *S*-aryl thiobenzoates (aryl thiolbenzoates). To our knowledge, there have been only a few reports in the literature on the mechanisms of these reactions.[1−3] There are contrasting results concerning some of these reports. The reactions of aryl thiolbenzoates with substituted anilines in methanol were claimed to be concerted, namely, a single-step mechanism, without the formation of a zwitterionic tetrahedral intermediate.[2a] On the other hand, the benzylaminolysis[2b] and pyridinolysis[2c] of the same thiolbenzoates in acetonitrile were found to be stepwise, through the formation and breakdown of the zwitterionic intermediate.

We have recently found that the reactions of secondary alicyclic amines with *S*-4-nitrophenyl 4-X-substituted thiobenzoates (**1**, **2**, and **3**) in aqueous ethanol proceed by stepwise mechanisms.[3] This was concluded on the basis of the curved Brønsted-type plots obtained for the two former aminolyses and the linear plot found for the latter reactions.[3] For the aminolysis of thiolbenzoates **1** and **2** the Brønsted slopes at low pK_a are $\beta_2 = 0.86$ and 0.84, respectively, whereas those at high pK_a are $\beta_1 = 0.27$ and 0.10, respectively.[3] These results were interpreted as a change in the rate-determining step, from a zwitterionic tetrahedral intermediate ($T^{\pm}$) breakdown to $T^{\pm}$ formation, as the secondary amine basicity increases.[3] The Brønsted slope value of 0.81 exhibited by the reactions of thiolbenzoate **3** is consistent with rate-limiting breakdown to products of the intermediate $T^{\pm}$.[3]

The reactions of 2,4-dinitrophenyl 4-X-substituted benzoates (X = Cl, CN, NO_2) with a series of pyridines in aqueous ethanol show linear Brønsted plots of slopes 0.94, 0.96, and 0.90, respectively, in agreement with stepwise mechanisms where the breakdown of the intermediate $T^{\pm}$ to products is the rate-determining step.[4a−c] For the pyridinolysis of 2,4-dinitrophenyl benzoate (X = H) a curved Brønsted plot was found, with slopes β_2 0.9

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(1) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505.

(2) (a) Lee, I.; Shim, C. S.; Lee, H. W. *J. Chem. Res., Synop.* **1992**, 90. (b) Lee, I.; Koh, H. J. *New J. Chem.* **1996**, *20*, 131. (c) Koh, H. J.; Han, K. L.; Lee, I. *J. Org. Chem.* **1999**, *64*, 4783.

(3) Castro, E. A.; Bessolo, J.; Aguayo, R.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 8157.

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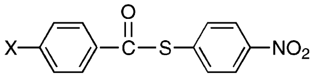
and β_1 0.4 at low and high pK_a, respectively, consistent with a stepwise process and a change in the rate-limiting step.[4d]

With the aim to analyze the discrepancies concerning some of the reactions above and to clarify the mechanisms of the aminolysis of aryl thiolbenzoates, in the present work we study kinetically the pyridinolysis of thiolbenzoates **1**−**3** in aqueous ethanol. By a comparison between these reactions the effect of the nonleaving group of the substrate on the kinetics and mechanism can be analyzed. Comparison of the reactions of the present work with those of secondary alicyclic amines with the same thiolbenzoates in the same solvent[3] will allow evaluation of the effect of the amine nature. By comparing the present reactions with the aminolysis of thiolbenzoates in other solvents[2] and the pyridinolysis of 2,4-dinitrophenyl benzoates in aqueous ethanol,[4] the influence of the solvent and the leaving group, respectively, can be assessed.



1 (X = H)
2 (X = Cl)
3 (X = NO_2)

Experimental Section

Materials. The series of pyridines were purified either by distillation or recrystallization.[4d,5] Thiolbenzoates **1**−**3** were synthesized as described.[6] Their melting points were in accordance with literature values,[7] and their ^1H and ^{13}C NMR spectra and elemental analyses agreed with their structures.

Kinetic Measurements. The reactions were studied spectrophotometrically at 420−425 nm by means of a diode array instrument. At these wavelengths an increase of absorbance was observed due to the appearance of 4-nitrobenzenethiolate anion. The experimental conditions of the reactions were 44 wt % ethanol−water solutions, at 25.0 ± 0.1 °C, and an ionic strength of 0.2 M (maintained with KCl). Two or three pH values were employed for the reactions of each pyridine. For the reactions of the substrates with the three more basic pyridines, the pH was kept constant by the amine and its conjugate acid, whereas for the reactions with the other pyridines, phosphate was used as an external buffer. At least a 10-fold excess of total amine over the substrate was employed. The initial substrate concentration was (2−5) × 10^{-5} M in all runs.

Pseudo-first-order rate coefficients (k_{obsd}) were found in all cases. For the reactions of the three thiolbenzoates with the three more basic pyridines and that of thiolbenzoates **2** and **3** with 4-amino-3-bromopyridine, the values of k_{obsd} were obtained by means of the kinetic software of the spectrophotometer, after ca. 3 half-lives. After these reaction times a slow decrease of absorbance at 420−425 nm was observed, due to the formation of bis(4-nitrophenyl) disulfide (see below). For the reactions of the three thiolbenzoates with the three less basic pyridines and that of thiolbenzoate **1** with 4-amino-3-bromopyridine, the values of k_{obsd} were determined by the initial rate method.[8]

TABLE 1. Experimental Conditions and k_{obsd} Values for the Pyridinolysis of *S*-4-Nitrophenyl Thiobenzoate (1)[a]

pyridine substituent	pH	F_N[b]	$10^2[N]_{tot}$ (M)[c]	10^3k_{obsd} (s^{-1})	no. of runs
3,4-diamino	9.15	0.333	0.23−2.09	2.5−18.7	9
	9.45	0.500	0.23−2.33	2.7−26.9	9
	9.75	0.667	0.23−2.33	4.0−37.0	9
4-dimethylamino	8.84	0.333	0.207−2.07	1.45−11.2	8
	9.14	0.500	0.207−1.86	2.38−18.6	8
	9.44	0.667	0.207−1.66	2.71−22.0	8
4-amino	8.68	0.333	0.70−2.09	1.42−5.41	7
	8.98	0.500	1.16−2.33	3.43−8.62	6
	9.28	0.667	0.23−2.09	1.66−11.9	7
4-amino-3-bromo	7.55[d]	0.817	0.49−2.23	0.075−0.368	7
	7.85[d]	0.899	0.35−1.73	0.085−0.390	8
3,4-dimethyl	7.55[d]	0.987	1.98−19.8	0.037−0.203	10
	7.85[d]	0.993	1.98−19.8	0.038−0.220	10
4-methyl	7.55[d]	0.994	1.98−19.8	0.020−0.112	9
	7.85[d]	0.997	1.98−19.8	0.029−0.122	9
3-methyl	7.55[d]	0.998	3.96−19.8	0.0147−0.0556	7
	7.85[d]	0.999	3.96−19.8	0.0163−0.0551	5

[a] In 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Fraction of free amine. [c] Concentration of total amine (free amine plus its conjugate acid). [d] Under the presence of phosphate buffer 0.01 M.

TABLE 2. Experimental Conditions and k_{obsd} Values for the Pyridinolysis of *S*-4-Nitrophenyl 4-Chlorothiobenzoate (2)[a]

pyridine substituent	pH	F_N[b]	$10^2[N]_{tot}$ (M)[c]	10^3k_{obsd} (s^{-1})	no. of runs
3,4-diamino	9.15	0.333	0.099−0.99	2.94−18.9	10
	9.45	0.500	0.099−0.99	4.19−26.7	10
	9.75	0.667	0.099−0.99	6.92−38.0	10
4-dimethylamino	8.84	0.333	0.099−0.99	1.04−7.90	8
	9.14	0.500	0.099−0.99	1.77−11.8	9
4-amino	8.98	0.500	0.099−0.99	1.11−7.70	10
	9.28	0.667	0.099−0.99	1.23−11.4	10
4-amino-3-bromo	7.55[d]	0.817	0.248−2.48	0.167−0.618	7
	7.85[d]	0.899	0.173−1.73	0.289−0.678	9
3,4-dimethyl	7.25[d]	0.974	2.97−14.9	0.0455−0.181	8
	7.55[d]	0.987	1.49−14.9	0.0284−0.186	10
	7.85[d]	0.993	2.97−14.9	0.0520−0.169	7
4-methyl	7.25[d]	0.988	5.94−26.7	0.0575−0.196	8
	7.55[d]	0.994	8.91−29.7	0.0785−0.230	7
	7.85[d]	0.997	2.97−29.7	0.0311−0.198	7
3-methyl	7.25[d]	0.995	2.97−29.7	0.0150−0.0975	9
	7.55[d]	0.998	4.95−49.5	0.0262−0.150	9
	7.85[d]	0.999	4.95−49.5	0.0053−0.151	10

[a] In 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Fraction of free amine. [c] Concentration of total amine (free amine plus its conjugate acid). [d] Under the presence of phosphate buffer 0.01 M.

The experimental conditions of the reactions and the k_{obsd} values are shown in Tables S1−S3 in Supporting Information and in Tables1−3.

Determination of pK_a Values. The pK_a values of 3,4-diamino and 4-amino-3-bromo pyridines were determined by a potentiometric method, in 44 wt % ethanol−water, at 25.0 ± 0.1 °C, and an ionic strength of 0.2 M (maintained with KCl). The values obtained are 9.45 ± 0.09 and 6.90 ± 0.08, respectively.

Product Studies. One of the products of the pyridinolysis of the thiolbenzoates is 4-nitrobenzenethiolate anion. The other final product is the corresponding benzoate anion. These anions and not their conjugate acids were identified as

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(4) (a) Castro, E. A.; Valdivia, J. L. *J. Org. Chem.* **1986**, *51*, 1668. (b) Castro, E. A.; Becerra, M. C. *Bol. Soc. Chil. Quim.* **1988**, *33*, 67. (c) Castro, E. A.; Steinfort, G. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 453. (d) Castro, E. A.; Santander, C. L. *J. Org. Chem.* **1985**, *50*, 3595.

(5) Bond, P. M.; Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Perkin Trans. 2* **1976**, 68.

(6) Bunton, C. A.; Foroudian, H. J.; Kumar, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 33.

(7) Cilento, G. *J. Am. Chem. Soc.* **1953**, *75*, 3748. Kanaoka, Y.; Tanizawa, K.; Sato, E.; Yonemitsu, O.; Ban, Y. *Chem. Pharm. Bull.* **1967**, *15*, 593.

(8) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018. Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 6362.

TABLE 3. Experimental Conditions and k_{obsd} Values for the Pyridinolysis of *S*-4-Nitrophenyl 4-Nitrothiobenzoate (3)[a]

pyridine substituent	pH	F_N[b]	$10^2[N]_{tot}$ (M)[c]	10^3k_{obsd} (s^{-1})	no. of runs
3,4-diamino	9.15	0.333	0.099−0.99	8.8−92.3	10
	9.45	0.500	0.099−0.99	20.5−136	9
	9.75	0.667	0.099−0.89	19.9−176	9
4-dimethylamino	9.14	0.500	0.099−0.99	13.3−80.6	10
	9.44	0.667	0.099−0.99	10.6−90.0	10
4-amino	8.98	0.500	0.099−0.99	4.20−54.2	10
	9.28	0.667	0.099−0.99	15.5−75.3	10
4-amino-3-bromo	7.55[d]	0.817	0.25−2.23	0.51−1.61	8
	7.85[d]	0.899	0.17−1.73	0.42−1.33	10
3,4-dimethyl	7.25[d]	0.974	0.99−9.90	0.058−0.47	8
	7.55[d]	0.987	0.99−9.90	0.126−0.537	9
	7.85[d]	0.993	0.99−9.90	0.077−0.485	8
4-methyl	7.25[d]	0.988	0.99−9.90	0.043−0.242	6
	7.55[d]	0.994	0.99−9.90	0.035−0.252	8
	7.85[d]	0.997	0.99−9.90	0.048−0.260	9
3-methyl	7.25[d]	0.995	0.99−9.90	0.0174−0.0902	8
	7.55[d]	0.998	0.99−8.91	0.0295−0.0975	8
	7.85[d]	0.999	0.99−9.90	0.0427−0.115	7

[a] In 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Fraction of free amine. [c] Concentration of total amine (free amine plus its conjugate acid). [d] Under the presence of phosphate buffer 0.01 M.

products since the experimental pH values were larger than those of the pK_a of 4-nitrobenzenethiol and the corresponding benzoic acid, respectively. The identification was realized by comparison of the UV−vis spectra after completion of the reactions (before oxidation of 4-nitrobenzenethiolate took place, see below) with those of an equimolar mixture of authentic samples of 4-nitrobenzenethiolate and the corresponding benzoate anion, under the same reaction conditions.

An intermediate in the reactions under scrutiny presumably is the amidic cation, 1-(4-X-benzoyl)-substituted pyridinium, as judged by a small increase and later decrease of absorbance at 300−302 nm, observed in the reactions of the three more basic pyridines. For the reactions of the other pyridines, a good isosbestic point at ca. 300 nm was noted, indicating that in these cases the amidic cation is highly unstable toward hydrolysis. This is reasonable since the less basic pyridines are better leaving groups in the hydrolysis reactions. Even the amidium cations derived from very basic pyridines are rapidly hydrolyzed. 1-Benzoyl-4-(dimethylamino)pyridinium could not be detected in the reaction of this pyridine with 4-nitrophenyl benzoate in water.[9] Nevertheless, the acetylpyridinium derivatives are more stable toward hydrolysis, as indicated by the fact that 1-acetyl-4-(dimethylamino)pyridinium has been observed spectrophotometrically in the reaction of this pyridine with acetic anhydride and 2,4-dinitrophenyl thiolacetate in aqueous solution.[10] On the other hand, these types of cations are stable in nonaqueous solvents, since 1-(4-nitrobenzoyl)-pyridinium was isolated in the pyridinolysis of *S*-4-bromophenyl 4-nitrotiobenzoate in acetonitrile.[2c]

For the title reactions a slow decrease of absorbance at 420 nm was observed after a long reaction time. This can be attributed to oxidation of 4-nitrobenzenethiolate anion to form bis(4-nitrophenyl) disulfide. The identification of this product was carried out by comparison of the UV−vis spectra of some of the reactions at very long reaction times with an authentic sample of bis(4-nitrophenyl) disulfide under the same experimental conditions. To avoid the interference of this oxidation reaction with the kinetic measurements for the formation of 4-nitrobenzenethiolate, two different methods (for fast and slow reactions) were employed to obtain the values of k_{obsd}, as described above. Oxidation of benzenethiolate and 4-nitrobenzenethiolate anions has been previously observed.[11]

Results and Discussion

The rate law found for all of the reactions subjected to this work is given by eqs 1 and 2, where NPS^-, S, and N represent 4-nitrobenzenethiolate anion, the thiolbenzoate ,and the free pyridine, respectively. The rate constants k_0 and k_N are those for solvolysis and pyridinolysis of the substrates, respectively.

$$\frac{d[NPS^-]}{dt} = k_{obsd}[S] \qquad (1)$$

$$k_{obsd} = k_0 + k_N[N] \qquad (2)$$

The value of k_0 was much lower than that of $k_N[N]$ in eq 2, except for the slow reactions of the three less basic pyridines, where the pyridinolysis term in eq 2 was also small. The values of k_0 varied with pH only for the reactions carried out under the presence of external (phosphate) buffer. The values of k_N for all reactions were obtained as the slopes of linear plots of k_{obsd} against [N]. The k_N values were found to be pH-independent; these are shown in Table 4, together with the pK_a values of the conjugate acids of the pyridines.

As expected, the values of k_N in Table 4 increase as the pyridine basicity increases. As found for the reactions of the same thiolbenzoates with secondary alicyclic amines, the k_N values also increase as the electron-attracting effect of the 4-substituent on the acyl group of the substrate increases.[3]

With the values of pK_a for the pyridinium ions and those of k_N for the reactions subjected to the present work, the Brønsted-type plots were obtained. These are shown in Figure 1 for the pyridinolysis of substrates **1** and **3**. Figure 2 exhibits the Brønsted-type plot for the reactions of thiolbenzoate **2**.

The curved line shown in the Brønsted-type plot for the reactions of thiolbenzoate **1** in Figure 1 was calculated by a semiempirical equation (eq 3) based on the hypothesis of a zwitterionic tetrahedral intermediate on the reaction pathway.[5,12,13] Curved Brønsted plots have been attributed to a change in the rate-limiting step, from decomposition of the intermediate to its formation as the pK_a of the conjugate acid of the amine increases.[5,12,13] The curved Brønsted line for the pyridinolysis of thiolbenzoate **1** was calculated by nonlinear least-squares fitting, yielding the following parameters: $\log k_N^0 = 0.54 \pm 0.05$, $pK_a^0 = 9.7 \pm 0.1$, $\beta_1 = 0.20 \pm 0.1$, and $\beta_2 = 0.94 \pm 0.05$. The parameters k_N^0 and pK_a^0 are those corresponding to the center of the Brønsted curvature and β_1 and β_2 are the slopes at high and low pK_a values, respectively.[5,12]

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[9] Um, I.-H.; Baek, M.-H.; Han, H.-J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1245.

[10] (a) Castro, C.; Castro, E. A. *J. Org. Chem.* **1981**, *46*, 2939. (b) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 63.

[11] (a) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. (b) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153. (c) Antonello, S.; Daasbjerg, K.; Jensen, H.; Taddei, F.; Maran, F. *J. Am. Chem. Soc.* **2003**, *125*, 14905. (d) Shah, S. T. A.; Khan, K. M.; Fecker, M.; Voelter, W. *Tetrahedron Lett.* **2003**, *44*, 6789.

[12] Castro, E. A.; Moodie, R. B. *J. Chem. Soc., Chem. Commun.* **1973**, 828.

[13] (a) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. (b) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.

TABLE 4. Values of pK_a for Conjugate Acids of Pyridines and k_N for the Pyridinolysis of *S*-4-Nitrophenyl Thiobenzoate (1), *S*-4-Nitrophenyl 4-Chlorothiobenzoate (2), and *S*-4-Nitrophenyl 4-Nitrothiobenzoate (3)[a]

pyridine substituent	pK_a	k_N (s^{-1} M^{-1})		
		1	**2**	**3**
3,4-diamino	9.45	2.3 ± 0.1	5.0 ± 0.2	26 ± 2
4-dimethylamino	9.14	1.8 ± 0.1	2.4 ± 0.1	14 ± 1
4-amino	8.98	0.86 ± 0.07	1.7 ± 0.1	10 ± 1
4-amino-3-bromo	6.90	$(2.3 \pm 0.1) \times 10^{-2}$	$(2.6 \pm 0.1) \times 10^{-2}$	$(7.2 \pm 0.5) \times 10^{-2}$
3,4-dimethyl	5.68	$(9.4 \pm 0.5) \times 10^{-4}$	$(1.1 \pm 0.1) \times 10^{-3}$	$(4.7 \pm 0.3) \times 10^{-3}$
4-methyl	5.35	$(5.4 \pm 0.2) \times 10^{-4}$	$(6.6 \pm 0.3) \times 10^{-4}$	$(2.3 \pm 0.1) \times 10^{-3}$
3-methyl	4.92	$2.4 \pm 0.1) \times 10^{-4}$	$(3.0 \pm 0.2) \times 10^{-4}$	$(8.4 \pm 0.8) \times 10^{-4}$

[a] Both the pK_a and k_N values were determined in 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl).

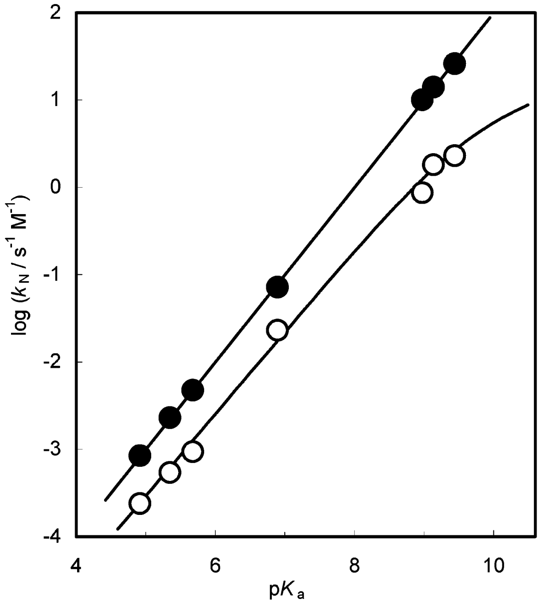

FIGURE 1. Brønsted-type plots obtained in the pyridinolysis of **1** (○) and **3** (●) in 44 wt % ethanol−water, at 25.0 °C, and an ionic strength of 0.2 M (KCl).

$$\log\left(\frac{k_N}{k_N^0}\right) = \beta_2(\mathrm{p}K_a - \mathrm{p}K_a^0) - \log\left[\frac{1+a}{2}\right]$$

$$\log a = (\beta_2 - \beta_1)(\mathrm{p}K_a - \mathrm{p}K_a^0) \tag{3}$$

According to the value of the slopes of the linear Brønsted-type plots for the pyridinolysis of thiolbenzoates **2** and **3** ($\beta = 0.94 \pm 0.05$ and 1.0 ± 0.1, respectively), the most likely mechanism for these reaction is that described in Scheme 1, where breakdown of the tetrahedral intermediate ($T^{\pm}$) to products (k_2 step) is the rate-determining step.[1,3–5,10,12,13] In these cases, the first step is at equilibrium.

Scheme 1 can also describe the mechanism of the pyridinolysis of thiolbenzoate **1**. In this case the k_2 step is rate-determining for all of the pyridines (pK_a < 9.7). For (hypothetical) pyridines of pK_a values similar to those of pK_a^0 (pK_a ca. 9.7), k_{-1} is similar to k_2 and there is no clear rate-determining step.[1,5,13]

The experimental points of log k_N vs pK_a for the pyridinolysis of thiolbenzoate **2** can also be accommodated by the semiempirical equation based on the hypothesis of the tetrahedral intermediate. In this case, the best fitting parameters are $\log k_N^0 = 0.94 \pm 0.07$, $\mathrm{p}K_a^0 = 9.9 \pm 0.1$, $\beta_1 = 0.20 \pm 0.1$, and $\beta_2 = 0.97 \pm 0.07$.

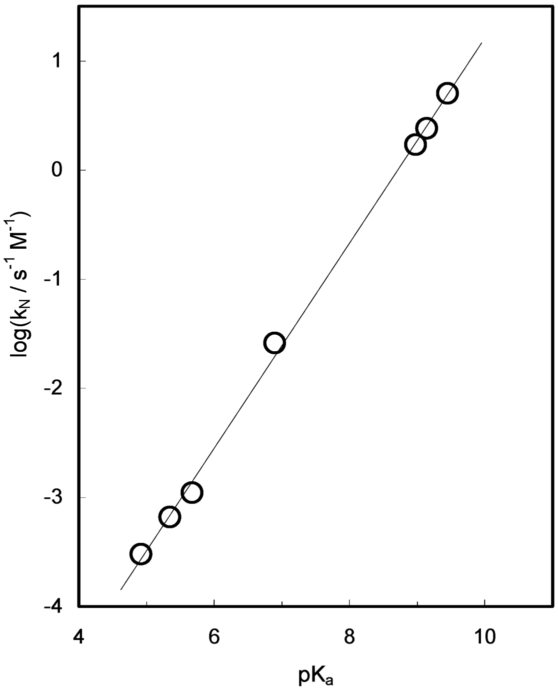

FIGURE 2. Brønsted-type plot obtained in the pyridinolysis of **2** in 44 wt % ethanol−water, at 25.0 °C, and an ionic strength of 0.2 M (KCl).

The amidium cation **4** in Scheme 1 undergoes hydrolysis to yield the substituted benzoate anion and the corresponding pyridine, according to the analysis of products. On the other hand, 4-nitrobenzenethiolate (**5**) is very slowly oxidized under the reaction conditions to yield the corresponding disulfide (see Experimental Section).

Table 5 shows the values of pK_a for the center of the Brønsted curvature (pK_a^0) for the reactions of secondary alicyclic (SA) amines[3] and pyridines (this work) with thiolbenzoates **1**−**3**.

As seen in Table 5, the increase of the pK_a^0 value with increasing electron withdrawal of the substituent on the acyl group of the thiolbenzoate, shown by the SA aminolysis, is also present in the pyridinolysis. This trend is also in agreement with that found by Gresser and Jencks in the reactions of quinuclidines with diaryl carbonates.[13b] This effect can be explained by the following way: as the substituent in the nonleaving group becomes more electron-withdrawing the central carbon of the zwitterionic tetrahedral intermediate ($T^{\pm}$) becomes more positive and favors the push provided by the sulfur

SCHEME 1

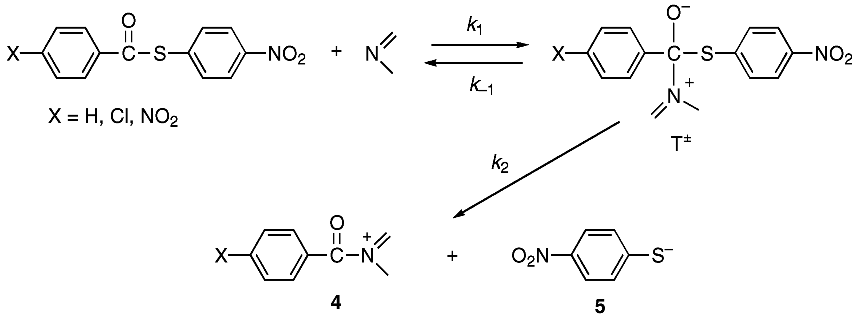

TABLE 5. Values of pK_a for the Center of the Brønsted Curvature (pK_a^0) for the Reactions of Secondary Alicyclic (SA) Amines and Pyridines with Thiolbenzoates 1−3[a]

thiolbenzoate	SA amines[b]	pyridines[c]
1	10.0	9.7
2	10.4	$\geq$9.9
3	>11	>10

[a] In 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl). [b] Data taken from ref 3. [c] Data from this work

atom in the leaving group of T± to expel the amine. The amino moiety in T± cannot exert a push to expel the leaving group since it does not possess an electron pair. As a result, electron withdrawal from the nonleaving group favors expulsion of the amine from T± relative to that of the leaving group. According to the hypothesis of the tetrahedral intermediate, an equation (eq 4) can be derived that relates the ratio of rate constants for amine and leaving group expulsion from T± (k_{-1}/k_2) to the pK_a^0 value.[14] Since the values of β_2 and β_1 are little sensitive to the substrate nature,[1,3−5,13,15] eq 4 predicts that as the k_{-1}/k_2 ratio becomes larger (as amine expulsion is more favored), the pK_a^0 value also increases.

$$\log\left(\frac{k_{-1}}{k_2}\right) = (\beta_2 - \beta_1)(\mathrm{p}K_a^0 - \mathrm{p}K_a) \qquad (4)$$

Table 5 shows that the value of pK_a^0 for the reactions of a given thiolbenzoate with SA amines is larger than that for the reactions of the same substrate with pyridines. This can also be accounted for through eq 4, as follows. It is known that SA amines are better nucleofuges from a T± intermediate than *isobasic* pyridines (see below). This means that the value of k_{-1} is larger for an SA amine compared with an isobasic pyridine. On the other hand, the value of k_2 is not affected by the amine basicity or nature.[13a] Therefore, the ratio k_{-1}/k_2 for a given SA amine is larger than that for an isobasic pyridine. Since the values of β_2 and β_1 are little sensitive to the amine nature,[1,13,15] eq 4 shows that the pK_a^0 value should be larger for the reactions with SA amines, as observed.

The better nucleofugality of SA amines compared to that of isobasic pyridines from the intermediate T± has been demonstrated in many studies. The reactions of SA amines and pyridines with 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates show curved biphasic Brønsted-type plots; the pK_a^0 values are larger for the reactions of SA amines.[10b] According to eq 4, this indicates a greater nucleofugality for SA amines. The SA aminolyses of *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) ethyl thiocarbonates in water are concerted,[16] whereas the pyridinolyses of the same substrates in the same solvent are stepwise, through the intermediate T±.[17] Similarly, the SA aminolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl methyl carbonates,[18] both in water, are concerted, in contrast to the pyridinolysis of the same compounds in water, which are stepwise.[19,20] The higher instability of the intermediate T± formed with the SA amines, compared with that formed with isobasic pyridines, has been attributed to the greater nucleofugality of SA amines from T± relative to that of isobasic pyridines.[10b,17−20]

The pyridinolyses of 2,4-dinitrophenyl 4-X-substituted benzoates (X = H, Cl, CN, and NO_2) in 44 wt % ethanol−water show a curved Brønsted-type plot for X = H[4d] and linear plots for the other benzoates.[4a−c] The center of the Brønsted plot curvature for X = H is located at pK_a = pK_a^0 = 9.5 and the linear plots exhibit slopes of ca. 0.9, which indicates that pK_a^0 is larger than 10 for these reactions. This trend (pK_a^0 increases as X becomes more electron-withdrawing) is similar to that found for the reactions of thiolbenzoates with SA amines[3] and pyridines (this work) in the same solvent.

The fact that the pK_a^0 value obtained in the pyridinolysis of 2,4-dinitrophenyl benzoate in 44 wt % ethanol−water[4d] is smaller than that found in the reactions of thiolbenzoate **1** with the same amines in the same solvent (this work) can be attributed to the superior leaving ability from T± of 2,4-dinitrophenoxide compared with 4-nitrobenzenethiolate. This stems from two causes: (i) the lower pK_a of 2,4-dinitrophenol (pK_a 4.1 in water)[21] compared to that of 4-nitrobenzenethiol (pK_a 4.6 in water),[11b] and (ii) the fact that phenoxide anions are a better leaving group than *isobasic* benzenethiolate anions

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[14] Castro, E. A.; Araneda, C. A.; Santos, J. G. *J. Org. Chem.* **1997**, *62*, 126.

[15] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622.

[16] Castro, E. A.; Ibañez, F.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1991**, *56*, 4819. Castro, E. A.; Salas, M.; Santos, J. G. *J. Org. Chem.* **1994**, *59*, 30.

[17] Castro, E. A.; Pizarro, M. I.; Santos, J. G. *J. Org. Chem.* **1996**, *61*, 5982.

[18] Castro, E. A.; Aliaga, M.; Campodonico, P.; Santos, J. G. *J. Org. Chem.* **2002**, *67*, 8911. Castro, E. A.; Cubillos, M.; Santos, J. G. *J. Org. Chem.* **2001**, *66*, 6000.

[19] Castro, E. A.; Gil, F. J. *J. Am. Chem. Soc.* **1977**, *99*, 7611.

[20] Castro, E. A.; Ibañez, F.; Lagos, S.; Schick, M.; Santos, J. G. *J. Org. Chem.* **1992**, *57*, 2691.

[21] Albert, A.; Serjeant, E. P. *The Determination of Ionization Constants*; Chapman and Hall: London, 1971; p 87.

from a tetrahedral intermediate.[22] Therefore, the value of k_2 for 2,4-dinitrophenoxide should be larger than that for 4-nitrobenzenethiolate. This means a lower k_{-1}/k_2 ratio for a given pyridine in the reactions with the benzoate substrate and, according to eq 4, a lower value of $\mathrm{p}K_\mathrm{a}^0$, as observed.

The pyridinolysis of aryl 4-nitrothiolbenzoates in acetonitrile exhibit biphasic Brønsted-type plots that have been explained by stepwise mechanisms.[2c] It is known that the zwitterionic tetrahedral intermediate is less stable in less polar solvents.[13b] The fact that the pyridinolysis of thiolbenzoate **3** in aqueous ethanol is stepwise (this work) and the same reactions in acetonitrile are stepwise indicates that the change of solvent from aqueous ethanol to acetonitrile does not destabilize the intermediate sufficiently as to change the mechanism from stepwise to concerted.

The pyridinolysis of 4-nitrophenyl benzoate in water shows a linear Brønsted-type plot with slope 1.1, consistent with a stepwise mechanism where breakdown of the intermediate $\mathrm{T}^{\pm}$ is rate-determining.[9] This result is in agreement with the curved Brønsted plot, with $\mathrm{p}K_\mathrm{a}^0 = 9.7$, obtained for the pyridinolysis of thiolbenzoate **1** in aqueous ethanol (this work), on the following grounds. The value of k_{-1} should not vary significantly in these two solvents because both are highly protic and polar. On the other hand, the value of k_2 should be larger for the reaction of thiolbenzoate **1** since 4-nitrobenzenethiolate ($\mathrm{p}K_\mathrm{a}$ of its conjugate acid = 4.6)[11b] should be a better nucleofuge from $\mathrm{T}^{\pm}$ than 4-nitrophenoxide ($\mathrm{p}K_\mathrm{a}$ of its conjugate acid = 7.1)[21] from the corresponding intermediate. This is also reflected in the larger k_N values shown by the reactions of the thiolbenzoate. These two effects should render the ratio k_{-1}/k_2 larger for the reaction of 4-nitrophenyl benzoate in water (relative to that for the thiolbenzoate in aqueous ethanol), and according to eq 4, the $\mathrm{p}K_\mathrm{a}^0$ value should be larger for the reaction of the benzoate, as found.

The reactions of *S*-4-nitrophenyl 4-X-thiobenzoates (X = H, Cl, $\mathrm{NO_2}$) with anilines in methanol were found to be concerted,[2a] namely, the hypothetical intermediate $\mathrm{T}^{\pm}$ formed in these reactions is either very unstable or nonexistent.[23] This is in contrast to the results of the present work since the two solvents involved, methanol and aqueous ethanol, are very similar and the stabilization of $\mathrm{T}^{\pm}$ conferred by both solvents should be similar.[13b] On the other hand, anilines are only little better leaving groups than isobasic pyridines[24] and should confer to $\mathrm{T}^{\pm}$ only a slightly greater destabilization relative to isobasic pyridines. Furthermore, the reactions of SA amines with the above substrates in aqueous ethanol are stepwise,[3] despite the fact that SA amines are better nucleofuges than isobasic anilines.[24]

For the reactions of *S*-aryl 4-X-thiobenzoates (X = H, Cl, $\mathrm{NO_2}$) with benzylamines in acetonitrile linear Brønsted-type plots were found.[2b] These plots were drawn using the $\mathrm{p}K_\mathrm{a}$ values in water but not in acetonitrile. The $\mathrm{p}K_\mathrm{a}$ value in water for the most basic amine employed was 9.5.[2b] Correction of this value for the change of solvent from water to acetonitrile, through an empirical equation,[2c] gives a $\mathrm{p}K_\mathrm{a}$ value of 17.9. Therefore, the center of the Brønsted curvature for these reactions in acetonitrile should be $\mathrm{p}K_\mathrm{a}^0 > 17.9$, a value that is much larger than that obtained for the pyridinolysis of thiolbenzoate **1** in aqueous ethanol ($\mathrm{p}K_\mathrm{a}^0 = 9.7$, this work). This can be accounted for by the facts that (i) benzylamines seem to be better nucleofuges than isobasic pyridines,[25] (ii) the value of k_{-1} is much larger in acetonitrile than in water,[26] and (iii) the value of k_2 is not much affected by the change of solvent.[13b,26] These three factors should make the k_{-1}/k_2 ratio and also the $\mathrm{p}K_\mathrm{a}^0$ value (see eq 4) larger for the reactions in acetonitrile,

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Supporting Information Available: Tables S1−S3 containing the individual values of k_obsd, amine concentrations, pH and free amine fractions, and other experimental conditions, for the pyridinolysis of thiolbenzoates **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] Jensen, J. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 1476. Douglas, K. T.; Alborz, M. *J. Chem. Soc., Chem. Commun.* **1981**, 551.

[23] Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345. Williams, A. *Chem. Soc. Rev.* **1994**, *23*, 93.

[24] Castro, E. A.; Leandro, L.; Millan, P.; Santos, J. G. *J. Org. Chem.* **1999**, *64*, 1953.

[25] The relative nucleofugality of benzylamines and pyridines has not been quantified, to our knowledge. Nevertheless, it is known that primary amines such as anilines are better nucleofuges than isobasic pyridines,[24] so it is likely that benzylamines would be better leaving groups than isobasic pyridines.

[26] Um, I.-H.; Seok, J.-A.; Kim, H.-T.; Bae, S.-K. *J. Org. Chem.* **2003**, *68*, 7742.