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Kinetics and Mechanism of the Pyridinolysis of *O*-Ethyl *S*-Aryl Thiocarbonates in Aqueous Solution

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The reactions of a series of 3- and 4-substituted pyridines with *S*-(4-nitrophenyl), *S*-(2,4-dinitrophenyl), and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiocarbonates (NPTC, DNPTC, and TNPTC, respectively) are subjected to a kinetic investigation in aqueous solution, 25.0 °C, ionic strength 0.2 M (KCl). Pseudo-first-order rate coefficients (k_{obsd}) are found under amine excess. Plots of k_{obsd} vs free amine concentration are linear and pH independent. The Brönsted-type plot for NPTC is linear whereas those for DNPTC and TNPTC are biphasic with slopes $\beta_1 = 0.2$ (high pK_a) for both, and $\beta_2 = 0.9$ and 0.8 (low pK_a) for DNPTC and TNPTC, respectively. The curvature center on the pK_a axis is p$K_a^o = 8.6$ (DNPTC) and 7.3 (TNPTC). The Brönsted plots are consistent with the presence of a zwitterionic tetrahedral intermediate on the reaction path where its breakdown is rate determining for NPTC and there is a change in the rate-limiting step for the reactions of the other two substrates. Comparison of the stepwise reactions of the present work with the concerted ones of DNPTC and TNPTC with secondary alicyclic amines shows that the latter amines greatly destabilize $\mathbf{T}^{\pm}$ relative to isobasic pyridines. Comparison of the present reactions with other pyridinolysis indicates that substitution of the oxygen phenoxy atom by sulfur increases pK_a^o and the change of methyl to ethoxy as the remaining group also enlarges the pK_a^o and besides destabilizes $\mathbf{T}^{\pm}$.

Introduction

Although the mechanisms of the aminolyses of acetate[1] and benzoate[2] esters and diaryl[3] and alkyl aryl carbonates[4] are well understood, much less is known about those concerning the thio derivatives of the above compounds.

There have been lately some reports on the aminolysis mechanisms of aryl thiobenzoates[5] and thiolacetates[6,7] and aryl *O*-ethyl thiolcarbonates.[8] Nevertheless, more kinetic studies are needed in order to clarify the mechanism of the latter reactions and to investigate the influence of the nucleophile, the nucleofuge, and the substrate remaining ("nonleaving") group on the mechanism and specifically on the stability of the tetrahedral intermediates formed in some of these reactions.[3,4,7,8]

In the present work we undertake a mechanistic study on the pyridinolysis of *O*-ethyl substituted-phenyl thiolcarbonates with the aim to (i) shed more light on the reaction mechanisms of thiolcarbonates, (ii) examine the influence of the nucleophile by comparison of the present reactions with those of secondary alicyclic amines with the same substrates,[8] (iii) assess the influence of the leaving group by comparison with the pyridinolysis of methyl aryl carbonates, and (iv) study the influence of the substrate remaining group by comparison with the pyridinolysis of aryl thiolacetates.[7]

Experimental Section

Materials. 4-Nitrophenyl,[9] 2,4-dinitrophenyl,[8a] and 2,4,6-trinitrophenyl[8b] *O*-ethyl thiolcarbonates were synthesized as described. The series of pyridines were purified as previously reported.[10]

Kinetic Measurements. These were carried out in aqueous solution at 25.0 ± 0.1 °C, ionic strength 0.2 M (KCl), by following spectrophotometrically the release of the corresponding substituted benzenethiolate anion at 412 nm (the 4-nitro derivative) or 400 nm (the other substrates), by the instruments and methods described.[7,8b] The initial substrate concentration was $(5-6) \times 10^{-5}$ M, and the amine was at least in 10-fold excess over the substrate.

The reactions were followed for 4−5 half-lives, except the slow reactions of 3-carbamoylpyridine (nicotinamide) with *O*-ethyl 4-nitrophenyl thiolcarbonate, where the initial rate method was used (reactions followed up to 2−5%). Pseudo-first-order rate coefficients (k_{obsd}) were found throughout. The experimental reaction conditions and the k_{obsd} values are shown in Table 1.

Product Studies. Some reactions were studied at 315 nm, where an initial increase followed by a decrease of absorbance was observed. Presumably this intermediate is 1-(methoxycarbonyl) substituted-pyridinium ion, in analogy with the intermediates observed in the pyridinolysis of methyl chloroformate[10] and methyl 2,4-dinitrophenyl carbonate.[4b]

4-Nitro, 2,4-dinitro, and 2,4,6-trinitro benzenethiolate anions were identified as one of the final products of the reactions. This was possible by comparison of the UV-vis

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Table 1. Experimental Conditions and k_{obsd} Values for the Pyridinolysis of *O*-Ethyl *S*-Aryl Thiocarbonates[a]

pyridine substituent	pH	$10^2[N]_{tot}{}^b$/M	10^3k_{obsd}/s^{-1}	no. of runs
O-Ethyl *S*-(4-Nitrophenyl) Thiocarbonate (NPTC)				
4-(dimethylamino)	9.57	0.9−8.0	9.45−92.3	6
	9.87	0.8−8.0	16.7−138	7
	10.17	0.5−5.0	10.6−108	7
4-amino	9.12	0.5−5.0	2.98−27.9	7
	9.42	0.5−5.0	4.24−41.6	7
	9.72	0.5−5.0	5.26−53.5	5
3,4-dimethyl	7.37	5.0−15	0.68−1.95	7
	7.72	4.0−13	0.65−1.77	5
4-methyl	8.6	3.0−30	3.74−22.0	7
	8.8	3.0−30	2.80−20.0	7
	9.0	8.0−30	7.10−21.7	5
none[c]	7.0	3.0−30	0.036−0.32	7
	7.5	3.0−30	0.042−0.33	7
	8.0	3.0−30	0.038−0.31	7
3-carbamoyl	7.0[c]	10−30	0.005−0.009	5
	9.0[d]	3.0−30	0.006−0.012	6
O-Ethyl *S*-(2,4-Dinitrophenyl) Thiocarbonate (DNPTC)				
4-(dimethylamino)	9.57	0.08−1.3	3.5−132	12
	9.87	0.06−0.60	8.2−87	10
	10.17	0.06−0.60	4.9−120	10
4-amino	9.12	0.1−1.5	7.6−68	6
	9.42	0.1−0.9	7.3−64	6
	9.72	0.07−0.8	6.5−68	7
3,4-dimethyl	6.47	3.0−30	4.0−34	7
	6.77	1.5−15	2.6−25	7
	7.07	2.5−10	5.5−22	4
4-methyl	5.95	4.0−10	1.7−4.2	4
	6.25	4.0−30	2.6−20	6
	6.55	3.0−30	2.7−24	7
none	5.67	3.0−28	4.3−37	6
	5.97	3.0−25	4.9−36	6
	6.32	2.4−22	4.8−35	7
3-carbamoyl[c]	7.00	3.0−30	0.02−0.14	7
	8.00	3.0−30	0.03−0.15	7
O-Ethyl *S*-(2,4,6-Trinitrophenyl) Thiocarbonate (TNPTC)				
4-dimethylamino	9.57	0.13−1.3	1.67−16.7	7
	9.87	0.07−0.7	0.97−12.2	7
	10.17	0.06−0.6	0.69−14.7	7
4-amino	9.12	0.08−1.0	4.90−73.8	9
	9.42	0.07−0.9	4.80−95.0	12
	9.72	0.06−0.6	7.10−87.0	7
3,4-dimethyl	6.47	2.0−20	25.1−84.3	6
	6.77	0.9−9.5	15.0−137	7
	7.07	1.5−10	30.8−196	5
4-methyl	5.96	4.0−10	18.8−39.8	4
	6.26	3.0−30	20.5−195	7
	6.56	2.0−20	18.6−165	7
3-methyl	5.56	3.0−30	7.6−68.9	7
	5.86	1.0−25	3.0−78.0	7
	6.16	3.0−20	14.0−85.0	5
none	5.67	3.0−25	5.6−39.3	5
	5.97	3.0−25	6.7−42.7	6
	6.32	2.4−22	6.5−43.9	8
3-carbamoyl[e]	4.90	3.0−30	0.83−3.53	5
	5.10	3.0−30	0.92−3.30	7
	5.30	8.0−30	1.42−3.44	6

[a] In aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl). [b] Concentration of total amine (free base plus protonated forms). [c] In the presence of 0.005 M phosphate buffer. [d] In the presence of 0.005 M borate buffer. [e] In the presence of 0.005 M acetate buffer.

Table 2. Values of pK_a for Pyridines and k_N for the Pyridinolysis of *O*-Ethyl *S*-Aryl Thiocarbonates[a]

pyridine substituent	pK_a	k_N/s^{-1} M^{-1}		
		NPTC[b]	DNPT[b]	TNPTC[b]
4-(dimethylamino)	9.87	3.4	31	38
4-amino	9.37	1.6	14	21
3,4-dimethyl	6.77	0.014	0.33	2.8
4-methyl	6.25	0.0066	0.12	1.3
3-methyl	5.86	–	–	0.64
none	5.37	0.0011	0.018	0.21
3-carbamoyl	3.43	2×10^{-5}	4×10^{-4}	0.010

[a] Both the pK_a and k_N values were obtained in aqueous solution at 25.0 °C, ionic strength 0.2 M (KCl); pK_a values from ref 7. [b] Abbreviations defined in Table 1.

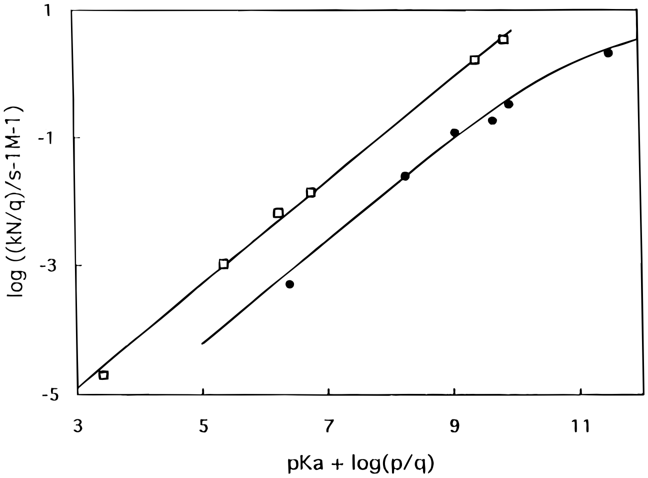

Figure 1. Brönsted-type plots obtained in the reactions of *O*-ethyl 4-nitrophenyl thiolcarbonate with pyridines (□, this work) and secondary alicyclic amines (●, ref 8c), in aqueous solution at 25.0 °C, ionic strength 0.2 M. The latter plot is statistically corrected.[8]

spectra at the end of the reactions with those of authentic samples of the benzenethiols, under the same experimental conditions.

Results and Discussion

Plots of k_{obsd} against free amine concentration at constant pH were linear, in accordance with eq 1, where N represents the substituted pyridine free base, and k_0 and k_N ar the rate coefficients for hydrolysis and pyridinolysis, respectively, of the thiolcarbonates.

$$k_{obsd} = k_0 + k_N [N] \qquad (1)$$

The k_0 values were negligible compared to the aminolysis term in eq 1, except in the reactions of the substrates with nicotinamide, where the aminolysis rate was relatively slow. At pH 5−7 the k_0 values (found as intercepts of plots of eq 1) were 4×10^{-6} s^{-1} (the mononitro derivative), 2×10^{-5} s^{-1} (dinitro), and 7×10^{-4} s^{-1} (trinitro).

The second-order rate coefficients for aminolysis (k_N) were obtained as the slopes of plots of eq 1 and were pH independent. These values, together with those of the pK_a of the conjugate acids of the pyridines, are shown in Table 2.

With the pK_a and k_N values of Table 2 the Brönsted-type plots in Figures 1−3 were obtained. Also shown in the figures, for comparison, are the plots found in the reactions of the same substrates with secondary alicyclic amines.[8] The latter Brönsted-type plots have been statistically corrected.[8,11] The linear plot for the pyridinolysis of *O*-ethyl 4-nitrophenyl thiolcarbonate (NPTC) has a slope of 0.8 (Figure 1). The curved lines for the dinitro (DNPTC) and trinitro (TNPTC) derivatives were calculated by means of a semiempirical equation (eq 2)

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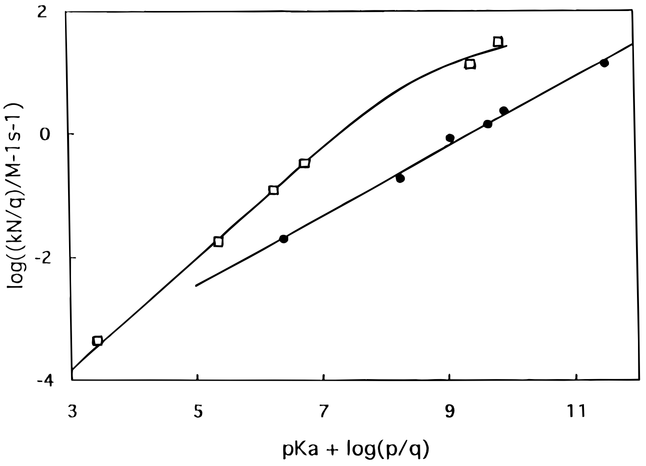


Figure 2. Brönsted-type plots obtained in the reactions of *O*-ethyl 2,4-dinitrophenyl thiolcarbonate with pyridines (□, this work) and secondary alicyclic amines (●, ref 8a). The latter plot is statistically corrected.[8] Experimental conditions as in Figure 1.

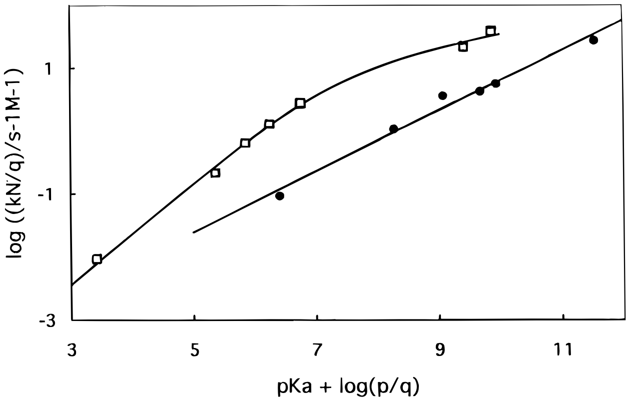


Figure 3. Brönsted-type plots obtained in the reactions of *O*-ethyl 2,4,6-trinitrophenyl thiolcarbonate with pyridines (□, this work) and secondary alicyclic amines (●, ref 8b). The latter plot is statistically corrected.[8] Experimental conditions as in Figure 1.

based on the existence of a tetrahedral intermediate on the reaction path.[4,7,8,10] Similar equations have been reported, which satisfactorily accounts for stepwise mechanisms.[3,12]

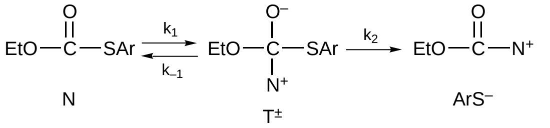
$$\log(k_{\mathrm{N}}/k^{\mathrm{o}}_{\mathrm{N}}) = \beta_2(\mathrm{p}K_{\mathrm{a}} - \mathrm{p}K_{\mathrm{a}}{}^{\mathrm{o}}) - \log[(1 + \mathrm{a})/2]$$

$$\log a = (\beta_2 - \beta_1)(\mathrm{p}K_{\mathrm{a}} - \mathrm{p}K_{\mathrm{a}}{}^{\mathrm{o}}) \qquad (2)$$

In eq 2, β_1 and β_2 are the Brönsted slopes at high and low pK_a, respectively, and k^o_N and p$K_a{}^o$ are the corresponding values at the center of the curvature.

The Brönsted curves for pyridinolysis in Figures 2 and 3 were calculated with the following parameters: DNPTC: $\log k^o_N = 0.87$, p$K_a{}^o = 8.6$, $\beta_1 = 0.20$ and $\beta_2 = 0.90$. TNPTC: $\log k^o_N = 0.70$, p$K_a{}^o = 7.3$, $\beta_1 = 0.20$, and $\beta_2 = 0.80$. The errors of the slopes are ±0.1, and those of p$K_a{}^o$ and $\log k^o_N$ are ±0.2 and 0.1, respectively.

The Brönsted-type curves can be explained by the mechanism described in eq 3, where N represents the substituted pyridine. The Brönsted break results from a change in the rate-determining step, from breakdown of $\mathbf{T}^{\pm}$ to products (k_2 step) to $\mathbf{T}^{\pm}$ formation (k_1 step) as the amine basicity increases.[1-4,7,8,10,12] The linear Brönsted-type plot for the pyridinolysis of NPTC (Figure 1) is consistent with the mechanism depicted by eq 3, where the k_2 step is rate limiting.



$$\underset{\mathrm{N}}{\mathrm{EtO{-}}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}SAr}} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathrm{T^{\pm}}}{\mathrm{EtO{-}}\underset{\underset{\mathrm{N^+}}{|}}{\overset{\overset{\mathrm{O^-}}{|}}{\mathrm{C}}}\mathrm{{-}SAr}} \xrightarrow{k_2} \underset{\mathrm{ArS^-}}{\mathrm{EtO{-}}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}N^+}} \qquad (3)$$

Nonlinear Brönsted-type plots have also been interpreted through structural variation of the transition state in a single step (concerted) mechanism, according to the Hammond postulate[13] and Marcus and Murdoch equations.[14] Nevertheless, we think the subject reactions of this work are stepwise for the following reasons, although a concerted mechanism for the pyridinolysis of the two more reactive thiolcarbonates cannot be rigorously excluded.

(1) Given the rather small pK_a range of the pyridines studied here (ca. 7 pK_a units) a slight and continous variation of the Brönsted slope is expected.[14,15] Although this could change for very low intrinsic barriers, the relatively large free-energy of activation of the reactions of this work ($\Delta G^{\neq}$ ca. 15 kcal/mol for the fastest reaction) makes it difficult to reconcile the rather sharp Brönsted break for the pyridinolysis of the dinitro (DNPTC) and trinitro (TNPTC) thiolcarbonates (Figures 2 and 3) with the one-step process. We have tried to fit an equation based on transition state variation in a single step[15] to our experimental Brönsted plots, without success, as in previous attempts.[15,16]

(2) The magnitude of the Brönsted slopes at low pK_a for the pyridinolysis of DNPTC and TNPTC ($\beta_2 = 0.9$ and 0.8, respectively) and that for NPTC in the whole pK_a range ($\beta_2 = 0.8$) are in line with the values obtained in the aminolysis of similar substrates where a stepwise mechanism has been found with the k_2 step of eq 3 as rate determining.[1-4,6,7,8c,10] Furthermore, the linearity of the Brönsted plots at low pK_a for DNPTC and TNPTC is not in accord with a structural variation of the transition state in a single step, since a *continuous* Brönsted curvature is predicted in this case.[14,15]

(3) In concerted mechanisms where curved Brönsted-type plots have been found the nature of the "nonleaving" group of the substrate does not affect the position of the curvature center on the pK_a axis (p$K_a{}^o$).[17] In the pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates the p$K_a{}^o$ values obtained are 6.6 and 4.9, respectively,[7] which are very different to those found in the present reactions (p$K_a{}^o = 8.6$ and 7.3 for DNPTC and TNPTC, respectively). Substantial p$K_a{}^o$ shifts have also been found in other stepwise aminolysis reactions by substitution of the "nonleaving" group of the substrate.[3,4,16]

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In the reactions of DNPTC and TNPTC with secondary alicyclic amines in water linear Brönsted-type plots with slopes $\beta = 0.56$ and 0.48, respectively, have been obtained (see Figures 2 and 3).[8a,b] The magnitude of the slopes together with the fact that the predicted hypothetical break for stepwise reactions was not observed led to the conclusion that the reactions are concerted.[8a,b] The fact that in the pyridinolysis of the above substrates a tetrahedral intermediate is formed in the reaction path ($\mathbf{T}^{\pm}$ in eq 3) indicates that substitution of a pyridine by a secondary alicyclic amine implies a substantial destabilization of $\mathbf{T}^{\pm}$; this is of such magnitude as to change the mechanism from stepwise to enforced concerted.[18]

It has been found that pyridines are expelled more slowly than isobasic quinuclidines (tertiary alicyclic amines) from the zwitterionic tetrahedral intermediate formed in the aminolysis of phenyl 4-nitrophenyl carbonate.[3] This means that tertiary alicyclic amines destabilize kinetically the intermediate relative to pyridines, which is in line with our findings.

Similar destabilizations of tetrahedral intermediates have been reported in the aminolysis of 2,4-dinitrophenyl methyl carbonate,[16a] 2,4-dinitrophenyl acetate,[19] 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates,[7] and 2,4-dinitrophenyl and 2,4,6-trinitrophenyl *O*-ethyl dithiocarbonates.[16b,20] In all these works the above destabilization has been attributed to a faster nucleofugality from the tetrahedral intermediate of a secondary alicyclic amine compared to an isobasic pyridine.

It is not clear to us why pyridines should stabilize a tetrahedral intermediate more than isobasic alicyclic amines. Gresser and Jencks have argued that this should be due to "a significant contribution of resonance stabilization by electron donation from the pyridine to the oxygen leaving group in the transition state for the breakdown of the intermediate".[3]

The pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl methyl carbonates exhibit biphasic Brönsted-type plots with the curvature center at $\mathrm{p}K_a = \mathrm{p}K_a^{\mathrm{o}} = 7.8$ and 6.5, respectively.[4b,d] These values are smaller than those obtained in this work for DNPTC and TNPTC ($\mathrm{p}K_a^{\mathrm{o}} = 8.6$ and 7.3, respectively). In other words, the change of the oxygen atom of the leaving group attached to the carbonyl carbon by a sulfur atom results in an increase of $\mathrm{p}K_a^{\mathrm{o}}$ (assuming that substitution of methoxy by ethoxy does not affect the $\mathrm{p}K_a^{\mathrm{o}}$ value). This is not in agreement with the results obtained in the pyridinolysis of the corresponding acetates and thiolacetates, where substitution of oxygen by sulfur in the leaving group produces a decrease of $\mathrm{p}K_a^{\mathrm{o}}$ of 0.7 and 0.1 units for the dinitro and trinitro derivatives, respectively.[4c,d,7] The discrepancy observed for the carbonates and thiolcarbonates could arise from a difference between the methoxy and ethoxy groups, although also other reasons should be invoked, in view of the similar basicities and Hammett σ values of the groups concerned.[21]

In the pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl thiolacetates biphasic Brönsted-type plots with break centers at $\mathrm{p}K_a$ 6.6 and 4.9, respectively, were obtained.[7] The corresponding values found in this work for DNPTC and TNPTC are larger, i.e. substitution of methyl by ethoxy as the remaining ("nonleaving") group of the substrate increases the value of $\mathrm{p}K_a^{\mathrm{o}}$. According to the hypothesis of the tetrahedral intermediate $\mathrm{p}K_a^{\mathrm{o}}$ is linearly dependent on $\log(k_{-1}/k_2)$.[22] On the other hand it is known that the above change increases both the k_{-1} and k_2 values from tetrahedral intermediates similar to those formed in the reactions of the present work.[23] This means that substitution of methyl by ethoxy as the substrate "nonleaving" group enlarges k_{-1} more than k_2, implying a kinetic destabilization of the addition intermediate.

Other examples of tetrahedral intermediates instability caused by similar changes are the following: (i) The stepwise acetyl transfer between substituted pyridines and primary and secondary amines,[24] which shifts to a concerted reaction when methoxycarbonyl is being transferred.[25] The concerted mechanism is enforced by the high instability caused to the tetrahedral intermediate by the change of a methyl group by methoxy. (ii) The pyridinolysis of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl acetates[4c,d] compared to the corresponding methyl carbonates,[4b,d] where a $\mathrm{p}K_a^{\mathrm{o}}$ increase of 0.5 and 1.5 units was found for the dinitro and trinitrophenyl carbonates, respectively, in relation to the acetates. (iii) The reactions of secondary alicyclic amines with 2,4-dinitrophenyl acetate[19] and 2,4-dinitrophenyl methyl carbonate,[16a] where a $\mathrm{p}K_a^{\mathrm{o}}$ increase of 0.4 unit was observed for the carbonate. (iv) The reactions of the latter amines with 4-nitrophenyl thiolacetate[22] compared to *O*-ethyl 4-nitrophenyl thiolcarbonate;[8c] the carbonate showing a larger $\mathrm{p}K_a^{\mathrm{o}}$ by 0.2 units.

Another type of destabilization of a tetrahedral intermediate is observed by comparison of the aminolysis of acetyl chloride[26] and benzoyl fluorides[17] in water. The former reactions are stepwise, whereas the latter are concerted, i.e. the change of methyl by phenyl as the acyl group produces a great destabilization of the addition intermediate. This was attributed to resonance with the benzene ring which accelerates the departure of both the amine and F^- from the intermediate (enhancement of k_{-1} and k_2), so that the addition "intermediate" does not have a significant lifetime and the concerted mechanism is enforced.[17]

We are at present investigating the kinetics of the pyridinolysis of *O*-ethyl substituted phenyl dithiocarbonates in water in order to compare it with the kinetics of the reactions of this work, and hence assess the influence of the thiocarbonyl group on the kinetics and mechanisms of these reactions.

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