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The nucleofuge in the pyridinolysis of *O*-(4-nitrophenyl) *S*-aryl thio and dithiocarbonates

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A kinetic investigation is undertaken on the pyridinolysis of *S*-phenyl *O*-(4-nitrophenyl) dithiocarbonate (1), *S*-(4-nitrophenyl) *O*-(4-nitrophenyl) dithiocarbonate (2) and *S*-phenyl *O*-(4-nitrophenyl) thiocarbonate (3) in aqueous ethanol. The Brønsted-type plots (log k_N versus pK_a) obtained are linear and are explained by a stepwise mechanism with the existence of a tetrahedral intermediate ($T^{\pm}$) and its breakdown to products as the rate determining step. The high-performance liquid chromatography analysis of the products of these reactions and that for the reaction of *S*-(4-chlorophenyl) *O*-(4-nitrophenyl) dithiocarbonate (4) with 4-oxypyridine shows that 4-nitrophenoxide is the principal (or the sole) leaving group in these reactions. From the results obtained in the reaction of compound 2, it can be concluded that 4-nitrophenoxide is a better nucleofuge than 4-nitrobenzenethiolate from the same tetrahedral intermediate, although the former is three pK_a units more basic than the latter. Reasons for this behaviour are given.

Supporting information may be found in the online version of this paper.

INTRODUCTION

Several works have appeared in the literature on the kinetics of the nucleophilic reactions of *O*-aryl *S*-aryl thio and dithiocarbonates.[1–6] Among these studies are the reactions of secondary alicyclic amines and pyridines with *O*-aryl *S*-(4-nitrophenyl) thiocarbonates,[3] and *O*-aryl *S*-(4-nitrophenyl) dithiocarbonates,[4,5] where there are two possible nucleofuges of different nature (benzenethiolates versus phenoxides). The question is which of the groups is the nucleofuge. In these cases, the *S*-(4-nitrophenyl) group was much less basic than the *O*-aryl groups and the former was always the nucleofuge.

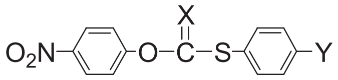
On the other hand, we recently reported the kinetics of aminolysis and phenolysis of a series of *S*-aryl *O*-4-nitrophenyl thiocarbonates, concluding that *O*-4-nitrophenyl is a better nucleofuge than *S*-aryl, despite being the former 0.7–1.7 pK_a units more basic than the latter.[6]

With the aim to assess the nucleofugality of *O*-aryl and *S*-aryl groups, in the present work we undertake a kinetic investigation on the pyridinolysis of the compounds *S*-phenyl *O*-(4-nitrophenyl) dithiocarbonate (**1**), *S*-(4-nitrophenyl) *O*-(4-nitrophenyl) dithiocarbonate (**2**) and *S*-phenyl *O*-(4-nitrophenyl) thiocarbonate (**3**). Also, a high-performance liquid chromatography (HPLC) analysis of the products of these reactions and that for the reaction of *S*-(4-chlorophenyl) *O*-(4-nitrophenyl) dithiocarbonate (**4**) with 4-oxypyridine is carried out to evaluate the nucleofugality of the leaving groups involved in the above compounds.

The pK_a values of the possible nucleofuges in the reactions of compounds **1**, **3** and **4** are similar (see Experimental section). Nonetheless, for the pyridinolysis of compound **2**, the difference of basicity between the possible nucleofuges is large (pK_a values of 4-nitrophenol and 4-nitrobenzenethiol are 7.5 and 4.5, respectively; see Experimental section). If basicity were the only parameter affecting nucleofugality, it would be expected a competition between 4-nitrophenoxide and the corresponding benzenethiolate as leaving groups in the pyridinolysis of compounds **1**, **3** and **4**. On the other hand, for the reaction of compound **2**, 4-nitrobenzenethiolate would be expected to be the nucleofuge.

The importance of the present work can be shown by the results obtained, which are opposite to the expectations mentioned previously. We found that in all the reactions studied in this work, 4-nitrophenoxide is the sole nucleofuge. The situation is remarkable in the case of the pyridinolysis of dithiocarbonate **2**, where 4-nitrophenoxide is the nucleofuge despite being 3 pK_a units more basic than 4-nitrobenzenethiolate.

Another aim of the present work was to compare the results in the pyridinolysis reactions of compounds **1–4** and of other related reactions. This will permit to determine the influence of the nucleophile, electrophile and nonleaving group on the leaving ability of the possible nucleofuge in these reactions.



1 X = S, Y = H
2 X = S, Y = NO_2
3 X = O, Y = H
4 X = S, Y = Cl

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RESULTS AND DISCUSSION

Under amine excess, pseudo-first-order rate constants (k_{obsd}) were found for all the reactions. These were obtained as described in the Experimental section. The conditions of the reactions and the values of k_{obsd} are summarized in Tables S1–S15.

The values of k_{obsd}, obtained under pyridine excess, for all the reactions are in accordance with Eqn (1), where k_0 and k_N are the rate coefficients for solvolysis and pyridinolysis of the substrates, respectively. The values of k_0 and k_N showed no dependence on pH within the pH range used. These values were obtained as the intercept and slope, respectively, of linear plots of k_{obsd} against free pyridine concentration, at constant pH.

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

For the studied reactions, the k_0 values were much smaller than the k_N [free pyridine] term in Eqn (1). The values of k_N for the reactions of compounds **1**, **2** and **3** with the series of pyridines are shown in Table 1.

Given the data in Table 1, the linear Brønsted-type plots of Figure 1 were obtained. The slopes are 1.2, 1.2 and 1.1 for the reactions of compounds **1**, **2** and **3**, respectively. These values are consistent with a stepwise mechanism, through a tetrahedral intermediate ($T^{\pm}$), as in Scheme 1, where its breakdown to products is the rate determining step.[1,2,7,8]

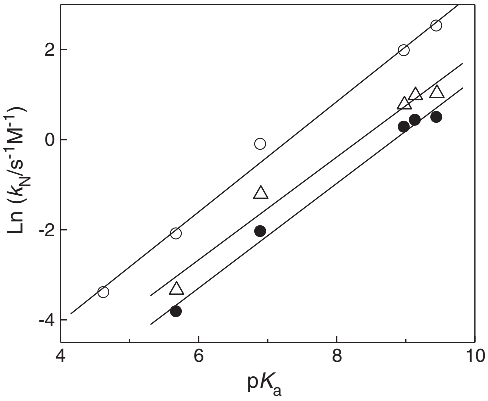


Figure 1. Brønsted-type plots for the reactions of pyridines with (●) *S*-phenyl *O*-(4-nitrophenyl) dithiocarbonate (**1**), (o) *S*-(4-nitrophenyl) *O*-(4-nitrophenyl) dithiocarbonate (**2**) and (Δ) *S*-phenyl *O*-(4-nitrophenyl) thiocarbonate (**3**) in 44 wt% ethanol–water, at 25.0 °C, ionic strength 0.2 M (KCl)

The stepwise nature of the pyridinolysis of compound **3** can be confirmed by the following analysis: The reactions of compound **3** with secondary alicyclic amines are stepwise.[6] Taking into account that pyridines stabilize a tetrahedral intermediate relative to that derived from secondary alicyclic amines,[1,2] the pyridinolysis of compound **3** should also be stepwise. In the same way, the stepwise pyridinolysis of compound **1** can be confirmed by the fact that the change of C–O$^-$ by C–S$^-$ in the tetrahedral intermediate stabilizes the corresponding intermediate.[1,2]

On the other hand, if the pyridinolysis reactions of compounds **1** and **2** are stepwise, the most probable mechanism for the pyridinolysis of compound **4** is stepwise. This is because 4-chlorobenzenethiol is of intermediate basicity between benzenethiol and 4-nitrobenzenethiol, its basicity being very similar to that of the former (the pK_a values for benzenethiol and 4-chlorobenzenethiol are 7.2 and 7.0, respectively; see Experimental section).

A quantitative HPLC analysis to the reactions of compounds **1**, **2** and **3** with 4-oxypyridine shows that 100% of 4-nitrophenol is formed, suggesting that 4-nitrophenoxide is the principal (or the sole) leaving group in these reactions. On the other hand, the same quantitative analysis to these reactions shows that benzenethiols are not obtained during the time of the kinetic measurements. 4-Oxypyridine was the amine used for these analyses because it is one of the most basic pyridines and therefore forms the most stable thionocarbamate (or dithiocarbamate) of pyridinium.

Good first-order kinetics with stable 'infinity' absorbance values during the kinetic studies were obtained in the pyridinolysis of compounds **1, 2** and **3** with all the pyridines used, in accordance with the fact that 4-nitrophenoxide ion is the principal nucleofuge.

To confirm that 4-nitrophenoxide found in the reaction of compound **2** is formed only from the pyridinolysis reaction and not from the hydrolysis of the hypothetical *O*-4-nitrophenyl thionocarbamate of 4-oxypyridinium ion, formed by the pyridinolysis of the substrates, the HPLC analyses were also realized at longer times. These analyses did not show further increase of 4-nitrophenoxide.

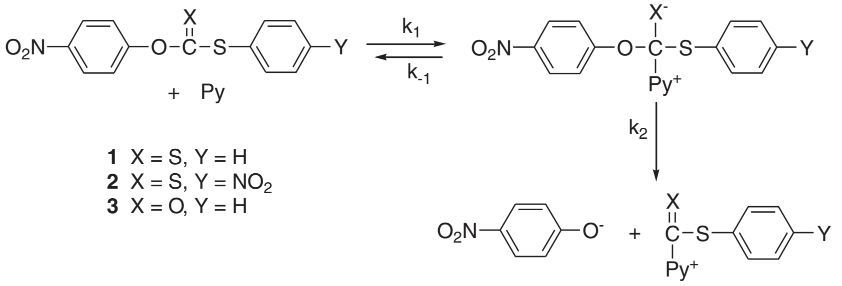
The kinetic behaviour and the product analysis permit to propose the reactions model of Scheme 1 as the mechanism of the studied reactions.

The fact that 4-nitrophenoxide is the nucleofuge in the reactions of compound **1** is not surprising for two reasons: (i) the similar basicities of the two possible leaving groups (pK_a of

Table 1. Values of pK_a for the conjugate acids of pyridines and k_N values for the reactions of pyridines with *S*-phenyl *O*-(4-nitrophenyl) dithiocarbonate (**1**), *S*-(4-nitrophenyl) *O*-(4-nitrophenyl) dithiocarbonate (**2**) and *S*-phenyl *O*-(4-nitrophenyl) thiocarbonate (**3**)[a]

		$10^2\ k_N$/s^{-1} M^{-1}		
Pyridine substituent	pK_a	1	2	3
3,4-Diamino	9.45	310 ± 18	33200 ± 500	1070 ± 40
4-Dimethylamino	9.14	268 ± 10	–	960 ± 30
4-Amino	8.98	188 ± 6	9400 ± 600	600 ± 20
4-Amino-3-bromo	6.90	0.90 ± 0.04	78 ± 2	6.2 ± 0.4
3,4-Dimethyl	5.68	0.015 ± 0.006	0.80 ± 0.02	0.046 ± 0.006
None	4.63	–	0.040 ± 0.002	–

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

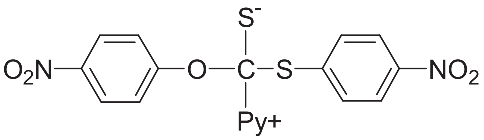


Scheme 1. Probable mechanism for the pyridinolysis of **1–3**

benzenethiol and 4-nitrophenol are 7.2 (this work) and 7.5,[9] respectively), and (ii) it is known that phenoxides are better nucleofuges than isobasic benzenethiolates.[10,11] On the other hand, in the pyridinolysis of compound **3**, also 4-nitrophenoxide is the nucleofuge, showing that, in this case, the change of CO by CS as the electrophile of the substrate does not change the nucleofuge from the corresponding tetrahedral intermediate.

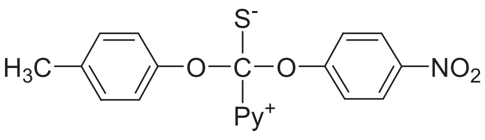
As in the pyridinolysis of compound **3** (this study) and in its aminolysis (secondary alicyclic amines),[6] the nucleofuge is 4-nitrophenoxide ion. Therefore, in these reactions, there is no effect of the nucleophile on the relative nucleofugality of benzenethiolate and 4-nitrophenoxide ions.

From the results obtained in the reaction of compound **2**, it can be concluded that 4-nitrophenoxide is a better nucleofuge than 4-nitrobenzenethiolate from the same tetrahedral intermediate (I), although the former is three pK_a units more basic than the latter (the pK_a values of 4-nitrophenol and 4-nitrobenzenethiolate are 7.5 and 4.5, respectively).[9]



I

These results contrast with those obtained by the comparison between the pyridinolysis of 4-methylphenyl 4-nitrophenyl thionocarbonate[12] and that of *O*-(4-methylphenyl) *S*-(4-nitrophenyl) dithiocarbonate,[4] which shows that 4-nitrophenoxide is a worse nucleofuge than 4-nitrobenzenethiolate from the corresponding tetrahedral intermediates II and III.

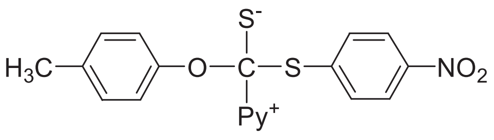


II

Nevertheless, this apparent contradiction evidences the effect of the nonleaving group on the nucleofuge expulsion from the tetrahedral intermediate. A possible explanation can be made, considering that from the tetrahedral intermediate I, both possible nucleofuges are electron withdrawing. Thus, in the transition state for decomposition of I to products, the charge attracted by the 4-nitrobenzenethio group is delocalized in its sulfur atom, and for the 4-nitrophenoxy group, the negative charge should be better localized in its O atom. Therefore, expulsion of 4-nitrophenoxide from I should be favoured relative to that of 4-nitrobenzenethiolate. In this case, the nonleaving group (4-nitrobenzenethio) plays an important role and is not a ‘spectator group’.

On the other hand, the nonleaving group in the intermediates II and III is electron donating. Therefore, the negative charge impelled by this group toward 4-nitrophenoxy in the transition state for decomposition of II prevents charge localization on its O atom. Thus, in the transition states from intermediates II and III, both nucleofuges are in a similar situation regarding charge delocalization, and therefore, basicity becomes the important issue. For this reason, 4-nitrobenzenethiolate should leave faster from III than 4-nitrophenoxide from II because the former is three pK_a units less basic than the latter.

From the proposed mechanism (Scheme 1) and the Brønsted plots obtained (Figure 1), it follows that $k_N = K_1 k_2$, where K_1 is the equilibrium constant of the first step for the reactions with the amine series. From Table 1, it can be observed that k_N is more than 50 times greater in the reaction of compound **2** than that of compound **1**. This result can be explained, in part, by the greater electron withdrawal of 4-nitrobenzenethiolate in compound **2** than that of benzenethiolate in compound **1**.[13] Also, by comparing the k_N values for the reactions of compounds **1** and **3**, it can be concluded that compound **3** is approximately three times more reactive toward this nucleofuges than compound **1**. This is in accordance with the greater rate of attack of pyridines toward thiolcarbonates relative to dithiocarbonates.[3,4,14,15]



III

CONCLUSIONS

In the pyridinolysis of compound **2**, 4-nitrophenoxide is a better nucleofuge than 4-nitrobenzenethiolate from the same tetrahedral intermediate (I), although the former is three pK_a units more basic than the latter. This behaviour is attributed to the fact that in the transition state for decomposition of I to products, the charge attracted by the 4-nitrobenzenethio group is delocalized in its sulfur atom and for the 4-nitrophenoxy group the negative charge should be better localized in its O atom. In this way, the nonleaving group plays an important role in the expulsion of 4-nitrophenoxide and is not a spectator.

From the kinetic point of view, compound **3** is approximately three times more reactive toward pyridines than compound **1**, and the 4-nitrobenzenethio group in compound **2** makes this compound more than 50 times more reactive against pyridines than the benzenethiol group in compound **1**.

EXPERIMENTAL

Materials

Pyridines were purified before use. Dithiocarbonate **1** was synthesized by a modification of Araki's procedure[16] by carrying out the reaction of phenyl chlorodithioformate with 4-nitrophenol, in dry acetone, in the presence of pyridine. This compound was identified by its spectroscopic properties and melting point. The latter was 100 °C–102 °C (103 °C–103.5 °C[16]). Compound **3** was prepared as in a previous work.[6]

The synthesis of dithiocarbonate **2** was carried out by the reaction of 4-nitrophenyl chlorothionoformate with 4-nitrobenzenethiolate in dichloromethane. Compound **2**: mp 157–158 °C (170 °C–171 °C[16]). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, 2H, J = 9.1 Hz); 7.61 (d, 2H, J = 8.9 Hz); 8.19 (d, 2H, J = 8.9 Hz); 8.37 (d, 2H, J = 9.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 123.1, 124.5, 125.6, 126.4, 144.1, 146.3, 147.0, 157.2 and 192.1.

Determination of pK_a

The pK_a values of benzenethiol and 4-chlorobenzenethiol were determined spectrophotometrically by the reported method.[17] The experimental conditions used were the same as those for the kinetic measurements: 44 wt% ethanol–water, 25.0 °C ± 0.1 °C and ionic strength 0.2 M (maintained with KCl). The pK_a values obtained for benzenethiol and 4-chlorobenzenethiol are 7.2 and 7.0, respectively. The pK_a of 4-nitrophenol and 4-nitrobenzenethiol were determined previously under the same conditions. These values are 7.5 and 4.5, respectively.[9]

Kinetic measurements

These were carried out using a diode array spectrophotometer in 44 wt% ethanol aqueous solution, at 25.0 °C ± 0.1 °C, ionic strength 0.2 M (KCl). Phosphate and borate buffers were used in some reactions. The reactions, studied under excess of the pyridine over the substrate, were started by the injection of a substrate stock solution in acetonitrile (10 μL) into the pyridine solution (2.5 mL in the spectrophotometric cell). The initial substrate concentration was approximately 5×10^{-5} M.

As in the reactions of the analogue substrates with tertiary amines,[4,18,19] in this work a consecutive reactions behaviour was observed: the formation and later hydrolysis of the cationic pyridinium thio or dithiocarbamate formed. For the studied reactions, the hydrolysis was more than 10 times slower than the formation of the thiocarbamates, so that both reactions can be considered kinetically independent.

Pseudo-first-order rate coefficients (k_{obsd}) were found for all reactions. These were determined through the spectrophotometer kinetic software, by least squares fitting of the experimental absorbance data to the single-exponential curve $A_t = A_0 \exp(-k_{obsd}\, t) + C$, where A_t and A_0 are the absorbances at time *t* and 0, respectively. The experimental conditions of the reactions and the k_{obsd} values are shown in Tables S1–S15.

Product studies

For the reactions of the three substrates studied with all the pyridines series, 4-nitrophenoxide was identified as one of the reaction products, by comparison of the UV-visible spectra at the end of the reactions with that of an authentic sample in the same experimental conditions.

HPLC analyses were performed for the reactions of compounds **1–4** with 4-oxypyridine using the following conditions: mobile phase of 50% CH_3CN/acetate buffer (0.01 M, pH 5.0), flow rate of 1.2 mL min^{-1} and UV-visible detection. The analyses carried out at short times showed the presence of 4-nitrophenoxide and the absence of the corresponding benzenethiolates (or their dimers). This was achieved by comparison of the retention times and UV-visible spectra with those of authentic samples (for the reaction of compound **2**, see Figures S1 and S2).

Acknowledgements

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