Structure–Reactivity Correlation in the Reactions of Pyrrolidine with *O*-Ethyl *S*-Aryl Dithiocarbonates in Aqueous Ethanol

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ABSTRACT

The reactions of pyrrolidine with *O*-ethyl *S*-(X-phenyl) dithiocarbonates (X = 4-methyl, 4-methoxy, H, 4-chloro, 4-nitro, 2,4-dinitro, and 2,4,6-trinitro) are subjected to a kinetic study in 44 wt% aqueous ethanol, 25.0°C, and ionic strength 0.2 M (maintained with KCl). Pseudo-first-order kinetics are found under amine excess. Linear plots of the pseudo-first-order rate coefficient against concentration of free-base pyrrolidine are obtained for all the reactions, the nucleophilic rate coefficient (k_N) being the slope of such plots. The Bronsted-type plot (log k_N vs. pK_a for the leaving group) is linear with slope $\beta_{lg} = -0.2$, which is consistent with a mechanism through a tetrahedral intermediate ($T^{\pm}$) where its formation is rate determining. The β_{lg} value is very similar to that found in the same reactions in water. There is a great difference in the mechanism of the reactions of *O*-ethyl *S*-phenyl dithiocarbonate with pyrrolidine (order one in amine) and piperidine (complex order in amine) in aqueous ethanol, and this is attributed to a greater nucleofugality from $T^{\pm}$ of piperidine rather than pyrrolidine.

INTRODUCTION

We have studied the mechanism of the reactions of a series of secondary alicyclic amines (HNR^1R^2 = piperidine, piperazine, 1-(2-hydroxyethyl)piperazine, morpholine, 1-formylpiperazine, and piperazinium ion) with *O*-ethyl *S*-(X-phenyl) dithiocarbonates (X = H, *p*-nitro, 2,4-dinitro, and 2,4,6-trinitro), see eq. (1), in 44 wt% aqueous ethanol [1,2,3]. We have found a concerted process in the aminolysis of *O*-ethyl *S*-(2,4,6-trinitrophenyl) dithiocarbonate [1] and a stepwise path through a tetrahedral intermediate in the other reactions [2,3]. In the reaction of *O*-ethyl *S*-phenyl dithiocarbonate the zwitterionic tetrahedral intermediate formed by the amine attack can be deprotonated to yield an anionic intermediate in a kinetically significant step [2].

$$\mathrm{EtO{-}CS{-}S(PhX)} + \mathrm{HNR^1R^2} \longrightarrow \mathrm{EtO{-}C(S){-}NR^1R^2} + \mathrm{XPhSH} \quad (1)$$

We have also studied the above reactions in water [4] and those of the same amines with the other three *O*-ethyl *S*-(X-phenyl) dithiocarbonates (X = *p*-chloro,

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p-methyl, and *p*-methoxy) in water [5]. We have also reported a kinetic investigation on the reactions of pyrrolidine with all the above dithiocarbonates in water [5].

We now report a kinetic study of the reactions of pyrrolidine with all the above substrates in 44 wt% aqueous ethanol. Our aim is three fold: (i) to assess the influence of the solvent on the kinetics and mechanism of the title reactions by comparison with the same reactions in water; (ii) to compare the behavior of pyrrolidine and the secondary alicyclic amines in aqueous ethanol; and (iii) to determine the sensitivity of the nucleofugality rate to leaving group basicity (β_{lg}) in aqueous ethanol (as the slope of a Bronsted-type plot) and to compare it with that in water.

EXPERIMENTAL

Materials

The dithiocarbonates were prepared as reported [4–6]. Pyrrolidine (Merck a.r.), ethanol (Merck a.r.), and substituted benzenethiols (Sigma) were used as purchased.

Kinetic Measurements

These were carried out by following spectrophotometrically the corresponding benzenethiolate anion release at 257 nm (substrates with X = H, 4-chloro, 4-methyl, and 4-methoxy), 420 nm (X = 4-nitro and 2,4-dinitro), and 390 nm (X = 2,4,6-trinitro) through the instruments and method described [1–5]. The reactions were carried out in 44 wt% aqueous ethanol at 25.0 ± 0.1°C and ionic strength 0.2 M (KCl). In all cases the initial substrate concentration was c.a. 10^{-5} M. Under pyrrolidine excess, pseudo-first-order rate constants (k_{obs}) were found for all reactions. The experimental conditions for the reactions and the k_{obs} values are shown in Table I.

Determination of pK_a

The pK_a values of *p*-chloro, *p*-methyl, and *p*-methoxy benzenethiols and that of pyrrolidinium ion were ob-

Table I Experimental Conditions and Values of k_{obs} and k_N for the Present Reactions[a]

Substrate Substituent (pK_a)[b]	pH	$10^2[N]_{total}$ [c] /M	$10^3\ k_{obs}$ /s^{-1}	No. of Runs	k_N [d] /$s^{-1}M^{-1}$
4-CH_3	10.70	1.0–25	3.9–68	8	
(7.78)	11.07	0.4–14	2.2–63	8	0.9
	11.67	1.0–8.0	5.3–54	5	
4-CH_3O	10.77	1.0–8.0	2.8–29	6	
(7.77)	11.07	0.5–5.0	2.6–29	4	1.1
	11.37	0.5–5.0	2.8–34	6	
None	10.70	0.2–8.0	0.4–15	9	
(7.70)[e]	11.20	0.1–2.7	0.5–16	7	1.0
	11.70	0.1–8.0	0.8–64	6	
4-Cl	10.77	0.9–10	2.6–46	5	
(6.95)	11.07	0.5–14	2.1–108	10	1.5
	11.37	0.6–11	4.1–105	10	
4-NO_2	10.77	0.3–2.1	2.5–16	6	
(4.77)[e]	11.07	0.1–1.8	1.2–21	6	2.2
	11.37	0.1–1.1	2.5–16	6	
2,4-$(NO_2)_2$	10.70	0.07–0.7	1.7–19	6	
(3.50)[e]	10.32	0.14–1.4	2.3–20	6	9.5
	11.07	0.04–0.4	1.6–20	6	
2,4,6-$(NO_2)_3$	10.32	0.14–1.4	1.3–11	6	
	10.70	0.07–0.7	1.3–10	6	5.0
	10.95	0.05–0.5	1.4–12	5	
	11.07	0.04–0.3	1.6–8.1	5	

[a] In 44 wt% aqueous ethanol, at 25.0°C, ionic strength 0.2 M (KCl).

[b] pK_a of substituted benzenethiol, obtained under the kinetic conditions. The pK_a of pyrrolidinium was 11.07.

[c] Concentration of total pyrrolidine (free amine + conjugate acid).

[d] Value of the slope of a k_{obs} vs. [free pyrrolidine] plot which includes all runs (at all the pH values).

[e] Values of pK_a taken from ref. [3].

tained spectrophotometrically at 270 nm (the three thiols) and 205 nm (pyrrolidinium), under the same conditions of the kinetic measurements, as reported [5,7,8]. The measurement of pH was made on a Radiometer PHM-62 pH-meter. The pK_a values of the benzenethiols are shown in Table I. The value for pyrrolidinium ion is 11.07. These are pK_a "mixed" values [8].

Product Studies

The presence of the substituted benzenethiolate ions was determined spectrophotometrically by comparison of the UV-vis spectra at the end of the reactions with those of the corresponding benzenethiolate ions under the same experimental conditions.

RESULTS AND DISCUSSION

The reactions of pyrrolidine with the title dithiocarbonates, depicted in eq. (2) where $HN(CH_2)_4$ is pyrrolidine, are governed by the rate law in eqs. (3) and (4), under the experimental conditions.

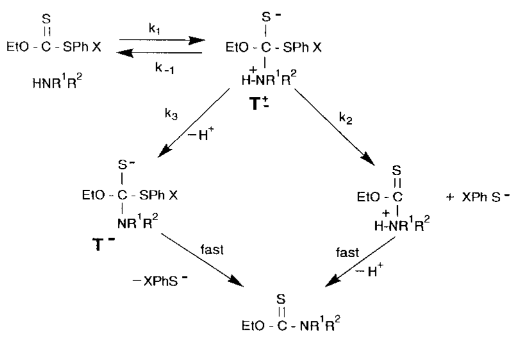
$$\mathrm{EtO{-}CS{-}S(PhX)} + \mathrm{HN(CH_2)_4} \longrightarrow \mathrm{EtO{-}CS{-}N^{+}H(CH_2)_4} + \mathrm{XPhS^{-}} \quad (2)$$

$$d[\mathrm{XPhS^{-}}]/dt = k_{\mathrm{obs}}\,[\mathrm{EtOCSSPhX}] \quad (3)$$

$$k_{\mathrm{obs}} = k_{\mathrm{N}}\,[\mathrm{HN(CH_2)_4}] \quad (4)$$

Plots of k_{obs} vs. free pyrrolidine concentration were linear with the slopes (k_{N}) independent of pH for all the reactions.

Scheme I shows the general mechanistic behavior exhibited by the reactions of six-member ring secondary alicyclic amines (6-SAA) with the title series of dithiocarbonates in 44 wt% aqueous ethanol [2]. In this scheme the k_3 step is deprotonation of the tetrahedral intermediate $T^{\pm}$ by the free amine to yield the anionic intermediate T^{-}.



Scheme I

In the reactions of 6-SAA with 4-nitrophenyl and 2,4-dinitrophenyl *O*-ethyl dithiocarbonates in 44 wt% aqueous ethanol, a first-order rate in free amine was found [3]. This was explained by a faster nucleofugality of $XPhS^{-}$ from $T^{\pm}$ compared to the deprotonation rate from the same intermediate, i.e., $k_2 >> k_3\,[\mathrm{HNR^1R^2}]$ in Scheme I [3].

In contrast, a complex order in amine, intermediate between one and two, was found in the same reactions with *O*-ethyl phenyl dithiocarbonate [2]. This was attributed to a lower nucleofugality rate of PhS^{-}, compared to the 4-nitro and 2,4-dinitro substituted anions, which makes possible a competition between the deprotonation step and the expulsion of the amine from $T^{\pm}$, such that $k_2 < k_3\,[\mathrm{HNR^1R^2}] \approx k_{-1}$ for these reactions [2].

The reaction of pyrrolidine with *O*-ethyl phenyl dithiocarbonate in 44 wt% aqueous ethanol (this work) exhibits a first-order dependence on the free amine, in spite of that the concentration of pyrrolidine was ca. 1/10 of that of piperidine in its reaction with the same substrate [2]. This means that for the pyrrolidine reaction $k_3[\text{pyrrolidine}] << k_2$, and according to the Bronsted-type plot obtained (see below), $k_{-1} << k_2$.

These results indicate a much lower nucleofugality from $T^{\pm}$ of pyrrolidine than piperidine (at least ten fold), in spite of their similar basicities (pK_a 11.1 and 10.8 in 44 wt% aqueous ethanol and 25°C, respectively).

The different behavior of pyrrolidine and piperidine has some precedents in the literature [9,10]. Bunnett et al. found a great rate difference between pyrrolidine and piperidine in their reactions toward substituted phenyl phenyl ethers in dioxane/water [9] and 2,4-dinitro-1-naphthyl ethyl ether in dimethyl sulfoxide solution [10]. They attributed the rate difference to the superior ability of the pyrrolidino moiety in a Meisenheimer complex to expel the leaving group from it, compared to the ability of a piperidino moiety from a similar complex [9,10]. The smaller ability of the latter group was explained by large steric compressions in the Meisenheimer complex of the piperidine reaction. Although the tetrahedral intermediate $T^{\pm}$ of Scheme I is different than the above complex, this explanation could also be valid to account for the larger nucleofugality from $T^{\pm}$ of piperidine compared to pyrrolidine, as found in this work.

With the k_{N} values for the reactions of this study (except that of the trinitro derivative) and the pK_a of the conjugate acids of the leaving groups of the substrates (Table I), the Bronsted-type plot of Figure 1 was obtained. The slope is $\beta_{\mathrm{lg}} = -0.20 \pm 0.05$, and the correlation coefficient 0.94. The reason for not in-

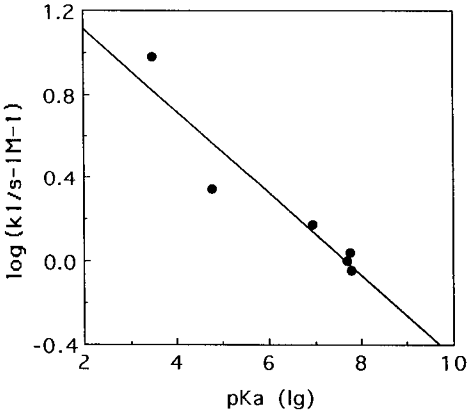


Figure 1 Bronsted-type plot for the leaving group for the reactions of pyrrolidine with *O*-ethyl *S*-(X-phenyl) dithiocarbonates in 44 wt% aqueous ethanol, 25.0°C, and ionic strength 0.2 M.

cluding the trinitro substrate in the Bronsted plot will be discussed later.

The above Bronsted slope is similar to the corresponding ones found in the aminolyses of acetate esters [11], diaryl carbonates [12], substituted triazinpyridinium ions [13], and *O*-ethyl dithiocarbonates in water [5]. It is also in line with those obtained in the reactions of piperidine with *O*-ethyl dithiocarbonates in 44 wt% aqueous ethanol [3] and in the title reactions in water [5]. In all these works the low β_{lg} value (between 0 and -0.3) has been associated with a stepwise mechanism where the formation of the tetrahedral intermediate is the rate-determining step. The fact that in the reactions of pyrrolidine with dithiocarbonates the β_{lg} value does not change in going from water ($\beta_{lg} = -0.23 \pm 0.1$) [5] to 44 wt% aqueous ethanol, means that the effective charge development on the leaving group from reactants to the transition state of the k_1 step is approximately the same in both solvents [13,14].

Therefore, according to these arguments, the k_N values obtained in this work (Table I) correspond to the k_1 values of Scheme I. This means that for all the present reactions $k_2 + k_3$ [pyrrolidine] $>> k_{-1}$ (with the k_2 path faster than that of k_3, see above).

A biphasic Bronsted-type plot was obtained in the reactions of a series of 6-SAA with 4-nitrophenyl and 2,4-dinitrophenyl *O*-ethyl dithiocarbonates in 44 wt% aqueous ethanol [3]. The experimental point for piperidine lies on the linear portion at high pK_a for both reactions; i.e., for the reactions of piperidine the rate-determining step is formation of the zwitterionic tetrahedral intermediate. If this is so for piperidine, it should be even more so for pyrrolidine in view of both the larger basicity and the smaller nucleofugality of the latter relative to the former amine (smaller k_{-1} for pyrrolidine). It is noteworthy that the k_2 value should not be much affected by the amine nature due to the absence of an electron pair on the nitrogen atom of the amino moiety in $T^{\pm}$ [11,12].

If the rate determining step is k_1 for the reactions of pyrrolidine with dithiocarbonates in aqueous ethanol ($k_2 >> k_{-1}$ in Scheme I), it is reasonable that the same step be rate-limiting in water [5] since: (i) the k_{-1} value should decrease by the change from aqueous ethanol to water in view that the transition state for the k_1 step is less polar than $T^{\pm}$ [12] and (ii) the k_2 value should not be significantly affected by the solvent polarity, in view that both the transition state for breakdown to products and $T^{\pm}$ are highly polar [12].

As expected, the $k_N = k_1$ value in Table I increases as the nucleofuge basicity decreases due to increasing electron withdrawal from the phenyl substituents in the leaving group, which results in an increasingly more positive thiocarbonyl carbon atom. An exception to this behavior is presented by the reaction of *O*-ethyl 2,4,6-trinitrophenyl dithiocarbonate which shows a smaller k_1 value than the 2,4-dinitrophenyl derivative. The same exception was found in the reactions of these two substrates with piperidine in both water [4b] and 44 wt% aqueous ethanol [1,3].

The above discrepancy regarding the k_1 values for the pyrrolidine reactions in 44 wt% aqueous ethanol (Table I) could be explained by steric reasons due to the extra ortho-nitro substituent in the trinitro derivative. Another explanation could be a change in the reaction mechanism from stepwise in the reaction of pyrrolidine with the dinitro substrate to concerted for that of the trinitro compound. This is the mechanistic change that was found in the reactions of piperidine with these substrates in 44 wt% aqueous ethanol [1,3]. This is the reason why the trinitro compound was not included in the Bronsted-type plot of Figure 1.

Comparison of the k_1 values obtained in the present work with those found for the same reactions in water [5] reveals that these values are ca. 3–5 times larger in water. This should be due to the fact that the transition state for the first step is more polar than reactants and therefore the former should be more stabilized (relative to reactants) by the change to a more polar solvent.

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