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Mechanisms of Acid Decomposition of Dithiocarbamates. 5. Piperidyl Dithiocarbamate and Analogues

Eduardo Humeres,* Byung Sun Lee, and Nito Angelo Debacher

Department of Chemistry, Universidade Federal de Santa Catarina, 88040-900 Florianópolis, SC, Brazil

humeres@mbox1.ufsc.br

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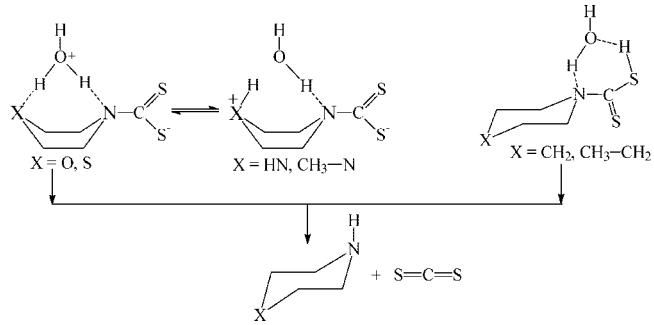

In this work, the acid cleavage at 25 °C in 20% v/v aqueous ethanol of a series of analogues of piperidine dithiocarbamate $X(C_2H_4)_2NCS_2^-$ (X = CH_2, $CHCH_3$, NH, NCH_3, S, O) was studied. The pH−rate profiles were obtained in the range of H_o −5 and pH 5. They all presented a dumbell shaped curve with a plateau from which the pH-independent first-order rate constant k_o (or the specific acid catalysis k_H) was calculated, in addition to the acid dissociation constant of the free (pK_a) and conjugate acid (pK^+) species of the DTC. LFERs of the kinetically determined pK_a and pK^+ versus pK_N (pK_a of parent amine) were used to characterize the reactive species and the structure of the transition state of the rate-determining step. For X = CH_2, CH_3CH the values of k_H agree with those of alkDTCs in the strong base region of the Brϕnsted plot of log k_H versus pK_N where the transition state is close to a zwitterion formed by intramolecular water-catalyzed S-to-N proton transfer of the dithiocarbamic acid. However, when X = NH, CH_3N, O, S, the reactive species is the DTC anion, which is as reactive as an arylDTC, and similarly, the pK^+ values correspond to a parent amine that is about 3−4 pK units more basic. The solvent isotope effect indicated that the acid decomposition of these dithiocarbamate anions is specifically catalyzed by a Hydron anchimerically assisted by the heteroatom through a boat conformation.

Introduction

Apart from their use in agriculture as fungicides, herbicides, and insecticides,[1] the dithiocarbamates are extensively used in the rubber industry as accelerators and antioxidants.[2] They are also used in the control of pollution by heavy metals[3,4] and in the pharmaceutical industry.[5−9]

The mechanism of acid decomposition of carbamates,[10−12] monothiocarbamates,[12] and dithiocarbamates[13−15] (DTC) relies heavily on the structure and the pK_a of the conjugate acid of the parent amine (pK_N) (eq 1). The mechanisms of decomposition of DTCs in the range of pK_N 1−11 may occur by a rate-

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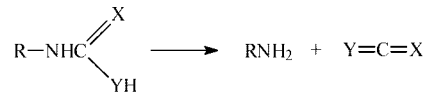
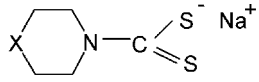
determining step of N-protonation to form a zwitterion, a rate-determining C−N breakage of this zwitterion, or through a new water-catalyzed mechanism.[13,15]



X and Y = O or S (1)

General acid catalysis was not observed in the acid cleavage of alkyl dithiocarbamates (alkDTC) because the pK_a of the N-protonated zwitterionic intermediate is much lower than that of the solvated proton, and general acid catalysis is expected only for acids stronger than Hydron.[14] ArylDTCs decomposed ca. 10^4-fold faster than alkDTCs with similar pK_N. Proton inventory[15] and theoretical calculations[16] showed that the rate acceleration was due to a multiproton transition state where an S-to-N proton transfer occurred through a water molecule. The driving force to reach the transition state is the consequence of the required torsion of the C−N bond that inhibits the resonance with the thiocarbonyl group and the aromatic moiety, increasing the basicity of the nitrogen and making the proton transfer thermodynamically favorable.

The dithiocarbamates from heterocyclic secondary amines (**I**),[17−21] analogues of piperidine, were considered to constitute an independent series because of their high reactivity, although no mechanism was proposed to explain their behavior.[12]



I

X = CH_2, CH_3CH, NH, CH_3N, O, S

This work aims to answer relevant questions about the reactivity of the dithiocarbamate analogues to piperidine, the mechanisms involved in their acid decomposition, and the role in the reaction of the heteroatom at the 4-position.

Results and Discussion

***cis*−*trans* Conformation.** The 4-methyl group of 4-methylpiperidine and 4-*N*-methylpiperazine is in the equatorial conformation.[22−27] Both compounds present the possibility of *cis*−*trans* conformation when forming the dithiocarbamate. The ^{13}C NMR chemical shift of the equatorial 4-methyl group is 22.6−23.0 ppm,[24−28] wheras for the axial group it is 18.8 ppm.[30] The equatorial N-CH_3 presents a signal at 46.4[27]−47.2[22] ppm and ∼37.2 ppm[22] when it is in the axial position. Therefore, in the case of 4-methylpiperidylDTC, the 4-methyl group (δ = 22.2 ppm) is in the equatorial position as well as the N-CH_3 group of 4-methylpiperazylDTC (δ = 49.8 ppm). The N-CH_3 group in *N*-methylpiperidine prefers the equatorial position and, depending on the solvent, the equatorial-axial barrier amounts to 2.4−3.0 kcal mol^{-1}.[24−26,29]

Piperidyl dithiocarbamate presented a preferred conformation with the DTC group in the equatorial position when complexed with Cr (δ = 209.7 ppm), Mo (δ = 211.6 ppm), and W (δ = 213.0 ppm).[30] For the DTC group of the pipDTC sodium salt, we observed δ = 204.5 ppm, so we assigned the position of this group as equatorial. We also did this for piperazyl dithiocarbamate, where δ = 210.9 ppm. The DTC signals of 4-methylpiperidylDTC and 4-methylpiperazylDTC appeared at 207.1 and 207.9 ppm, respectively, and we concluded that both compounds had undergone tetrahedral inversion to produce the *trans*-conformation.

pH−Rate Profiles. The pH−rate profiles of the acid cleavage of cycloDTCs were all similar to those found for simple alkDTCs[13] and arylDTCs.[15] They showed a dumbell-shaped curve as shown in Figure 1 for piperidylDTC. The observed first-order rate constant can be expressed by eq 2 where a_{H^+} = antilog(−pH or H_o). The value of k_o was obtained from the average value of k_{obs} at the plateau of the profile; pK_a and pK^+ are the acid dissociation constants of the dithiocarbamic acid and its conjugate acid, respectively.

$$k_{obs} = \frac{k_o}{\frac{K_a}{a_{H^+}} + 1 + \frac{a_{H^+}}{K^+}} \quad (2)$$

The reaction can be kinetically described as occurring according to Scheme 1 through the species SH_2^+, SH, or S^-. The rate constant k_o represents the rate constant of the decomposition through the free dithiocarbamic acid (k_1 in Scheme 1), and it is kinetically equivalent to $k_H K_a = k_{OH} K_w / K^+$, where k_H and k_{OH} are the specific acid and base catalysis rate constants, respectively. However, the alternative of specific base-catalyzed decomposition cannot be considered because k_o is of the order of 0.10−1.0 s^{-1} and $K^+ \approx 10^3$, so k_{OH} should be ca. 10^{17} M^{-1} s^{-1}, much larger than the diffusion-controlled rate constant. The values of k_o and k_H are shown in Table 1, together with the pK_a and pK^+ obtained from the pH−rate profiles of the acid decompositions of the series of piperidylDTC and analogues according to eq 2. Considering k_o, the acid decomposition of cycloDTCs is about 10^2-fold faster than that of alkDTCs[5] from parent amines with p$K_N \approx 10$, but it is 10^2-fold slower than the acid decomposition of arylDTCs.[13,15]

Acid Dissociation Constants of cycloDTCs. The relationship between the acid dissociation constants calculated from the

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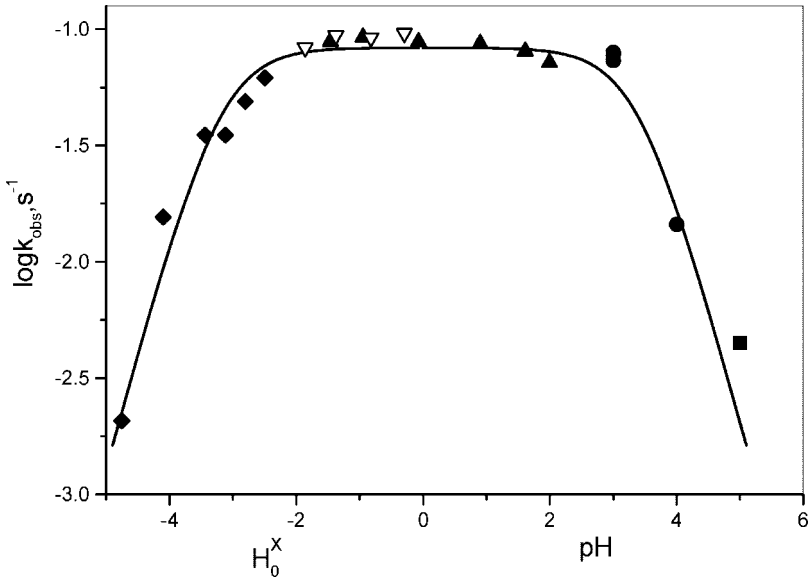
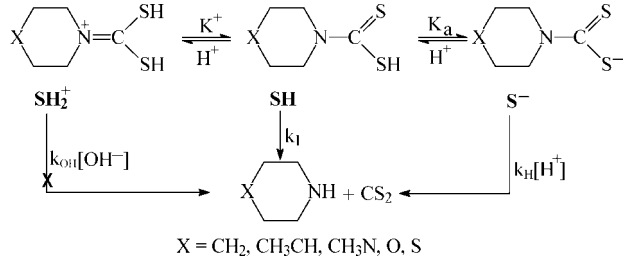


FIGURE 1. pH−rate profile of the acid decomposition of piperidylDTC in 20% aqueous ethanol at 25 °C: ■, buffer succinate; ●, buffer formate; ▲, HCl; ▽, H_2SO_4; ◆, $HClO_4$. The continuous theoretical line was calculated from eq 2 ($r = 0.999$, $sd_y = 0.014$).

SCHEME 1. Kinetic Scheme of the Hydrolyses of cycloDTCs



pH−rate profiles and the pK_N values of the parent amines is related to the mechanism of acid decomposition of the dithiocarbamates. There must be three events for the acid cleavage to occur: S−H dissociation, N−H protonation, and C−N bond breakdown. AlkDTCs decompose by specific acid catalysis through a zwitterion intermediate,[13,16] and pK_a and pK^+ calculated from the pH−rate profiles correspond to the thermodynamic values obtained by titration as can be observed in Figure 2. The initial state is the dithiocarbamate anion S^- (after S−H dissociation),[12,13] and the protonation occurs on the nitrogen, which presents a basicity similar to the conjugate acid SH_2^+ because p$K_\pm$ of the nitrogen, N^+−H bond of the zwitterion $SH^\pm$, is linearly related to pK^+ (Scheme 2).[13] However, for arylDTCs, which decompose by a concerted water-catalyzed mechanism, there is a considerable difference between the pK values obtained from the pH−rate profiles and those obtained by titration (Figure 2). The pK_a values of the arylDTCs in Figure 2a are much higher than those of the alkDTCs with similar pK_N's, corresponding to alkyl amines with basicities of about 5−7 units of pK more basic than the pK_N of the parent anilines (Table 2, eqs 3 and 5). The difference in the dissociation constants of the conjugate acids is even higher, and the pK^+'s of the aryl series are similar to those of the alkyl amines that are ca. 8 pK units more basic. Alkyl- and arylDTCs follow different linear relationships between pK^+ and pK_N (Table 2, eqs 6 and 8).

The initial state of the arylDTCs is the dithiocarbamic acid SH (Scheme 2), and the lower acidity of the sulfur (pK_a) and higher basicity of the nitrogen (p$K_\pm$ linearly related to pK^+) can be explained as a consequence of the torsional effect of the water molecule that catalyzes the reaction, decreasing the double-bond character of the C−N bond and also decreasing the resonance of the nitrogen and the aromatic ring.[15] The proton transfers from the S−H dissociation and N-protonation, and C−N bond breakdown are concerted, with no formation of a zwitterionic intermediate.[16] In fact, the pK's calculated from the rate constants represent the acidity of the S−H and N^+−H bonds of the transition state and the deviation of the kinetically calculated pK's from the titration values is indicative of its structure.[31]

This analysis can be extended to the acid cleavage of cycloDCTs. The pK_a values of alkDTCs, including those determined by titration, follow eq 3 in Table 2. The dissociation constants of the thiocarbamic acids of the cycloDTCs are very close to the relationship of alkDTCs (Figure 2a), and considering the standard deviation, the values of both series produced the same LFER (Table 2, eq 4). Therefore, for this series the dithiocarbamate moiety at the transition state of the rate-determining step is similar to an anion.

A different situation can be observed in Figure 2b for the dissociation constants of the conjugate acids. There is a clear distinction between piperidyl- and 4-methylpiperidyl dithiocarbamates and the other members of the series with a heteroatom in the 4-position. The N-basicity of all members of the series is higher than that of an alkDTC of similar pK_N, and for those containing a heteroatom, the increase is more than 3 pK units (eqs 6 and 7, Table 2). This fact will be discussed below.

Brϕnsted Plot. The plot of the log of the calculated specific acid catalysis rate constants k_H versus the pK_N of the leaving amine of the acid decomposition of alkDTCs (Figure 3) shows a change in the rate-determining step near pK_N 9 from N-protonation to form a zwitterion intermediate to the C−N bond breakdown of this intermediate.[13] At a pK_N near 10, a minimum of k_H indicates a change of mechanism with a subsequent fast increase of the rate constant in relation to the basicity of the parent amine. This change of the rate constant

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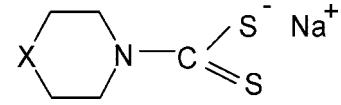
TABLE 1. Acid Dissociation and Rate Constants Related to the Acid Cleavage of Piperidyl Dithiocarbamate and Analogues in 20% Aqueous Ethanol at 25 °C[a]



no. order	X	pK_{N1}[b]	pK_{N2}[b]	pK_a	pK^{+}[c]	$10^2\ k_o\ (s^{-1})$	$10^{-2}\ k_H\ (M^{-1}\ s^{-1})$
1	CH_2	11.16 ± 0.04[d,e]		3.4 ± 0.2	-3.2 ± 0.2	8.83 ± 0.08	2.2[f,g]
2	CH_3CH	11.07[e,h]		3.1 ± 0.1	-3.0 ± 0.2	12.3 ± 0.3	1.6
3	HN	9.81 ± 0.04[d,e,i,j]	5.6 ± 0.1[d,e,i,j]	3.0 ± 0.5	-2.6 ± 0.5	48.8 ± 0.9	4.9
4	CH_3N	9.18[j]	4.81[j]	3.0 ± 0.5	-2.8 ± 0.5	68.26 ± 0.01	6.8
5	S	8.7 ± 0.2[j,k]	(−6.2) [l,m]	2.65 ± 0.05	-3.25 ± 0.05	108 ± 5	4.8
6	O	8.5 ± 0.1[d,i,j,n]	(−3.6)[m,o,p]	2.85 ± 0.05	-3.45 ± 0.05	116 ± 5	8.2

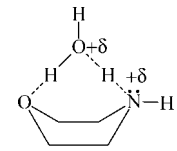
[a] This work unless indicated. [b] pK_a of the conjugate acid of the parent amine. [c] From the pH−rate profile where $H_o^X = -(X + \log C_{H^+})$. [d] *CRC Handbook of Chemistry and Physics*, 64th ed.; Weast, R.C., Ed.; CRC Press: Cleveland, 1983–1984. [e] *Handbook of Biochemistry*; Sober, H. A., Hart, R. A., Eds.; CRC Press: Cleveland, 1968. [f] $k_H = 48.3\ M^{-1}\ s^{-1}$ (ref 21). [g] $k_H = 100$ and $117\ M^{-1}\ s^{-1}$; Takami, F.; Ikawa, K.; Tokuyama, K.; Shigeru, W.; Maeda, T. *Chem. Pharm. Bull.* **1974**, *22*, 275−279. [h] For 3-methylpiperidine. [i] Hetzer, H.B.; Robinson, R.A.; Bates, R.G. *J. Phys. Chem.* **1968**, *72*, 2081−2086. [j] De Filippo, D.; Devillanova, F.; Trogu, E. F.; Verani, G. *Gazz. Chim. Ital.* **1974**, *104*, 1227−1235. [k] Krishnamurthy, M.; Babu, K.S.; Muralikrishna, U. *Curr. Sci.* **1988**, *57*, 598−600. [l] For dimethylsulfide. [m] Arnett, E.M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223−403. Bagno, A.; Scorrano, G. *Acc. Chem. Res.* **2000**, *33*, 609−616. [n] Hetzer, H.B.; Bates, R.G.; Robinson, R.A. *J. Phys. Chem.* **1966**, *70*, 2869−2872. [o] For diethylether and dioxane. [p] Somera, N.; do Amaral, L. *Anais da I Conf. Fís. Quím. Org.* Brazil, **1982**, 133−140.

is incompatible with a Brønsted slope and with the increased instability of the zwitterion and slower C−N bond cleavage. The methyl-, ethyl-, and *n*-butylDTC and also piperidyl- and 4-methylpiperidylDTC are in this range. Theoretical calculations indicated that in this case the reaction was water-catalyzed.[16] Scheme 3 shows the mechanism where in the first step there is a water-assisted intramolecular S-to-N proton transfer through the transition state **TS2**. The transition state structure corresponds to a situation where the proton from the SH group has been almost completely transferred to the water molecule. This arrangement looks very similar to a Hydron coordinated to a dithiocarbamate anion. The formation of the zwitterionic intermediate **II** is followed by the C−N cleavage through transition state **TS3**. For arylDTCs, both processes are concerted with only one transition state (**TS1**). Because of the above considerations, for pip- and MepipDTC, the rate-determining TS should be **TS1.** The involvement of the water in this transition state is consistent with the higher value of pK^+ for these two compounds as shown in Figure 2b.

Activation Parameters. There is a clear difference between the mechanisms involved in the decomposition of the alicyclic amine dithiocarbamates and those with an heteroatom in position 4, as was observed from the dependency of pK^+ on pK_N (Figure 2b) and the Brønsted plot (Figure 3). Table 3 compares the activation parameters of several dithiocarbamates. The increase in reactivity of phenylDTC with respect to 2-ammonium-ethylDTC is mainly due to a decrease in the enthalpy of activation. The magnitude of $\Delta S^{\ddagger}$ is practically the same for both. The rate-determining step of the 2-ammonium-ethylDTC is the N-protonation to form the zwitterion intermediate, and for the arylDTC it is the concerted water-catalyzed decomposition as was explained above.

We concluded above that the decomposition of pipDTC is water-catalyzed and that the rate-determining step is the N-protonation that produces the zwitterion. The enthalpy of activation is 19 kcal mol^{-1}, similar to that of the 2-ammonium-ethylDTC, but $\Delta S^{\ddagger}$ is nearly zero. The activation parameters of the morpholyl and thiomorpholylDTC are very similar: $\Delta H^{\ddagger}$ (15 kcal mol^{-1}) and $\Delta S^{\ddagger}$ −9 cal $mol^{-1}\ K^{-1}$, indicating a common mechanism with higher steric requirement to reach the transition state.

Nature of the Nitrogen−Heteroatom Interaction. The study of the inductive effect of substituents on the pK_N in the series of 2-substituted ethylammonia, $X\text{-}CH_2\text{-}CH_2\text{-}NH_3^+$, was used to compare the effect when X = CH_2 and O in the series $X(C_2H_4)_2NCS_2^-$. As can be observed in Figure 4, the pK_N of piperidinium correlates very well with the ethylammonium series, whereas the pK_N of the N-protonated morpholine is ca. 3 p*K* units higher than expected, indicating that the effect of the heteroatom is not only inductive. The effect may be a consequence of a strong intramolecular H-bonding (O−H···N) through a water molecule as reported in conformational studies of methyl-hydroxypiperidine,[32] quinolizidine,[33] and dimethylamino naphthalene systems.[34] Proton transfers involving oxygen and nitrogen acids and bases can be dramatically slowed by internal hydrogen bonding. When the proton accepted by the nitrogen is placed in a tight hydrogen bond, the nitrogen behaves as a stronger base and the pK_a is higher than expected.[35] However, this explanation is insufficient because if the conjugate acid of morpholine forms an intramolecular hydrogen bond with the 4-oxygen through a water molecule, the second N^+−H bond should dissociate normally, which should decrease the rate of dissociation by a factor not higher than 2. We have to conclude that the two N^+−H bonds are not equivalent and that the conjugate acid looks more like a Hydron hydrogen-bonded to morpholine as shown in structure **III**.



III

The reason for the increase of 3 p*K* units of the pK_N is that the rate of N-deprotonation of **III** is about 3 orders of magnitude slower than that of the series of 2-substituted ethylammonia, as has been observed for *p*-aminosalicylate ion,[36] because the

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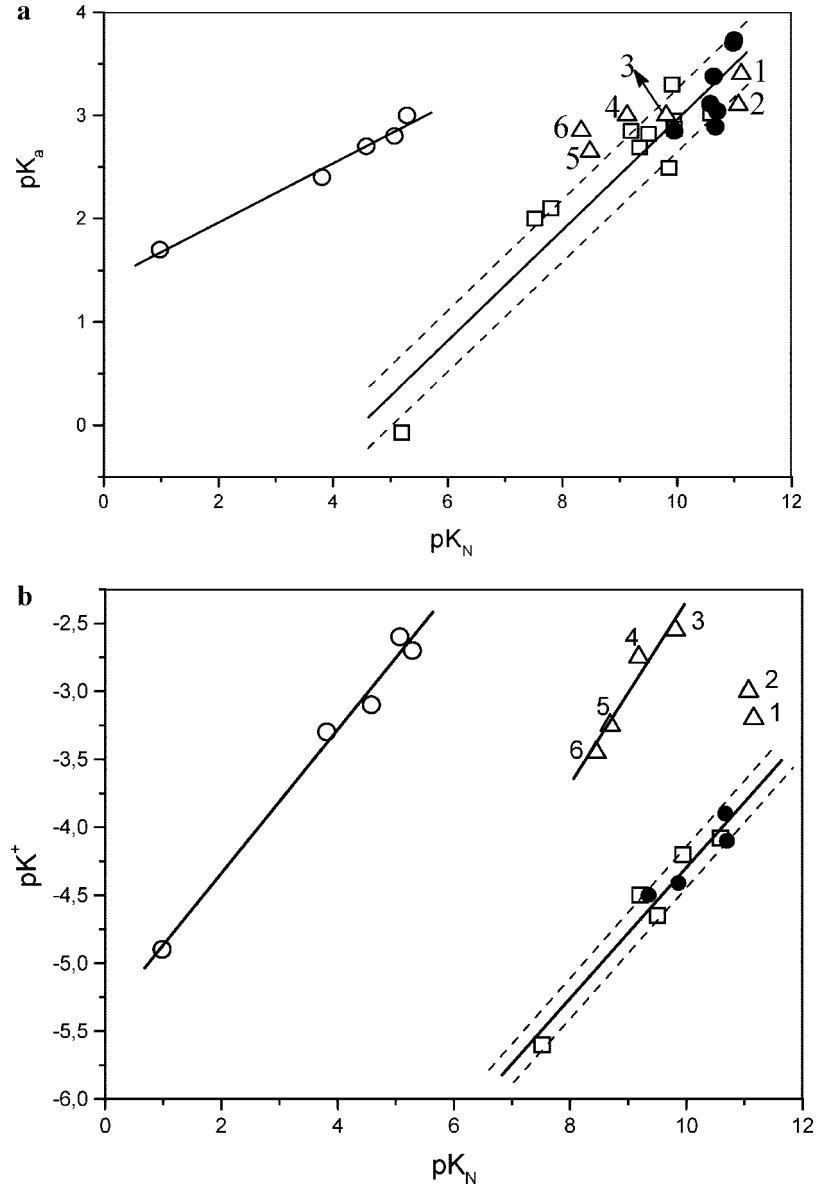
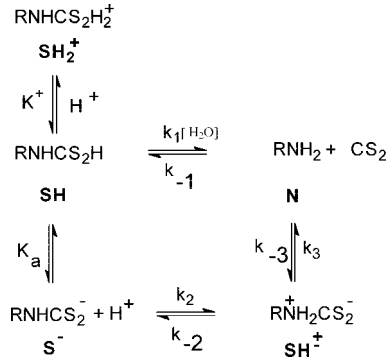


FIGURE 2. Dependence of pK_a and pK^+ of dithiocarbamic acids on the pK_N of the parent amine at 25 °C; alkDTC, in water; cycloDTC, and arylDTC, in 20% aqueous ethanol; ●, alkDTC, pK titration values; empty symbols, pK values calculated from the pH−rate profile; ○, arylDTC; □, alkDTC; △, cycloDTC, $X(C_2H_4)_2NCS_2^-$, X = **1**, CH_2; **2**, $CHCH_3$; **3**, NH; **4**, NCH_3; **5**, S; **6**, O. The dashed lines indicate the standard deviation of the line drawn considering only the alkDTC series.

SCHEME 2. Mechanistic Paths of the Acid Decomposition of Dithiocarbamates



positive charge is distributed between the Hydron-oxygen and the nitrogen, making this atom more basic.

Kinetic Solvent Isotope Effect. MorpholylDTC. The inverse kinetic solvent isotope effect of the acid decomposition of sodium morpholyl dithiocarbamate in 20% v/v EtOL/L_2O at 25 °C, 1 M L_2SO_4, μ = 1 (KCl) was $k_o^{D_2O}/k_o^{H_2O} = 1.87 \pm 0.25$. This value is much lower than those observed for alkyl and arylDTCs (Table 4) and suggests that there is a different mechanism operating in this acid decomposition.

As shown above, considering the dissociation constants of thiocarbamic acids, the reactive species of the initial state of the decomposition of the cycloDTC series is the dithiocarbamate anion, and the measured solvent isotope effect is the ratio of the specific acid catalysis rate constants k_L. The relationship $k_o = k_H K_a$ from Scheme 1 produced eq 9. Dithiocarbamic acids are weak and present low isotopic fractionation factors ($\phi_{S\text{-}L}$ = 0.40−0.46).[37] The K_a^L ratio can be calculated from eq 10 considering l = 0.69, the isotopic fractionation factor of the Hydron.[38] Consequently, for morphDTC k_D/k_H = 2.43.

TABLE 2. LFER of the Dissociation Constants of Some Dithiocarbamates at 25 °C[a]

equation	series		*n*	*r*	SD
3	alkDTC	$pK_a = (0.54 \pm 0.05)pK_N - (2.40 \pm 0.47)$	18	0.941	0.292
4	alkDTC and cycloDTC[b]	$pK_a = (0.48 \pm 0.05)pK_N - (1.76 \pm 0.49)$	24	0.896	0.336
5	arylDTC	$pK_a = (0.29 \pm 0.02)pK_N + (1.39 \pm 0.09)$	5	0.991	0.078
6	alkDTC	$pK^+ = (0.49 \pm 0.05)pK_N - (9.14 \pm 0.45)$	9	0.970	0.129
7	cycloDTC[c]	$pK^+ = (0.68 \pm 0.12)pK_N - (9.13 \pm 1.10)$	4	0.970	0.126
8	arylDTC	$pK^+ = (0.53 \pm 0.04)pK_N - (5.40 \pm 0.15)$	5	0.993	0.124

[a] AlkDTC, in water; CycloDTC and ArylDTC, in 20% aqueous ethanol. [b] $X(C_2H_4)_2NCS_2$, X = **1**, CH_2; **2**, $CHCH_3$; **3**, NH; **4**, NCH_3; **5**, S; **6**, O. Compounds **1**−**6**. [c] Compound **3**−**6**.

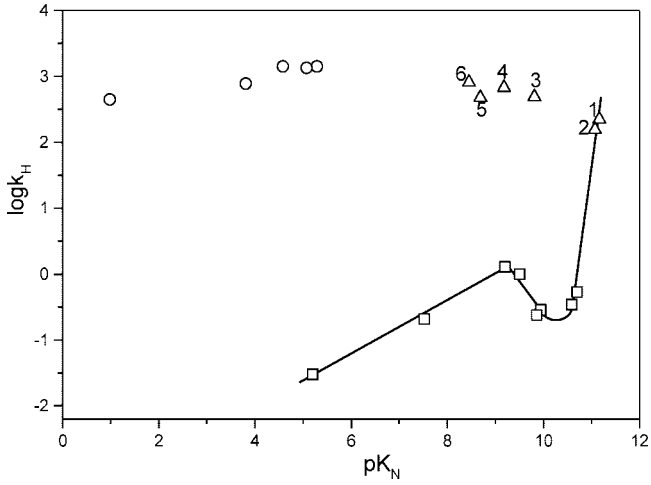


FIGURE 3. Brønsted plot of the rate constants of the specific acid catalysis and the pK_N of the leaving amine for the acid decomposition of dithiocarbamates in water at 25 °C: ○, arylDTC, in 20% aqueous ethanol; □, alkDTC, in water; △, cycloDTC, in 20% aqueous ethanol; $X(C_2H_4)_2NCS_2^-$, X = **1**, CH_2; **2**, $CHCH_3$; **3**, NH; **4**, NCH_3; **5**, S; **6**, O.

$$\frac{k_D}{k_H} = \frac{k_o^{D_2O}}{k_o^{H_2O}}\frac{K_a^H}{K_a^D} \tag{9}$$

$$\frac{K_a^H}{K_a^D} = \frac{l^3}{\varphi_{S-L}} = 1.30 \tag{10}$$

The heterocyclicDTC members of the series (X = N, CH_3-N, O, S) showed pK^+ values that correspond to parent amines that are ca. 3 p*K* units more basic. This effect has been related to water catalysis in the rate-determining step.[15,16] It was shown above that in the case of morpholonium ion **III**, the effect of the O_{morph} on the nitrogen occurs through a Hydron. It is quite reasonable to assume that the mechanism of acid decomposition of the heterocyclicDTCs occurs by the rate-determining transition states shown in Scheme 4. Mechanism **a** in Scheme 4 assumes that the initial state is the O_{morph}-protonated DTC anion with a hydrogen-bonded water molecule and that at the TS there are two concerted proton transfers: O to O and O to N. The SIE is given by eq 11 where the functions ϕ_i are the fractionation factors of the hydrogenic positions.

$$\frac{k_D}{k_H} = \left(\frac{\left(\varphi_{O-L_2}^{T_1}\right)}{\left(\varphi_{O-L_2}\right)}\right)_{sec}\left(\frac{\left(\varphi_{O-L_1-O-L_3-N}^{T_2}\right)}{\left(\varphi_{O^+-L_1}\right)\left(\varphi_{O-L_3}\right)}\right)_{pri} \tag{11}$$

The transition state for O to N Hydron transfer is

$$\mathbf{O}^{1-\chi}\text{----}\mathbf{L}\text{----}\mathbf{N}^{\chi}$$

where χ is the bond order of the bond being formed. In the initial state $\chi = 0$ and there is no SIE, while inversed SEI occurs at $\chi > 0.9$.[13,39] Since the maximum primary SEI $(k_D/k_H)_{pri}^{max} = 11.4$,[13] for morpholylDTC $\chi = 0.95$. At equilibrium, $\chi = 1$, and from eq 12 ($\phi_{O^+-L_1} = 0.69$, $\phi_{L_3-N^+} = 0.97$) the primary SEI at equilibrum is 1.41. This value implies that the secondary SEI is very close to 1.0 and consequently the primary SEI would be higher than the equilibrium value. The concerted mechanism **a** for morpholylDTC should therefore be disregarded. The stepwise mechanism **a** to **b** cannot be distinguished because the ratio $\phi_{O^+-L_3}/\phi_{O^+-L_1} = 1$.

$$\left(\frac{k_D}{k_H}\right)_{equil} = \left(\frac{\left(\varphi_{L_3-N^+}\right)}{\left(\varphi_{O^+-L_1}\right)}\right)_{pri} \tag{12}$$

Let us consider mechanism **b** in Scheme 4 where the initial state is a Hydron hydrogen-bonded to the O_{morph} and the nitrogen of the DTC anion. In this case the SEI is given by eq 13, and the secondary SEI can be estimated from eq 14 considering $\chi = 0.95$. Therefore, the primary SIE is 1.20.

$$\frac{k_D}{k_H} = \left(\frac{\left(\varphi_{O-L_1}^{T_1}\right)\left(\varphi_{O-L_2}^{T_2}\right)}{\left(\varphi_{O^+-L_1}\right)\left(\varphi_{O^+-L_1}\right)}\right)_{sec}\left(\frac{\left(\varphi_{O-L_3-N}^{T_3}\right)}{\left(\varphi_{O^+-L_1}\right)}\right)_{pri} \tag{13}$$

$$\left(\frac{k_D}{k_H}\right)_{sec} = \left(\frac{\left(\varphi_{O-L_i}\right)^2}{\left(\varphi_{O^+-L_i}\right)^2}\right)^{\chi}_{sec} = 2.02 \tag{14}$$

$$\varphi_{O-L_3-N}^{T_3} = \left(\varphi_{O^+-L_3}\right)^{1-\chi}\left(\varphi_{L_3-N^+}\right)^{\chi} \tag{15}$$

From eq 15 $\phi_{O-L_3-N}^{T_3}$ can be calculated as 0.95, and by the same procedure $\phi_{O-L_1}^{T_1} = \phi_{O-L_2}^{T_2} = 0.98$. Considering eq 13, $\phi_{O^+-L_i} = 0.72$. If the change of ϕ_{O-L} from 1.0 to 0.69 (ϕ_{O^+-L}) is proportional to the charge on the O^+-L bond, the charge shown by the Hydron is only 89% from expected as a consequence of the interaction between O-4 of the morpholyl ring and the Hydron in the initial state. The Hydron must be also weakly hydrogen-bonded to the nitrogen in the initial state because the low basicity of this atom when bound to the DTC group.[13]

Mechanism **b** is consistent with an initial state where a Hydron is hydrogen-bonded to the O_{morph} and the nitrogen, and a late transition state with the characteristic of a zwitterion.

Intramolecular Specific Acid Catalysis. The mechanism of decomposition of the heterocyclic members of the series must be similar to that proposed for morpholylDTC, considering the smooth change of reactivity shown by the Brønsted plot that is consistent with a common mechanism and the pK^+-pK_N relationship (Figure 2b) that indicates an increase of the basicity

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SCHEME 3. Mechanisms of the Acid Decomposition of Aryl and Alkyl Dithiocarbamates from Strong Basic Amines

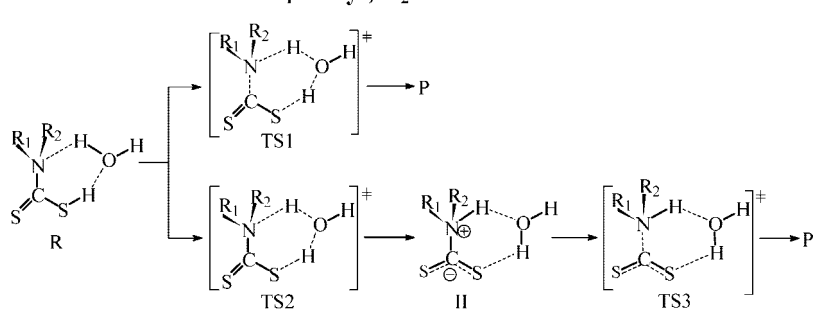


TABLE 3. Activation Parameters for Some Selected Dithiocarbamates in 20% v/v Aqueous Ethanol

R-DTC	pK_N	k_o[a] (s^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger b}$ (cal mol^{-1} K^{-1})
phenyl	4.58	2.80[c]	16.81 ± 0.74	15.10 ± 0.37	−5.74 ± 1.25
2-AmEt	7.52	20.9×10^{-4}[d]	21.14 ± 0.72	19.49 ± 0.36	−5.54 ± 1.19
piperidyl[e]	11.16	8.83×10^{-2}	19.52 ± 0.77	19.21 ± 0.38	1.03 ± 1.3
thiomorpholyl[f]	8.69	1.08	17.45 ± 0.63	14.79 ± 0.32	− 8.94 ± 1.06
morpholyl[e]	8.45	1.16	17.35 ± 1.05	14.78 ± 0.52	−8.64 ± 1.77

[a] At 25 °C. [b] Standard state 1 M, at 25 °C. [c] 0.1 M H_2SO_4, μ = 1.0 (KCl).[15] [d] In water, μ = 1.0 (KCl).[13] [e] At 3.6 M HCl. [f] At 2.4 M HCl.

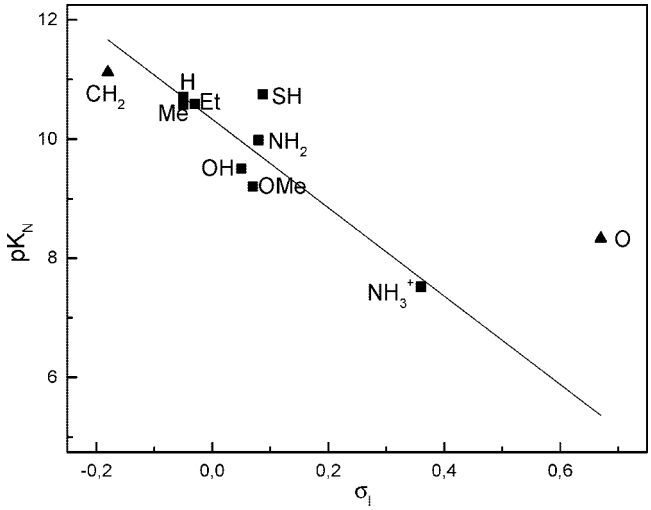


FIGURE 4. LFER of pK_N versus the inductive substituent constant σ_I for the series of 2-substituted ethylammonia X-$(CH_2)_2$-NH_3^+ (■); ▲(CH_2), piperidino; ▲(O), morpholino.

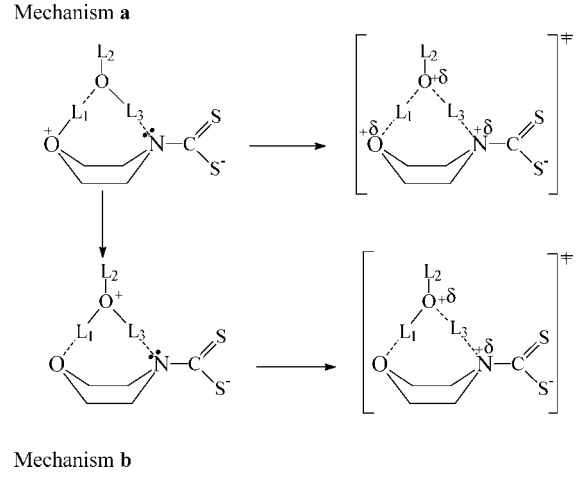
TABLE 4. Solvent Isotope Effect for the Acid Decomposition of some Dithiocarbamates at 25 °C.

R	k_o^D/k_o^H
ethyl	3.05 ± 0.10[a]
phenyl	2.51 ± 0.04[b]
morpholyl	1.87 ± 0.25

[a] Reference.13 [b] Reference.15

of nitrogen by more than 3 p*K* units in the transition state due to the strain of the N−H hydrogen bond of the boat conformation. That magnitude is the same observed for the increase of pK_N observed for morpholine when compared to the alkyl series (Figure 4). This step is an intramolecular specific acid catalysis as has been observed in dithiocarbamates for acids that are similar to, or more acid than, Hydron.[14]

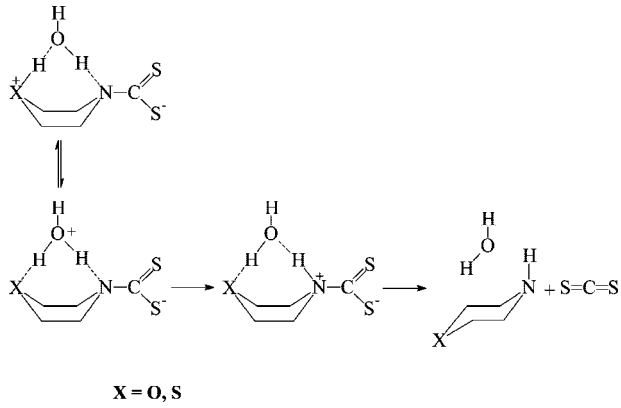
SCHEME 4. Kinetic Solvent Isotope Effect and Mechanism of the Acid Decomposition of Morpholyl Dithiocarbamate



The basicity of the heteroatom in the series varies by about 12 p*K* units and the nature of the hydrogen bond X···H···O^+ may change from a protonated X^+−H for piperazyl and *N*-methylpiperazyl to H−O^+ for morpholyl and thiomorpholyl. As mentioned above, it is possible that mechanism **a** (Scheme 4) proceeds stepwise through **b** for the N-protonated members.

With the present results we cannot distinguish between a stepwise formation of the zwitterion followed by the expulsion of the DTC moiety (Scheme 5) and a concerted process of N-protonation and C−N bond breakage. However, perusal of the activation parameters of phenylDTC and also those of morpholyl and thiomorpholylDTC shows that they have the same enthalpy of activation of 15 kcal mol^{-1} (Table 3), although the steric requirements for the cyclic compounds are higher ($\Delta S^{\ddagger}$ −9 cal mol^{-1} K^{-1}) as a consequence of the strained boat conformation.

SCHEME 5. Mechanism of Acid Decomposition of the Heterocyclic Members of the Series of Analogues of Piperidine Dithiocarbamate



X = O, S

Conclusions

It is proposed that the acid cleavage of a series of analogues of piperidine dithiocarbamate $X(C_2H_4)_2NCS_2^-$ (X = CH_2, $CHCH_3$, NH, NCH_3, S, O) occurs through two mechanisms. Piperidine and 4-methylpiperidine dithiocarbamates decompose by intramolecular water-catalyzed S-to-N proton transfer through a rate determining transition state whose structure is close to a zwitterionic intermediate, followed by a fast expulsion of the dithiocarbamate moiety.

The heterocyclic members of the series (X = NH, CH_3N, O, S) decompose from their dithiocarbamate anion in the boat conformation by specific catalysis of the Hydron hydrogen-bonded to the heteroatom. The N-protonated zwitterion intermediate expels the DTC moiety in a fast step. Alternatively, the N-protonation may occur concerted with the DTC expulsion.

Experimental Section

Materials. All reagents were of analytical grade and were used without further purification, except when indicated. Deuterium oxide (Sigma, 99.8% D) and deuterated ethanol (Aldrich, 99.5% D) were previously deoxygenated. Deuterated sulfuric acid (99.5% D) was from Aldrich. The deuterium content of the kinetic solution was calculated from the NMR spectrum using acetone as internal standard. Morpholine, p.a. 99%, Riedel-de Haën, was left for 2 h over KOH pellets and distilled under vacuum. Isopropanol was left over CaO overnight and subsequently distilled (bp 82.4 °C). The distilled water employed was deionized and deoxygenated.

Sodium Piperidyl Dithiocarbamate and Analogues. All of these salts were obtained by adding 20 mmol of the corresponding amine diluted in diethyl ether, 1.5 mL (24.8 mmoles) of carbon disulfide, and 1 g (25 mmoles) of NaOH in an erlenmeyer flask capped with a septum. The mixture was magnetically stirred for 4 h (X = CH_2, O) or 24 h (X = S, NH, CH_3N) at room temperature. The product was crystallized in isopropanol, filtered, washed with cold isopropanol and acetone, and dried under vacuum over phosphorus pentoxide.

Piperidyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 262 and 280 nm. Elemental analysis: calculated (experimental) for $C_6H_{10}NS_2Na.2H_2O$: C 32.9 (32.2), H 6.4 (6.7), N 6.4 (6.0), S 29.2 (29.9). ^{13}C NMR (D_2O), δ(ppm): 204.5 (CS_2), 54.5 (C-2), 27.2 (C-3), 23.2 (C-4), 25.0 (C-5), 52.4 (C-6). ^1H NMR (D_2O), δ(ppm): 3.7 (4H), 6.3 (6H), 6.9 (H_2O). IR: 518 cm^{-1} (SCS), 616 cm^{-1} (C−S), 854 cm^{-1} (C═S), 966 cm^{-1} (CSS), 1070 cm^{-1} (C−N), 1130 cm^{-1} (C═S), 1222 cm^{-1} (C−N), 1422 cm^{-1} (−N═C−S−), 1470 cm^{-1} (−N−C═S), 1624 cm^{-1} (C═N), 2850 cm^{-1} and 2930 (C−H).

Morpholyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 262 and 286 nm. Elemental analysis: calculated (experimental) for $C_5H_8NOS_2Na\cdot1.5H_2O$: C 28.3 (28.5), H 5.2 (5.9), N 6.6 (6.6), S 30.2 (28.5). ^{13}C NMR (D_2O), δ(ppm): 210.7 (CS_2), 67.5 (C-2), 39.9 (C-3), 39.5 (C-5), 52.8 (C-6). IR: 538 cm^{-1} (SCS), 635 cm^{-1} (C−S), 891 cm^{-1} (C═S), 979 cm^{-1} (CSS), 1022 cm^{-1} (C−N), 1112 cm^{-1} (C═S), 1215 cm^{-1} (C−N), 1417 cm^{-1} (−N═C−S−), 1461 cm^{-1} (−N−C═S), 1624 cm^{-1} (C═N), 2851 cm^{-1} and 2898 (C−H).

4-Methylpiperidyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 262 and 280 nm. ^{13}C NMR (D_2O), δ(ppm): 207.1 (CS_2), 53.5 (C-2), 35.2 (C-3), 31.6 (C-4), 22.2 (CH_3). IR: 678 cm^{-1} (SCS), 866 cm^{-1} (CSS), 999 cm^{-1} (C═S), 1132 cm^{-1} (C−N), 1448 cm^{-1} (−N═C−S−), 1648 cm^{-1} (C═N).

Thiomorpholyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 262 and 286 nm. ^{13}C NMR (D_2O), δ(ppm): 210.3 (CS_2), 55.4 (C-2,6), 28.4 (C-3,5). IR: 563 cm^{-1} (SCS), 615 cm^{-1} (C−S), 924 cm^{-1} (CSS), 997 cm^{-1} (C−N), 1138 cm^{-1} (C═S), 1185 cm^{-1} (C−N), 1410 cm^{-1} (−N═C−S−), 1459 cm^{-1} (−N−C═S), 1624 cm^{-1} (C═N).

Piperazyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 264 and 286 nm. ^{13}C NMR (D_2O), δ(ppm): 210.9 (CS_2), 51.8 (C-2,6), 45.0(C-3,5). Substitution on the two nitrogens would have made four magnetically equivalent carbons. IR: 553 cm^{-1} (SCS), 655 cm^{-1} (C−S), 897 cm^{-1} (C═S), 1000 cm^{-1} (CSS), 1148 cm^{-1} (C═S), 1208 cm^{-1} (C−N), 1417 cm^{-1} (−N═C−S−), 1459 cm^{-1} (−N−C═S), 1616 cm^{-1} (*C*═N).

4-Methylpiperazyl Dithiocarbamate, Sodium Salt. UV−vis (H_2O): λ_{max} 260 and 286 nm. ^{13}C NMR (D_2O), (ppm): 207.9 (CS_2), 43.3 (C-2,6), 51.8(C-3,5), 49.8(CH_3). IR: 594 cm^{-1} (SCS), 847 cm^{-1} (C═S), 998 cm^{-1} (CSS), 1142 cm^{-1} (C═S), 1465 cm^{-1} (−N═C−S−), 1693 cm^{-1} (C═N).

Kinetics. The rate of disappearance of the dithiocarbamates was followed at λ_{max} for more than 4 half-lives, and the first-order rate constants (k_{obs}) for the pH−rate profiles were calculated by the spectrophotometer software from the average of at least three runs with correlations no less than 0.99. The acidity ranged from H_o^X − 5 to pH 5. For acid concentrations higher than 0.01 M the acidity was calculated from $H_o^X = -(X + \log C_{H^+})$, where X is the excess acidity function and C_{H^+} is the acid molarity.[40,41] The ionic strength of the runs at pH > 0 was kept constant at 1.0 by addition of KCl. Buffers were used for runs at pH 5−3. No general acid catalysis was observed for formate buffer at pH 3 in the range of 0.05−0.5 M for piperidyl-, 4-methylpiperidyl-, and thiomorfolyl dithiocarbamate.

Kinetic Solvent Isotope Effect. The rate constant of the acid decomposition of sodium morpholyl dithiocarbamate in 20% v/v EtOD/D_2O at 25 °C, 1 M D_2SO_4, μ = 1 (KCl), was k_o = 1.94 ± 0.18 s^{-1}. The deuterium content of the acid solution was 89.97%, measured by NMR. Linear extrapolation gave k_o = 2.15 ± 0.20 s^{-1} at 100% D. In 20% v/v aqueous EtOH k_o was 1.16 ± 0,05 s^{-1}, and in consequence the inverse kinetic solvent isotope effect was $k_o^{D_2O}/k_o^{H_2O}$ = 1.87 ± 0.25.

Activation Parameters. Activation parameters were calculated from k_o values in the range of 15.0−30.0 °C by least-squares fitting to the Eyring equation (eqs 16 and 17).

$$\ln \frac{k_i}{T_i} = \left(-\frac{\Delta H^{\ddagger}}{R}\right)\frac{1}{T_i} + \ln \frac{k_B}{h} + \frac{\Delta S^{\ddagger}}{R} \qquad (16)$$

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \qquad (17)$$

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