Rates of Hydrogen Exchange in Thioamides

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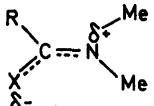
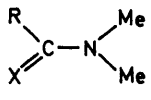
The rates of acid- and base-catalysed proton exchange in *N*-methylthioacetamide and of protonation of *NN*-dimethylthioacetamide have been measured in aqueous solution by using n.m.r. line-broadening techniques. *N*-Methylthioacetamide shows an increase of *ca.* 10^3-fold in the rate constant for hydroxide-catalysed exchange, and a 10-fold decrease in the rate constant for acid-catalysed exchange, relative to *N*-methylacetamide. Both results are consistent with a considerably greater degree of polarisation in the thioamide. The rate of *N*-protonation of *NN*-dimethylthioacetamide is *ca.* 50 times less than the rate of acid-catalysed proton exchange of *N*-methylthioacetamide. It is suggested that proton exchange in the latter may proceed *via* the thionium ion.

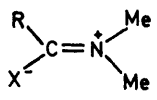
THE barrier to internal rotation about the central C–N bond is considerably higher in *NN*-dialkylthioamides than in the corresponding *NN*-dialkylamides.[1-3] This may be reasonably attributed to a higher double-bond character of the CN bond in thioamides. According to valence bond theory, this may be described in terms of



(1)



(1a)



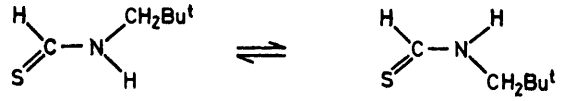
(1b)

X = S or O

a greater contribution from polar resonance structures, as in (1b) (for *NN*-dimethylamides). The higher polarity and polarisability of the thioamides, as reflected in their spectroscopic properties and their considerably higher dipole moments,[4] are also consistent with this explanation.

Increased polarity of the thioamides should also affect their acid–base properties, in particular, the rates of acid- and base-catalysed proton exchange of NH-containing thioamides. Thus, deprotonation of the NH group should be facilitated in thioamides relative to amides, and the rates of protonation of the NH group should be decreased. Following earlier work[5] on *N*-methylacetamide, factors influencing rates of acid- and base-catalysed exchange of the NH group protons of *N*-alkylamides have been studied extensively.[6,7] Rates of proton exchange for the corresponding *N*-alkylthioamides have not been reported. Walter and his co-workers[8,9] have, however, shown that for thioamides the rate of rotation about the CN partial double bond is increased in dilute acid, and that the isomerisation of *N*-neopentylthioformamide (Scheme) is acid-catalysed, providing evidence for kinetically important *N*-protonation of thioamides in dilute acid solution.

In the present paper we report the results of an n.m.r. study of the rates of acid- and base-catalysed proton exchange of *N*-methylthioacetamide and the acid-catalysed internal rotation of *NN*-dimethylthioacetamide. The results are compared with those of earlier studies on the corresponding acetamides.



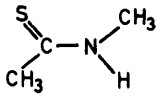
SCHEME

EXPERIMENTAL AND RESULTS

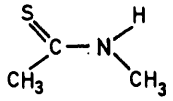
Materials.—*N*-Methyl- and *NN*-dimethyl-thioacetamide were prepared from the corresponding amides by reaction with phosphorus pentasulphide,[10] and purified by vacuum sublimation.

Rate Measurements.—Spectra were recorded on a JEOL 60 MHz n.m.r. spectrometer with a probe temperature of 30.7 (±0.5) °C.

(i) N-*Methylthioacetamide.* In non-polar solvents, *N*-methylthioacetamide exists predominantly (97%)[10] in conformation (2a). In the present study involving dilute aqueous solutions of the amide (≤0.1M) we obtained evidence for only one isomer, presumably (2a). In the pH



(2a)



(2b)

range *ca.* 2—4 the *N*-methyl signal appears as a doublet [*J* 4.95 (±0.1) Hz] as a result of spin–spin interactions with the adjacent amide proton. On an expanded scale it was possible to resolve the signals into two quartets (due to coupling with the *C*-methyl protons) with *J* 0.77 (±0.05) Hz. In earlier studies involving amide protonation or rotation, long-range coupling has been allowed for by using an effective linewidth of the magnitude of the quartet splitting[5,6,11-13] in standard equations for the exchange broadening of a doublet,[14] or avoided by using an amide

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[8] W. Walter and E. Schaumann, *Chem. Ber.*, 1971, **104**, 3361.
[9] W. Walter, M. Franzen-Sleveking, and E. Schaumann, *J.C.S. Perkin II*, 1975, 528.
[10] J. Sandström and B. Uppström, *Acta Chem. Scand.*, 1967, **21**, 2254.
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[12] T. Schleich, B. Rollefson, and P. H. von Hippel, *J. Amer. Chem. Soc.*, 1971, **93**, 7070.
[13] B. G. Cox and P. De Maria, *J.C.S. Perkin II*, 1975, 942.
[14] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Spectroscopy,' McGraw-Hill, New York, 1959, ch. 10.

with a fully deuteriated *C*-methyl group.[3] The former procedure has been shown to give acceptable results provided that the exchange broadening of the multiplet components is greater than the multiplet splitting.[11] However, in the present case, because the coupling constant with the amide proton is only *ca.* 6 times that with the *C*-methyl protons, we have analysed the spectra by using equations for the exchange broadening of a pair of quartets. Comparison of the results obtained by using different equations shows good agreement at the coalescence point, but at other exchange rates, values determined from line-shape parameters such as the half-width beyond coalescence, or ratio of maximum to minimum height before coalescence, can be in error by more than 30% when equations for the collapse of a doublet are used.[15] The dependence of the peak separation upon the exchange rate is, however, essentially the same for the two sets of equations.

The base-catalysed exchange rate of the NH proton was determined in acetate buffers. As the pH increases above 4, the *N*-methyl signals broaden, coalesce, and finally sharpen to give a single quartet by pH 6.8. Further increase in pH has no effect on the spectrum, which remains unchanged even in strongly basic solutions containing up to 1M-sodium hydroxide. However, at constant buffer ratio in acetate, phosphate, and imidazole buffers there was a general broadening of the whole spectrum when the base concentration was increased above *ca.* 0.02M (depending upon the buffer). This could be explained by the formation of a weak complex between the thioamide and the base, which would have the effect of reducing the correlation time of the thioamide, thus increasing the natural line-widths of the signals.[16] Quantitative measurements were all made in dilute buffer solutions ($\leqslant$0.02M-acetate) where there was no evidence of this effect. Below this concentration, the exchange rates were independent of the buffer concentration at constant buffer ratio.

Table 1 lists results obtained in acetate buffers. The rate constants reported include a statistical factor of 2 to allow for the fact that there is a probability of 1/2 of the on-coming proton having the same spin as the departing proton. The hydroxide concentrations in the various buffers were calculated from the known acidity constant of

TABLE 1

Rates of exchange of the amide proton of *N*-methylthioacetamide in acetate buffers [a] at 30.7 ($\pm$0.5) °C

[OAc$^-$]/ mol dm^{-3}	[HOAc]/ mol dm^{-3}	10^9[OH$^-$] [b]/ mol dm^{-3}	k_e [c]/ s^{-1}	k [d] (calc.)/ s^{-1}
0.01	0.015	0.590	2.5	2.8
0.01	0.01	0.885	5.6	4.2
0.01	0.007	1.27	6.0	6.1
0.02	0.01	1.77	9.0	8.5
0.01	0.003	2.95	14.3	14.1
0.01	0.002	4.43	22.0	21.3
0.01	0.001	8.85	37.0	42.5

[a] Ionic strength 0.1 with NaCl. [b] Calculated by using the known K_a of acetic acid (1.74×10^{-5} mol dm^{-3}) at 30.7 °C (ref. 17). [c] Obtained from n.m.r. measurements on the N·CH$_3$ signal, including a statistical factor of 2 (see text). [d] k(calc.) = k_{OH}[OH$^-$], with $k_{OH} = 4.8 \times 10^9$ mol^{-1} dm^3 s^{-1}.

acetic acid at 30.7 °C.[17] Included in the Table are results calculated according to equation (1) with $k_{OH} = 4.8 \times 10^9$

$$k_e = k_{OH}[OH^-] \quad (1)$$

dm^3 mol^{-1} s^{-1}, where k_e/s^{-1} is the observed first-order rate constant for the exchange reaction. The value of $k_{OH} = 4.8 \times 10^9$ dm^3 mol^{-1} s^{-1} may be compared with earlier values for *N*-methylacetamide of 5.2×10^6 (21 °C) [5] and 4.6×10^6 dm^3 mol^{-1} s^{-1} (25 °C).[7]

The exchange rate of the NH protons was also measured in perchloric acid solutions. In dilute acid solution the exchange rate was proportional to the hydrogen ion concentration [equation (2)], but at higher acid concentrations

$$k_e = k_H[H^+] \quad (2)$$

(>1M) the rate passed through a maximum, as has been observed in studies of the rates of protonation of amides.[11,18,19] The rate constants quoted for the reactions in the concentrated acid solutions are less reliable, as it has been assumed that the coupling constants are independent of the acid concentration. Measurements in concentrated electrolyte solutions in the absence of added acid showed the coupling constants to be dependent upon electrolyte concentration. However, as the variation depended in both sign and magnitude upon the particular electrolyte used, we could see no satisfactory way of allowing for this effect in the concentrated acid solutions. The effects were found to be negligible at electrolyte concentrations below 1M.

Table 2 lists the results obtained in the perchloric acid

TABLE 2

Rates of exchange of the amide proton of *N*-methylthioacetamide in perchloric acid solutions at 30.7 ($\pm$0.5) °C

[HClO$_4$]/mol dm^{-3}	k_e [a]/s^{-1}	k [b](calc.)/s^{-1}
0.073 8	3.1	3.4
0.123	6.7	5.7
0.246	10.0	11.3
0.369	22.0	17.0
0.615	29.0	28.3
0.80 [c]	34.0	36.8
1.23	52	
2.46	50	
4.92	21	

[a] Obtained from n.m.r. measurements on the N·CH$_3$ signal, including a statistical factor of 2 (see text). [b] k(calc.) = k_H[H$^+$] with $k_H = 46$ dm^3 mol^{-1} s^{-1}. [c] Hydrochloric acid.

solutions, together with values in dilute acid solution calculated from equation (2) with $k_H = 46$ dm^3 mol^{-1} s^{-1}. This value of k_H may be compared with values reported for *N*-methylacetamide of 380 (23 °C) [5] and 360 dm^3 mol^{-1} s^{-1} (25 °C).[7]

(ii) NN-*Dimethylthioacetamide*. The rates of *N*-protonation of *NN*-dimethylthioacetamide were obtained from the rates of rotation about the central CN bond of the amide,[11,18,19] and include a statistical factor of 2 to convert rates of rotation to rates of protonation. There was no observable rotation at acid concentrations below *ca.* 1.2M. At this concentration, the chemical shift difference of the protons in the two *N*-methyl groups was 5.3 ($\pm$0.1) Hz. It was assumed that this value remained constant as the acid concentration increased. The signals were also broadened owing to long-range coupling, the effect being different for the two *N*-methyl groups. In this case,

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[16] P. Laszlo and P. Stang, ' Organic Spectroscopy,' Harper and Row, New York, 1971, ch. 5.

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however, equations for the exchange broadening of a doublet were used to analyse the spectra. This was partly because the signals could not be properly resolved, and partly because in view of the assumptions concerning the effect of the very concentrated (up to 7M-$HClO_4$) acid solutions on the natural linewidths and the chemical shift differences of the protons, it was thought that the use of the more complicated equations to analyse the spectra would not lead to an increase in the reliability of the results. The very high concentrations of acid required to produce sufficiently rapid rotation make quantitative interpretation of the results very difficult in any case. The results are listed in Table 3. They refer to freshly prepared solutions

TABLE 3

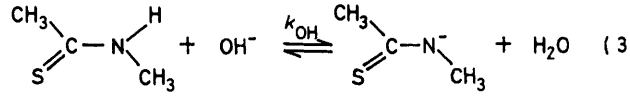
Rates of protonation of *NN*-dimethylthioacetamide in perchloric acid solutions at 30.7 (±0.5) °C

$[HClO_4]$/mol dm^{-3}	1.23	1.84	2.46	3.69	7.38
k_e/s^{-1}	≤1	10.3	77	110	113

of the amide in the perchloric acid media, as the signals showed increasing broadening.

DISCUSSION

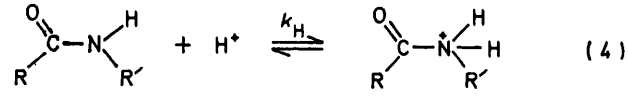
The most striking effect on the protolysis of amides on replacing the C=O group by C=S is the large increase in the base-catalysed proton exchange rate. Thus, *N*-methylthioacetamide is *ca.* 1 000 times more reactive towards hydroxide-catalysed proton exchange than *N*-methylacetamide. The observed kinetics are consistent with the rate-determining step being the formation of amide anion [equation (3)], as has been assumed



(3)

for *N*-alkylamides.[5-7] In this case however, the value of k_{OH} (4.8×10^9 dm^3 mol^{-1} s^{-1}) approaches that expected for a diffusion-controlled reaction. In order to achieve a similar rate increase in substituted *N*-methylacetamides, it is necessary to go to the trichloro- or trifluoroamide (k_{OH} 1.7×10^9 and 4.1×10^9 dm^3 mol^{-1} s^{-1}, respectively, at 25 °C).[7]

Although the base-catalysed exchange reaction appears to be relatively straightforward, with the only sensible mechanistic possibility being the removal of the NH proton by the base, a number of different possibilities for the acid-catalysed exchange reaction have been suggested.[5,9,20] However, the evidence available [4,9,20] supports the original suggestion [5] that the exchange proceeds simply by protonation on nitrogen [equation (4)], despite the greater thermodynamic

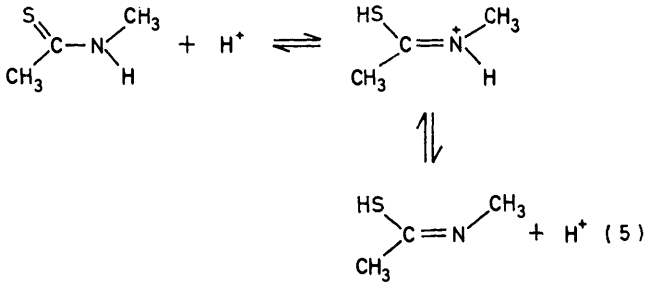


(4)

basicity of the carbonyl oxygen. This mechanism also accounts for the acid-catalysed rotation about the central CN bond, rotation being essentially free in the *N*-protonated species. Walter and his co-workers [9] found that a similar mechanism could account for the acid-catalysed isomerisation of *N*-neopentylthioformamide,[9] the isomerisation again requiring rotation about the central CN bond.

A comparison of the rates of rotation of *NN*-dimethylthioacetamide in acid solution (Table 3) with results obtained earlier for *NN*-dimethylacetamide [11,18,19] shows the latter to be *ca.* 500 times more reactive in dilute acid solution. Thus the rate of rotation of *NN*-dimethylacetamide is linearly dependent upon the acid concentration (up to *ca.* 1M-HCl) [19] with $k_H = 400$ dm^3 mol^{-1} s^{-1} at 29 °C,[11] which may be compared with a value of $k_e \leqslant 1$ s^{-1} in 1.2M-acid for *NN*-dimethylthioacetamide (Table 3). This is again indicative of considerably greater polarisation of the thioamide. The levelling off of the rate in concentrated acid solution may be explained in terms of the formation of appreciable amounts of the thermodynamically more stable,[4] but kinetically inert, thionium ion in these solutions. Similar behaviour has been observed with *NN*-dimethylamides.[18,19]

The acid-catalysed proton exchange of *N*-methylthioacetamide is also slower than that of *N*-methylacetamide, but the effect is much smaller (*ca.* 10-fold). It is also noticeable that in 1.2M-$HClO_4$, where the formation of the thionium ion should not be important,[4] the rate of proton exchange of *N*-methylthioacetamide is *ca.* 50 times that of protonation of *NN*-dimethylthioacetamide. This contrasts sharply with the corresponding amides, where there is less than a factor of 2 between the *N*-methyl- and *NN*-dimethyl-amides. This suggests that an alternative mechanism involving the thionium ion [equation (5)], that could lead to proton exchange in



(5)

N-methylthioacetamide (but not to rotation in *NN*-dimethylthioacetamide) should not be ruled out. Such a mechanism appears not to be important in the proton exchange of amides,[20] but the considerable shift of electron density away from the nitrogen in thioamides, as shown by the results of the present and earlier [4] studies, should favour the operation of such a mechanism.

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