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NMR Spectra and Conformations of Some Simple N-Methylthioamides

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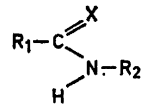
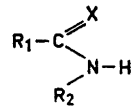
It can be shown by the magnitude of the coupling constants across the C—N bond and by the effect of dilution with benzene that N-methylthioformamide and N-methylthioacetamide occur mainly in the *trans* forms, though small amounts of the *cis* forms can also be detected. In N-methylthiopropionamide, N-methylthioisobutyramide, and N-methylthiopivalamide only one form has been observed, and steric considerations and chemical shift values indicate that this is the *trans* form.

Using Raman and infrared spectra, Mizushima [1] could show that N-methylacetamide exists mainly if not exclusively in the conformation with the methyl groups in *trans* position (Ia, $R_1 = R_2 = CH_3$, X = O). La Planche and Rogers [2] investigated the conformations of a series of N-monosubstituted



Ia



Ib

amides by NMR technique. They found that in N-alkylformamides (I, $R_1 = H$, X = O) both conformations existed in equilibrium with the molar ratio (Ia/Ib) varying from 11.5:1 ($R_2 = CH_3$) to 4.6:1 ($R_2 = t\text{-}C_4H_9$). In the higher amides (I, $R_1 = CH_3$ and higher alkyls) only the spectra of the *trans* forms (Ia) could be observed. The configurations were established by the shifts on dilution with benzene and by the magnitude of the coupling constants.

Recently, Barker and Boudreaux [3] have reported that N-methylacetamide in water contains 3 % of the *cis* isomer, a result which we have been able to confirm.

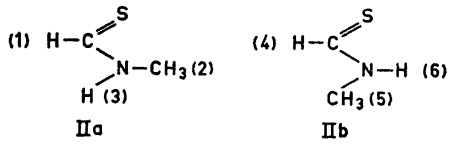
The reason for the preference for the *trans* configuration has been much discussed, but no generally acceptable explanation seems to have been pre-

sented. The distribution is particularly unexpected in molecules like N-t-butylformamide, where steric factors should be anticipated to favour the *cis* form more distinctly. The phenomenon may be related to the *trans* arrangement of esters [4] and possibly also to the preferred *gauche* conformation in isobutyraldehyde, in which one methyl group and the carbonyl group are eclipsed.[5]

It could be expected that in the corresponding thioamides the greater van der Waals radius of sulphur should shift the equilibrium in favour of the *cis* configuration. In agreement with this, Suzuki [6] interpreted the infrared spectrum of N-methylthioformamide (II) in such a way that the pure liquid contains a small amount of the *cis* form, though larger than the amount in N-methylformamide. In N-methylthioacetamide only one form was observed.

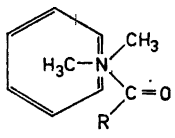
In connection with current investigations of barriers to internal rotation in N,N-dimethylthioamides [7,8] it was desirable to know more about the steric requirements of the sulphur atom and of the dimethylamino group, and it was expected that useful information could be obtained from the NMR spectra of simple N-methylthioamides.

N-Methylthioformamide (II). This compound gave well separated spectra for the CH protons of the *trans* (IIa) and *cis* (IIb) forms in deuterochloroform, benzene, and water, whereas the formyl proton signal of the *cis* form partly



overlapped the NH signal in the pure liquid and in acetone solution (Table 1). In all cases a *trans*/*cis* ratio in the range 6.9:1—7.5:1 was observed, corresponding to a difference in free energy between the *cis* and the *trans* forms of about 1.2 kcal/mole. Mizushima [9] has suggested that the preference for the *trans* configuration is due to its greater ease of forming linear hydrogen bonded chains, but the rather constant ratio in several solvents including water, where chain association is very unlikely, indicates that this is not an important factor.

The assignment of the set of strong signals to the *trans* form (IIa) can be made by aid of the shift on dilution with benzene and by the coupling constants. Hatton and Richards [10] have shown that in N,N-dimethylamides both methyl signals are shifted upfield on dilution with aromatic solvents, but that the signal corresponding to the methyl group which is *trans* to the carbonyl group is shifted most strongly. This effect is ascribed to the structure of the collision



complexes, in which the methyl group *trans* to the carbonyl group is assumed to lie above the center of an aromatic ring and the other methyl group outside the ring (III). The effect seems to be rather general and to apply to thioamides as well.[11] In the present case the minor signal is shifted most strongly on dilution with benzene (Table 1).

Table 1. Chemical shifts *versus* tetramethylsilane as internal standard (for water as solvent external standard).

Compound	Solvent	ν_{CH}	ν_{NCH_3}[a]	*trans/cis*
IIa	—	570	189	6.9
IIb	—	552	162	
IIa	$CDCl_3$	566.5	191	7.5
IIb	$CDCl_3$	549	193.5	
IIa	$(CD_3)_2CO$	568	188	7.5
IIb	$(CD_3)_2CO$	553	190	
IIa	C_6H_6[b]	555.5	167	6.9
IIb	C_6H_6[b]	528.5	142	
IIa	H_2O	585	211.5	6.9
IIb	H_2O	571	213.5	
		$\nu_{C\cdot CH_3}$		
N-Methylthioacetamide (*trans*)	$CDCl_3$	152	190	
D:o (*trans*)	CCl_4	151.5	187	38
D:o (*cis*)	CCl_4	147	183	
D:o (*trans*)	C_6H_6[c]	143	175.5	36
D:o (*cis*)	C_6H_6[c]	130	148.5	
N-Methylthiopropionamide (*trans*)	$CDCl_3$		190.5	
D:o (*trans*)	CCl_4		187.5	
N-Methylthioisobutyramide (*trans*)	$CDCl_3$		191	
D:o (*trans*)	CCl_4		188.5	
N-Methylthiopivalamide (*trans*)	$CDCl_3$		192	
D:o (*trans*)	CCl_4		189	

[a] Center of doublet. [b] Molar fraction of (II) 0.20. [c] Molar fraction of (II) 0.33.

Both conformers (IIa) and (IIb) should give ABX_3 or APX_3 spectra, but due to rapid exchange the couplings with the NH protons are not manifested unless special precautions are taken. Normally, the formyl proton signals appear as quartets and the methyl proton signals as doublets (Fig. 1). The coupling constant is 1.1—1.2 cps in the major and 0.5—0.7 cps in the minor component. It is generally accepted[12,13] that the *trans* coupling is stronger than the *cis* coupling, and thus the major component in this case should be the *trans* form. J_{12} and J_{45} are the only coupling constants which can be obtained from the spectra in pure organic solvents and in water. However, the rate of exchange of the NH proton can be considerably diminished by adding a small quantity of acetic acid to a solution in an organic solvent or by buffering a

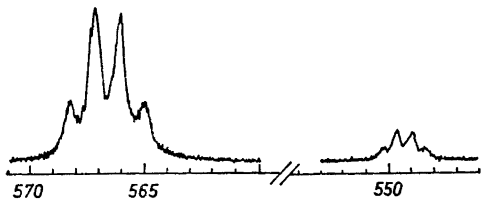


Fig. 1a. Formyl proton quartets of (IIa) and (IIb) in $CDCl_3$.

Fig. 1b. N-Methyl proton doublets of (IIb) and (IIa) in $CDCl_3$.

water solution to the pH range 0.5—3.5. As would be expected, lowering the temperature also slows down the exchange rate. In this way both J_{13} and J_{23} could be observed (7.3 and 5.5 cps, respectively, in water, 6.3 and 5.0 cps in benzene), though all signals were still considerably affected by the exchange. In this *cis* form only J_{56} could be observed (6.0 cps in water), since the formyl proton signal was too low and broadened by exchange to show fine structure. The distortion of the methyl proton signals in the *trans* form is rather un-

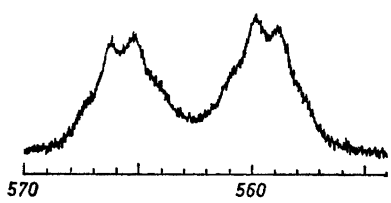


Fig. 2a. Formyl proton signals of (IIa) in 0.2 N acetic acid in benzene at + 10°C.

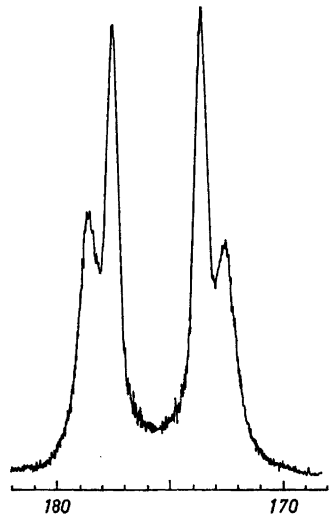


Fig. 2b. N-Methyl proton signals of (IIa) under the same conditions.

expected (Fig. 2b). It seems as if only the outer components of the quartet are affected by the exchange. The formyl proton double quartet also shows considerable broadening, but the exchange seems to affect all eight signals equally (Fig. 2a).

The constants for coupling across the C—N bond in N-methylthioformamide are generally higher than the corresponding constants in formamide and its N-methyl derivatives (Table 2). It is tempting to relate this to the stronger

Table 2. Coupling constants in cps for N-methylthioformamide, formamide, and its N-methyl derivatives. For numbering, see (IIa) and (IIb).

	Thioamide	Amide	
J_{12}	1.1—1.2	0.8—0.9 [a],	1.0 ± 0.1 [b]
J_{13}	6.3—7.3	2.1—2.3 [a]	
J_{23}	5.0—5.5	4.9—5.0 [a, b]	
J_{45}	0.6—0.7	0.4 [c]	
J_{46}	?	13.4 [d]	
J_{56}	6.0	4.7 [d]	

[a] In water, Ref. 14. [b] Neat, Ref. 15. [c] Ref. 13. [d] Neat, Ref. 16.

mesomeric interaction in the thioamides, which leads to higher C—N bond order and also to a higher barrier to rotation.[7] This effect is also in harmony with the observation by Fraenkel and Franconi [17] and by Randall and Baldeschwieler [14] that the coupling constants in amides increase on protonation. It is known that protonation occurs on the oxygen atom, which increases the electron attracting power of the oxygen atom and thereby its capacity for mesomeric interaction with the nitrogen atom.

N-Methylthioacetamide. In carbon tetrachloride and in benzene solution this compound shows two spectra, corresponding to the *trans* and *cis* forms in a ratio of about 37:1, quite similar to that in N-methylacetamide.[3] This corresponds to a difference in free energy between the *cis* and *trans* forms of about 2.2 kcal/mole. If it is assumed that the non-bonded van der Waals interactions N—H···S, N—H···CH_3 and C—H···CH_3—N make no contribution to the free energies of the molecules, which is supported by molecular models and current radii of interaction, a *cis* C—CH_3···CH_3—N interaction should increase the energy of the molecule by about 1 kcal/mole. Such an interaction should also increase the energy of the planar or nearly planar ground state of N,N-dimethylthioacetamide relative to that of N,N-dimethylthioformamide. In the transition state of the rotation around the C—N bond no such interaction should be present in either molecule, and consequently this effect should lower the barrier of N,N-dimethylthioacetamide relative to that of N,N-dimethylthioformamide by about 1 kcal/mole. The free energies of activation for the rotation of the two compounds are 21.6 and 24.0 kcal/mole, respectively,[7] though it is probable that other effects as well, such as the

+I effect of the methyl group, are included in the difference. (This result is somewhat at variance with the conclusion based on molecular models given in Ref. 7 that no $CH_3 \cdots CH_3$ interaction of importance should be present in N,N-dimethylthioacetamide.)

The spectrum of the *trans* form appears as two small quartets for the N-methyl group with a separation of 4.7 cps due to the $H-\overset{|}{N}-CH_3$ coupling. and one large quartet for the C-methyl group. The quartet structures are due to the *trans* $CH_3-\overset{\|}{C}-N-CH_3$ coupling of 0.55 cps, similar to the value found for N,N-dimethylthioacetamide,[7,18] whereas for N,N-dimethylacetamide the *trans* coupling constant is given as 0.45—0.50 [12] or 0.4 cps.[13] In the spectrum of the *cis* form the N-methyl signal is a doublet (J about 5 cps) and the C-methyl signal a singlet. The lack of fine structure in these signals may be due both to their low intensity and the low *cis* $CH_3-\overset{\|}{C}-\overset{|}{N}-CH_3$ coupling constant. The assignment of the *cis* conformation to the minor component of the spectrum is supported by the large upfield shift of its N-methyl doublet of dilution with benzene.

In these spectra no effect of high rate of exchange of the NH-proton could be observed, but when a moderate amount of triethylamine was added, the N-methyl double quartet collapsed into a single quartet.

Other N-methylthioamides. In the spectra of N-methylthiopropionamide, N-methylthioisobutyramide, and N-methylthiopivalamide only signals from one conformer could be observed. In all cases the N-methyl resonance appeared as doublets with a separation of 5 cps due to coupling with the NH proton, which collapsed into singlets on addition of triethylamine. Since the signals fall very close to those of the *trans* form of N-methylthioacetamide (Table 1) and are only moderately displaced upfield on dilution with benzene, they are all ascribed to the *trans* isomer, which is also in agreement with an anticipated steric effect. The acyl radicals gave signals according to expectation.

EXPERIMENTAL

N-Methylthioformamide and *N-methylthioacetamide* were prepared according to Suzuki.[6] The following thioamides were prepared by refluxing the corresponding amides with phosphorus pentasulphide in toluene. *N-Methylthiopropionamide* was obtained in 20 % yield as a colourless liquid, b.p. 120°/20 Torr, $n_D^{20} = 1.5610$, lit.[19] 128°/10 Torr, $n_D^{20} = 1.5602$. (Found: C 46.9; H 8.62; N 13.9; S 31.6. C_4H_9NS, (103.21) requires C 46.6; H 8.79; N 13.6; S 31.3). *N-Methylthioisobutyramide* was obtained in 36 % yield as a colourless liquid, b.p. 105°/8 Torr. (Found: C 50.9; H 9.23; N 11.7; S 27.6. $C_5H_{11}NS$ (117.21) requires C 51.2; H 9.46; N 11.9; S 27.4). *N-Methylthiopivalamide* was obtained in 19 % yield as colourless needles, m.p. 33.5—35°. (Found: C 54.7; H 9.89; N 10.6; S 24.5. $C_6H_{13}NS$ (131.26) requires C 54.9; H 9.98; N 10.7; S 24.4). The two latter compounds do not appear to have been described earlier.

The NMR spectra have been recorded with a Varian Model A-60 analytical NMR spectrometer.

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