On the Structure of Thioamides and their Derivatives. Part XXXIII.[1] Kinetics of the Acid-catalysed $E \rightarrow Z$-Isomerisation of *N*-Neopentylthioformamide in *o*-Dichlorobenzene

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The isomerisation of the *E*-form of *N*-neopentylthioformamide has been studied in the presence of dilute acids in *o*-dichlorobenzene. The reaction is first order in thioamide and in acid, the rate increasing with increasing acid concentration. These results as well as the dependence of the rate on acid strength, the kinetic isotope effect, and the activation entropy are discussed as indicating an *N*-protonated species as being responsible for the catalysis of the isomerisation in dilute acid solutions.

It is known that amides are protonated on oxygen rather than on nitrogen in strong concentrated acids.[2,3] Recently it has been conclusively proven that the analogous thioamides are protonated on sulphur rather than the nitrogen atom in a very strong acid medium.[4] However, the site of protonation of amides and thioamides in dilute acid solutions remains a source of contention. Studies on N–H exchange in amides [5] and on hindered rotation around the C–N partial double bond [6,7] all indicate that the *N*-protonated molecule is the kinetically important species in dilute acid solutions. However, the catalytic effect of dilute acids on N–H exchange has also been postulated *via* an *O*-protonated intermediate.[8,9] It has been shown that for thioamides the rate of rotation around the C–N partial double bond is accelerated in the presence of dilute acids.[10]

This paper presents a systematic study of this phenomenon for *N*-neopentylthioformamide and gives conclusions on the site of protonation of thioamides in dilute acid solution.

EXPERIMENTAL

Materials.—*N*-Neopentylthioformamide was prepared from *O*-ethyl thioformate and neopentylamine. The *E*-isomer was obtained by preparative layer chromatography and recrystallised from light petroleum, m.p. 74—76·5°, in agreement with the literature value.[10]

Trifluoroacetic acid (Merck uvasol), trichlorobenzoic acid (Merck pro analysi), and benzoic acid (Merck sublimed powder) were used without further purification. *m*-Chlorobenzoic acid and *o*-bromobenzoic acid were sublimed before use. *o*-Dichlorobenzene (Merck) was stored over molecular sieve 4 Å.

Kinetics.—The kinetic measurements were performed on the Varian A 60 and NV 14 n.m.r. spectrometers with tetramethylsilane as internal standard. Temperatures were measured with the help of the chemical shifts of the methanol or ethylene glycol spectrum.

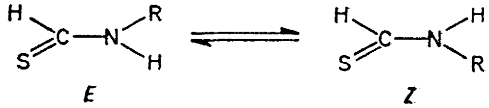
Stock acid solutions were prepared by weighing the acid in a volumetric flask and diluting with *o*-dichlorobenzene to 10 ml. The acid concentrations were spot checked by titration.

The n.m.r. samples were prepared by directly weighing thioamide (42 mg) into the n.m.r. tube and adding the prepared acid solution (0·4 ml) to give 0·79M-thioamide solution. The n.m.r. sample was placed directly in the spectrometer, which had already been set at the desired temperature (±2°). The first measurement was taken within three minutes of mixing. The isomerisation was followed for at least four half-lives, measurements being taken at set time intervals.

The pseudo-first-order rate constants listed in Table 1 were obtained using the ALGOL least squares program,[11] and the errors are standard deviations. The Arrhenius parameters were obtained likewise. Identical separate runs produced rate constants in agreement within 6%. The second-order rate constants k' listed in Table 2 were calculated from the equation $k = k_0 + k'[\mathrm{HA}]$, where k is the observed rate constant and k_0 the rate constant for the uncatalysed reaction. The k_0 values were obtained from the Arrhenius parameters for the uncatalysed reaction in *o*-dichlorobenzene [10] and are of the order of 10^{-5} s^{-1}.

RESULTS AND DISCUSSION

Thioamides in contrast to amides are well suited for conventional equilibration kinetic studies on the barrier to rotation around the C–N double bond, since they are separable into *E*- and *Z*-isomers. *N*-Neopentylthioformamide was chosen for this study, since it has a favourable equilibrium isomer ratio (60 : 40/*Z* : *E*) as well as a suitable rotational barrier (>100 kJ mol^{-1}).



E *Z*

R = CH_2Bu^t

The isomerisation of the thermodynamically less stable *E*-isomer can be followed easily by n.m.r. spectroscopy, the *E*-signals becoming less intense and the *Z*-signals appearing. The relatively inert solvent *o*-dichlorobenzene was chosen in order to alleviate solvent effects and therefore to keep the kinetics of the reaction as simple as possible.

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[6] L. M. Jackman, T. E. Kavanagh, and R. C. Haddon, *Org. Magnetic Resonance*, 1969, **1**, 109.

[7] M. Liler, *J. Chem. Soc.* (*B*), 1971, 334.

[8] R. B. Martin, *J.C.S. Chem. Comm.*, 1972, 793.

[9] R. B. Martin and W. C. Hutton, *J. Amer. Chem. Soc.*, 1973, **95**, 4752.

[10] W. Walter and E. Schaumann, *Chem. Ber.*, 1971, **104**, 3361.

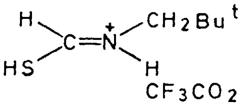
[11] E. Schaumann, Dissertation, Hamburg, 1970.

The observed pseudo-first-order rate constants for the isomerisation of *E*-neopentylthioformamide in the presence of a series of concentrations of trifluoroacetic acid in *o*-dichlorobenzene are listed in Table 1. The isomerisation rates increase linearly with increasing acid concentration, indicating a first-order dependence of the reaction on acid concentration.

TABLE 1

$k_{E\rightarrow Z}$ and $k_{Z\rightarrow E}$ for the isomerisation of *E*-*N*-neopentylthioformamide in the presence of trifluoroacetic acid at 24·5° (solvent: *o*-dichlorobenzene; [thioformamide]$_0$ = 0·79M)

$[CF_3CO_2H]$/M	$10^{-4}k_{E\rightarrow Z}/s^{-1}$	$10^{-4}k_{Z\rightarrow E}/s^{-1}$
0·00	0·092 ± 0·002	0·058 ± 0·001
0·004	0·32 ± 0·04	0·23 ± 0·03
0·015	0·53 ± 0·01	0·36 ± 0·01
0·028	1·34 ± 0·05	1·02 ± 0·04
0·0515	2·05 ± 0·06	1·50 ± 0·05
0·078	3·2 ± 0·1	2·8 ± 0·1
0·103	6·5 ± 0·2	4·6 ± 0·2
0·125	6·8 ± 0·3	4·7 ± 0·2
0·161	9·9 ± 0·5	7·4 ± 0·5



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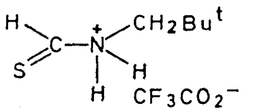

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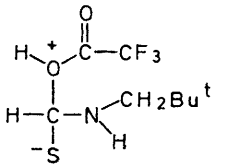

(3)

The observed acid catalysis of the reaction renders an intermediate *S*-protonated species (1) unlikely, since protonation on sulphur would be accompanied by an increase in the double bond character of the C–N bond and consequently an increase in the barrier to rotation around this bond.[4] However, there are two further mechanisms which fit the kinetic data, one proceeding *via* an *N*-protonated intermediate (2), the other involving a tetrahedral intermediate (3). In both cases rotation around the C–N bond in the intermediate is essentially free.

With the help of ^{18}O exchange studies it could be shown for amides that the acid catalysis of rotation about the C–N bond is not due to the formation of a tetrahedral intermediate.[6] In the present study on neopentylthioformamide, information about the intermediate could be obtained from a study of the effect of acid strength on the rate of isomerisation. The negative logarithms of the second order catalytic constants (Table 2) correlate well with the pK_a values of the acids (*r* 0·986) *via* the Brønsted equation for general acid catalysis (Figure 1): $-\lg k' = \alpha pK_a + G$.

Inspection of Figure 1 shows that the rate for *o*-bromobenzoic acid is too slow compared with the others utilised. This is probably a result of steric effects caused by bromine in the *ortho*-position. The observed α of 0·27 for the forward and reverse reactions indicates that as is the case for *N*-methylacetamide (α 0·25),[14] the dependence of catalytic effectiveness on acid strength is not strong. However, the fact that a dependence does exist, the rate of isomerisation increasing with increasing acid strength, allows a tetrahedral intermediate to be ruled out for the catalysed reaction, since there is no proton transfer involved in such a mechanism.

TABLE 2

Catalytic rate constants for the isomerisation of 0·79M-*N*-neopentylthioformamide in dilute acid solutions in *o*-dichlorobenzene

Acid	*T*/°C	pK_a	$10^{-3}k'_{E\rightarrow Z}$/ l mol^{-1} s^{-1}	$10^{-3}k'_{Z\rightarrow E}$/ l mol^{-1} s^{-1}
CF_3CO_2H	40	0·23 [a]	15·6	12·2
	38		8·17	5·48
	32		4·82	3·49
	24·5		4·51	3·47
	19		1·59	1·18
	14		1·27	1·00
	7		0·882	0·731
	2·5		0·534	0·373
CF_3CO_2D	24·5		3·51	2·37
CCl_3CO_2H	40	0·70 [b]	11·7	8·90
o-$BrC_6H_4CO_2H$	40	2·84 [b]	2·08	1·77
m-$ClC_6H_4CO_2H$	40	3·82 [b]	1·48	1·41
$C_6H_5CO_2H$	40	4·19 [b]	1·25	1·17

[a] Ref. 12. [b] Ref. 13*a*.

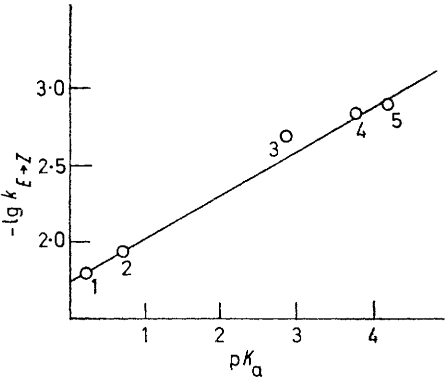

FIGURE 1 Correlation of the catalytic rate constants for the isomerisation of *N*-neopentylthioformamide in 0·03M-acid solution in *o*-dichlorobenzene at 40° with acid strength: 1, trifluoroacetic acid; 2, trichloroacetic acid; 3, *o*-bromobenzoic acid; 4, *m*-chlorobenzoic acid; 5, benzoic acid

Table 2 lists the catalytic constants for the isomerisation of *E*-*N*-neopentylthioformamide with trifluoroacetic acid and deuteriotrifluoroacetic acid as catalysts. The kinetic isotope effect for the isomerisation k'_H/k'_D is 1·37. This would indicate an asymmetrical position

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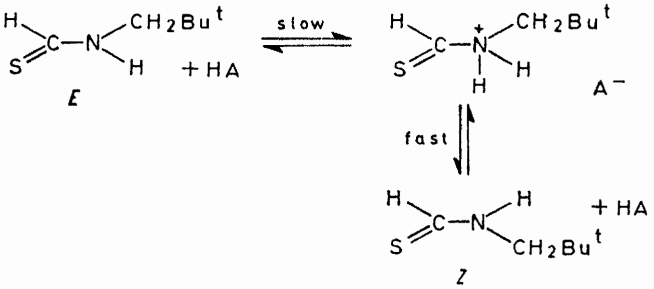
[12] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Wiley, New York, 1962, p. 124.

[13] Handbook of Chemistry and Physics, The Chemical Rubber Co., Cleveland, 1971—1972, 52nd edn., (*a*) pp. D-120–D-121; (*b*) E-45.

[14] I. M. Klotz and B. H. Frank, *J. Amer. Chem. Soc.*, 1965, **87**, 2721.

of the proton in the transition state for the rate-determining step of the reaction.[15] The small isotope effect (k_H/k_D 1·25) found for the acid catalysis of hindered rotation for *NN*-dimethylacetamide has been interpreted as indicating substantial proton transfer from acid to amide in the transition state.[16] However, the Brønsted catalysis constant α found for the isomerisation of *E*-*N*-neopentylthioformamide, which is close to zero, is in accord with a reaction having a transition state which more resembles the reactants, neopentylthioformamide, and undissociated acid than the intermediate protonated thioamide.[17] Taking into consideration the small α found for the N–H exchange of *N*-methylacetamide,[14] it seems probable that a transition state with little proton transfer must be considered for amides also.

From the kinetic evidence already discussed it can be deduced that the mechanism responsible for the acid catalysis of the isomerisation of *E*-neopentylthioformamide is composed of the rate determining *N*-protonation of the thioamide with essentially free rotation around the C–N bond, followed by the comparatively fast deprotonation to the *Z*-form. This mechanism is also supported by the activation parameters measured for the reaction. The Arrhenius diagram for the thioamide with trifluoroacetic acid over a range of 30° is found in Figure 2. The activation enthalpies (25°) for the *E* ⟶ *Z* and *Z* ⟶ *E* isomerisations are 54 ± 4 and 53 ± 4 kJ mol^{-1} respectively. Of particular interest are the activation entropies (25°) for the forward and reverse reactions of −99 ± 15 and −105 ± 15 J K^{-1} mol^{-1}. The negative activation entropy can be explained by a transition state showing more order due to the combination of thioamide with acid. However, a transition state with almost complete proton transfer should produce random solvent reorganisation, with the consequence of a more positive activation entropy than found here. The transition state proposed here with little proton transfer would require little medium reorganisation and thus best fits the activation entropy for the isomerisation of thioamides in dilute acids.



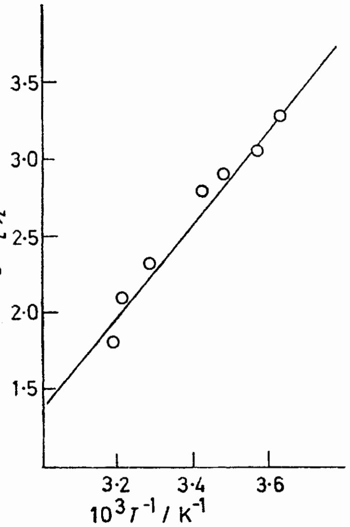


FIGURE 2 Arrhenius diagram for *E*-*N*-neopentylthioformamide with trifluoroacetic acid in *o*-dichlorobenzene

It should be pointed out that here *N*-protonation is found in the absence of water, which has been postulated to be necessary for the *N*-protonation of amides.[2] This could be due to a different mechanism of proton transfer: in the case of *N*-neopentylthioformamide in *o*-dichlorobenzene, a solvent of low dielectric constant (ε 9·9 [13b]), a proton is transferred directly from the acid molecule to the nitrogen atom of the thioamide *via* a hydrogen-bonded complex. According to the results presented here, such complexes, which could be pre-equilibrium intermediates for the proton transfer step, must be a loose association of acid and thioamide similar to the transition state for the proton transfer postulated above. The kinetically important species remains the *N*-protonated molecule.

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[16] B. G. Cox, *J. Chem. Soc.* (*B*), 1970, 1780.

[17] J. Hine, ' Physical Organic Chemistry,' Kogakusha, Tokyo, 1962, 2nd edn., pp. 116—119.