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The Thione-Thiol Tautomerism in Simple Thioamides

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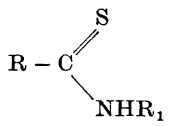
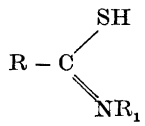
The thioamide/imidothiol ratios found (K_T) in thioacetamide and thiobenzamide and their mono-*N*-methyl derivatives have been measured by the basicity method. pK_T was found to be −8.6 for thioacetamide, −9.6 for *N*-methylthioacetamide, −8.3 for thiobenzamide and −8.9 for *N*-methylthiobenzamide. The thioamides were found to deviate from ideal Hammett base behaviour in aqueous sulphuric acid. pK_T values and ultraviolet spectra are discussed in relation to HMO and PPP calculations.

The concept of a thione-thiol tautomerism (I ⇌ II) in thioamides is one of long standing, and the thiol form has often been invoked to explain *S*-alkylations and *S*-acylations of thioamides. The complete dominance of the



I



II

thiol form has been advocated on the grounds that carbon and sulphur atoms have a low tendency to form double bonds.[1] However, as early as in 1931, Hantzsch [2] showed that the thione form must dominate in thioacetamide, by comparing the ultraviolet spectra of thioacetamide, thioacetpiperidide, and ethyl thioacetimidate, and it can be stated quite generally that chemical reactivity is a poor guide for judging the position of a tautomeric equilibrium. We have found it desirable to attempt an estimation of the tautomeric ratio in some simple thioamide systems to provide a basis for a more detailed discussion of the factors influencing the tautomerism in different cyclic systems showing a similar type of equilibrium.

A quantitative estimation of the tautomeric ratio is hampered by the low concentration of the imidothiol form II, which precludes a direct measurement

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by normal physical methods. Claims have recently been made for a large proportion of thiol form in thionicotinic and thioisonicotinic amides based on infrared absorption bands in the S – H stretching region,[3,4] but these claims have been refuted by X-ray crystallographic [5,6] and infrared spectroscopic [6] arguments. In previous quantitative studies of thione-thiol tautomerism in thiopyridones [7,8] and azoline-2-thiones [9] the basicity method has been used. This method is thoroughly discussed in Ref. 10, but to aid the discussion a brief derivation is given as follows, with AH and HA denoting the tautomeric forms I and II:

$$AH + H^+ \rightleftharpoons HAH^+ \rightleftharpoons HA + H^+ \quad (1)$$

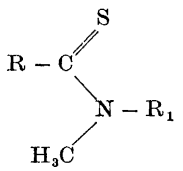
$$K_{aI} = [H^+]\,[AH]/[HAH^+] \quad (2a)$$

$$K_{aII} = [H^+]\,[HA]/[HAH^+] \quad (2b)$$

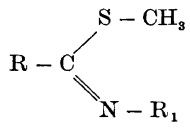
$$K_{obs} = \frac{[H^+]\,([AH] + [HA])}{[HAH^+]} = K_{aI} + K_{aII} \quad (2c)$$

$$K_T = [AH]/[HA] = K_{aI}/K_{aII} \quad (3)$$

Instead of the non-isolable forms I and II, the corresponding *N*- and *S*-methyl derivatives III and IV can be used under the assumption that methylation does not seriously affect the basicity. Since $K_{aI} \gg K_{aII}$, K_{obs} can be



III



IV

substituted for K_{aI} in (3), thus obviating the effect of methylation on this form. Another problem is posed by the observation [11,12,9] that thioamides in general do not behave as ideal Hammett bases.

EXPERIMENTAL

Thioacetamide was a commercial sample, and *N*-methylthioacetamide, *N*,*N*-dimethylthioacetamide and the analogous thiobenzamides were prepared by standard procedures. The thioacetamides were purified by vacuum sublimation, followed by recrystallization, and the thiobenzamides by recrystallization only. The methyl thiolacetimidates and -benzimidates were obtained as hydroiodides by reaction of the corresponding thioamides with methyl iodide in dry acetone. These compounds were fairly labile and were used for measurement immediately after isolation and drying.

The pK_a values of the thioamides were measured as described in Ref. 9. The thiolimidate hydroiodides were dissolved in water and immediately the pH measured by potentiometric titration with 0.01 N sodium hydroxide and with a total base concentration of less than 2×10^{-3} M, using a Radiometer pH meter Model 25 with scale expander. Titration of the thiolimidate hydroiodides with standard alkali and back-titration with standard acid within a few minutes followed the same curve, indicating that hydrolysis of the thiolimidates was without importance. The glass electrode was attached to a Radiometer titrator Type TTT 1c and the curve was recorded on a Radiometer titrigraph Model SBR 2c.

The pK_a and pK_T values are given in Table 1, and literature values of thioamide and thiolimidate basicities in Table 2. Ultraviolet spectra have been recorded with a Beckman DK-2 spectrophotometer. The absorption maxima of the thioamides, the thiolimidates and their protonated forms are given in Table 3.

DISCUSSION

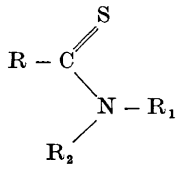
One fundamental assumption made in using the basicity method, *viz.* that the basicity of the thiocarbonyl sulphur atom is not seriously affected by *N*-methylation, is justified by the data in Table 1. Since sulphur is only a moderately efficient transmitter of electronic effects, *S*-methylation should be expected to influence the basicity of the nitrogen atoms of thiolimidates even less. *N*-Methylation, on the other hand, raises the basicity by 0.6 – 1.0 pK units.

The pK_T values found for these thioamides show a dominance of thione over thiol form which is greater than in the previously studied systems, where the thioamide group forms part of a heterocyclic ring. From the literature data (Table 2) a pK_T value of -11.0 can be obtained for thiourea, and this seems to be the highest ever reported for a thioamide.

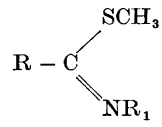
The dominance of the thione form in these compounds is due to a combination of different effects, which can be divided into two groups:

1. *Electronic effects.* Here, the difference in π-electron stabilization should be the dominant effect, though the importance of inductive and/or hyperconjugative effects is shown by the basicity increases in the thiolimidates caused by N-alkylation.

Table 1. pK_a and pK_T values for thioamides (A) and thiolimidates (B) in water (H_2SO_4) at +25°C.



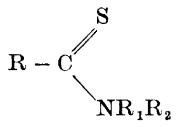
A



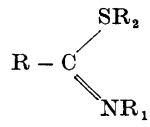
B

R	R_1	R_2	pK_a A	pK_a B	pK_T
CH_3	H	H	-1.9 ± 0.2	6.71 ± 0.01	-8.6 ± 0.2
CH_3	CH_3	H	-1.9 ± 0.2	7.71 ± 0.01	-9.6 ± 0.2
CH_3	CH_3	CH_3	-1.6 ± 0.2	–	–
Ph	H	H	-2.5 ± 0.2	5.83 ± 0.01	-8.3 ± 0.2
Ph	CH_3	H	-2.5 ± 0.3	6.42 ± 0.02	-8.9 ± 0.3
Ph	CH_3	CH_3	-2.3 ± 0.2	–	–

Table 2. Collection of pK_a values from the literature.



A



B

R	R_1	R_2	pK_a A	Ref.	pK_a B	Ref.
CH_3	H	H	−1.76[a]	13		
CH_3	H	C_2H_5			6.9	14
CH_3	CH_3	CH_3	−1.53	15		
CH_3	C_2H_5	CH_3			7.75[b]	16
CH_3	H	C_2H_5			6.97[b]	17
Ph	H	C_2H_5			5.86[b]	17
H_2N	H	H	−1.26	18		
H_2N	H	H	−1.19	15		
H_2N	H	CH_3			9.83	19

[a] With hydrochloric acid: no temperature given.
[b] At 30°C in 10 % aqueous acetonitrile.

2. *Solvation and entropy effects.* The solvation energies of the thione and thiol forms depend on their polarities and their capacity to take part in hydrogen bonding. This capacity is determined by the power of the NH and SH groups to act as proton donors in basic solvents, and of the thiocarbonyl sulphur atom and the thiolimidate nitrogen atom to act as proton acceptors in protic solvents. Reasoning by analogy from pyridones, one would conclude that the thione form is generally favoured by the solvation effects, since Beak and Bonham [22] have found that *N*-methyl-2-pyridone and *N*-methyl-4-pyridone are more stabilized relative to the corresponding methoxypyridines in the condensed than in the gaseous phase.

The π-electron effect is probably responsible for the increase of pK_T in the order thiopyridone, azolinethione, acyclic thioamide. In the cyclic compounds, the thiol form gains an extra stabilization by its superior aromatic resonance, and this effect is probably more important in the thiopyridones than in the azolinethiones. These differences have been qualitatively reproduced by MO calculations with an HMO method with α,β-variation.[23,9] Katritzky *et al.*[24] have recently shown that the aromatic resonance in 2-thiopyridone is *ca.* 5.3 kcal/mol less efficient than in pyridine. On the other hand, pyridine-2-thiol can be expected to have a greater resonance energy than pyridine.

Calculations similar to those described in Ref. 9 have been performed for the simple thioamide, thiobenzamide, thiourea, and for the corresponding iminothiol forms. The calculations described in Ref. 9 were performed using parameter set 3 of Ref. 23. However, an inspection of the transition energies reveals that set 3 is not quite suitable to reproduce UV spectra. Therefore,

Table 3. Ultraviolet spectra of thioamides, $R-CS-NR_1R_2$ (A), thiolimidates, $R-C(SCH_3)=NR_1$ (B), protonated thioamides (C), and protonated thiolimidates (D). Spectra of A, B, and D in water, and of C in sulphuric acid.

R	R_1	R_2	System	λ_{max} nm	ε_{max}
CH_3	H	H	A	262	13 800
CH_3	H	–	B	226	15 700
CH_3	H	H	C	234	10 400
CH_3	H	–	D	228	26 000
CH_3	CH_3	H	A	255	16 100
CH_3	CH_3	–	B	226	19 100
CH_3	CH_3	H	C	230	9 600
CH_3	CH_3	–	D	228	25 000
CH_3	CH_3	CH_3	A	264	18 000
CH_3	CH_3	CH_3	C	237	13 000
Ph	H	H	A	287	8 700
Ph	H	–	B	239	27 000
Ph	H	H	C	271	16 000
Ph	H	–	D	258	17 800
Ph	CH_3	H	A	275	17 600
Ph	CH_3	–	B	226	21 000
Ph	CH_3	H	C	264	27 600
Ph	CH_3	–	D	257	16 800
Ph	CH_3	CH_3	A	271	6 500
Ph	CH_3	CH_3	C	249	6 600
H_2N	H	H	A	235[a]	11 200[a]
H_2N	H	–	B	238[b]	38 100[b]
H_2N	H	H	C	End absorption[a]	–[a]
H_2N	H	–	D	220[b]	5 500[b]

[a] Ref. 20. [b] Ref. 21.

the same calculations were performed with parameter set 1, which has previously been found to give good correlations between calculated and experimental transition energies for a large number of simple thiones.[25]

For comparison, calculations have also been performed by the Pariser-Parr-Pople method,[26] with the two-center repulsion integrals calculated according to the Nishimoto-Mataga scheme,[27] and with the parameters proposed by Fabian.[28] All parameters are collected in Table 4. An idealized geometry was

Table 4. Parameters for HMO (α,β variation) [23] and PPP [28] calculations.

Atom	h_x Set 1	h_x Set 3	U_x eV	γ_{xx} eV	Bond	k_{xy} Set 1	k_{xy} Set 3	β_{xy} eV
C	0	0	−11.42	10.84	C–C	1.0	0.75	−2.318
$\dot{N}$	0.5	0.5	−14.12[a]	12.34[a]	C–N	1.2	0.8	−2.318
$\dot{N}$	1.5	1.5	−23.13	12.98	C–S	0.6	0.4	−1.159
S	0.5	0.5	−12.86	9.92	C=S	0.6	0.4	−1.623
S	1.0	1.0	−21.00	10.84				

[a] From Ref. 29.

Table 5. Total π-electron energies ($\sum E_\pi$) and energies of first $\pi \rightarrow \pi^*$ transition ($\Delta E_{\pi \rightarrow \pi^*}$) in units of $-\beta$ for $R-CSNH_2$ (A), $R-C(SH)=NH$ (B), and $[R-C(SH)=NH_2]^+$ (C).

R	System	Set 1		Set 3	
		$\sum E_\pi$	$\Delta E_{\pi \rightarrow \pi^*}$	$\sum E_\pi$	$\Delta E_{\pi \rightarrow \pi^*}$
CH_3	A	6.4171	1.5967	5.1871	1.1025
CH_3	B	6.3154	2.6173	4.7605	1.7633
	$E(A)-E(B)$	0.1017	–	0.4266	–
CH_3	C	–	2.1814	–	–
Ph	A	17.4092	1.1598	13.4702	0.8332
Ph	B	17.2496	1.9394	12.9961	1.3412
	$E(A)-E(B)$	0.1596	–	0.4741	–
Ph	C	–	1.7253	–	–
H_2N	A	10.2444	1.6982	8.5736	1.0896
H_2N	B	9.9885	2.7845	8.0875	1.7759
	$E(A)-E(B)$	0.2589	–	0.4860	–
H_2N	C	–	2.5976	–	–

assumed with all bond angles equal to 120°. The bond lengths of thioacetamide and thiobenzamide were taken from the X-ray structure determination of thioacetamide by Truter.[5] The length of the Ph–C bond in thiobenzamide and the corresponding thiolimidate was assumed to be 1.48 Å. The bond lengths in thiourea were taken from the work of Kunchur and Truter,[30] and the C=N (1.32 Å) and C–S (1.73 Å) bond lengths in all thiolimidates from the work of Flippen and Karle.[31]

The total π-electron energies and the energies of the first $\pi \rightarrow \pi^*$ transitions obtained by the HMO method are collected in Table 5. For comparison with UV spectra, transition energies for the protonated thiolimidates (C and D) have been calculated with parameter set 1 and with the PPP method.

With parameter set 3, the difference in π-electron energy between thione and thiol form, ΔE_π, was -0.046 β for 2-thiopyridone, -0.064 β for 4-thiopyridone, and between -0.289 β and -0.375 β for the azoline thiones.[9] It is apparent that the values given in Table 5 reproduce the higher pK_T values for the acyclic thioamides, although the ΔE_π value obtained for thiobenzamide is too high. The high pK_T for thiourea is reproduced by both parameter sets.

The total π-electron energies obtained by the PPP method are found in Table 6. It appears that the thione forms generally show the higher π-electron

Table 6. Total π-electron energies (E_π) and differences in core repulsion energies (ΔE_{core}) in eV for $R-CS-NH_2$ (A) and $R-C(SH)=NH$ (B).

R	$E_{\pi,A}$	$E_{\pi,B}$	$\Delta E_{core,I}$	$\Delta E_{\pi,I}$	$\Delta E_{core,II}$	$\Delta E_{\pi,II}$
CH_3	−83.103	−81.445	2.613	0.955	1.311	−0.347
Ph	−300.272	−296.709	5.277	1.714	2.193	−1.370
H_2N	−153.907	−150.445	5.876	2.414	3.227	−0.235

Table 7. Calculated π-electron densities (q) and π-bond orders (p) in $R-CS-NH_2$ (A) and $R-C(SH)=NH$ (B)

R	Atom	Set 1		Set 3		PPP	
		A	B	A	B	A	B
CH_3	q (S)	1.471	1.932	1.332	1.939	1.422	1.918
	q (C)	0.839	0.916	0.834	0.885	0.844	0.757
	q (N)	1.690	1.152	1.834	1.176	1.734	1.324
Ph	q (S)	1.449	1.936	1.341	1.954	1.432	1.926
	q (C)	0.861	0.925	0.862	0.901	0.858	0.782
	q (N)	1.722	1.164	1.858	1.196	1.754	1.354
H_2N	q (S)	1.658	1.947	1.394	1.949	1.557	1.944
	q (C)	0.823	0.908	0.823	0.880	0.858	0.806
	q (N)	1.760	1.319	1.858	1.279	1.793	1.480
	Bond						
CH_3	p (C–S)	0.783	0.271	0.882	0.260	0.817	0.318
	p (C–N)	0.600	0.959	0.407	0.986	0.555	0.916
Ph	p (C–S)	0.725	0.256	0.790	0.239	0.858	0.292
	p (C–N)	0.552	0.908	0.395	0.889	0.519	0.853
	p (C–Ph)	0.373	0.316	0.427	0.365	0.357	0.349
H_2N	p (C–S)	0.635	0.242	0.796	0.240	0.711	0.259
	p (C–N)	0.532	0.862	0.409	0.898	0.487	0.788
	p (C–NH_2)	0.532	0.436	0.409	0.347	0.487	0.524

stabilization. However, the difference $E_A - E_B$ must be corrected for the difference in core repulsion energy (E_{core}) between thione and thiol form. Two models have been used to calculate this contribution, *viz.* the point charge model [32] (I) and the orbital-like positive hole model [33] (II). The differences in E_{core} calculated by the two models are given in Table 6. It appears that E_{core} is larger for the thiones than for the thiols here, thus reducing the greater π-stabilization of the thiones. With model I, the thiones become less stable than the thiols. Del Re *et al.*[34] have recently studied the two models and come to the conclusion that model II is most adequate for SCF π-electron calculations. However, the precise value of ΔE_{core} depends strongly on the geometry of the systems, and therefore the $\Delta E_{\pi,II}$ values in Table 6 must be regarded as very approximate. The values for thioacetamide and thiourea are of the right order of magnitude, and the less negative value for thiourea need not be in error. As can be seen in Table 7, the thione sulphur atom has a very high π electron density, which should give extra stabilization to the thione form in water solution.

Calculated π-electron charges and π-bond orders are shown in Table 7. All three models give qualitatively the same relations between charges and bond orders in the different systems, and the agreement between the results from set 1 and the PPP calculations is in most cases remarkably close.

Table 8. Experimental and calculated transition energies for $R-CS-NH_2$ (A), $R-C(SH)=NH$ (B) and $[R-C(SH)=NH_2]^+$ (C) in eV.

R	System	Calc.		Exp.	
		$\Delta E_{\pi\rightarrow\pi^*}$	f	$\Delta E_{\pi\rightarrow\pi^*}$	ε
CH_3	A	4.883	0.479	4.73	13 800
	B	4.898	0.165	5.49	15 700
	C	6.563	0.272	5.41	17 800
Ph	A	3.888	0.409	4.32	8 700
	B	4.795	0.446	5.19	27 000
	C	3.468	0.658	4.63	11 400
H_2N	A	4.643	0.392	5.28	11 200
	B	5.470	0.201	5.21	38 100
	C	6.202	0.265	5.64	5 500

Ultraviolet spectra. An inspection of Table 3 shows that in general the $\pi\rightarrow\pi^*$ transition energies are lower for the thioamides than for the thiolimidates or for the protonated species. This relation is somewhat obscured by the solvents employed, which causes considerable hypsochromic shifts of the thioamide absorption bands. The transition energies calculated by set 1 and set 3 in Table 5 show the same relation, but with set 3 the transition energy for thiourea is smaller than for thioacetamide, whereas the experimental results come in the opposite order. In the thioacetamides and thiobenzamides, the protonated species C and D absorb at longer wavelengths than the thiolimidates B, and this order is reproduced with set 1. The same order is predicted for thiourea, but it is not found experimentally. The differences observed in absorption between forms C and D, which have the same chromophoric system, is partly due to the effects of *N*- and *S*-methyl groups and partly to solvent effects, since the protonated thioamides (C) had to be measured in fairly strong sulphuric acid solution (8 – 9 M).

The transition energies calculated by the PPP method with configuration interaction including all singly excited configurations are given in Table 8 together with pertinent experimental values. The agreement is not very satisfactory, especially not with the protonated forms, and it is probable that the parametrization needs revision.

Non-ideal Hammett behaviour. All thioamides studied give linear plots of $\log([BH^+]/[B])$ *versus* H_0, but the slopes are in the range 1.2 – 1.7 instead of unity, as required by simple theory. Similar behaviour has previously been observed for *N*,*N*-dimethylthioamides,[12] thiolactams,[11] and azolinethiones,[9] and the slopes of the $\log([BH^+]/[B])$ *versus* H_0 plots vary between 1.25 and 2.0. This large variation precludes the introduction of a new acidity scale for thioamides, as has been done for amides by Katritzky *et al.*[35] However, it is evident that the use of an appropriate acidity function would have given higher pK_a values for the thioamides and thus higher pK_T values. Still, one can safely assume that the pK_a values are about equally affected and that the pK_T values fall in the right order.

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