Steric and Electronic Effects on Self-association of Potentially Bifunctional Catalysts: Δ^4-Thiazoline-2-thiones

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The self-association in CCl_4 of some 4,5-dialkyl-Δ^4-thiazoline-2-thiones (1) has been studied by i.r. spectroscopy. The experimental data can be explained in terms of an equilibrium between monomer and cyclic dimer. Both steric and electronic effects affect the self-association constant *K*. The increase in *K* parallels the increase in nucleophilicity of the sulphur atom. The steric effect of substituents *ortho* to the N–H bond decreases the self-association constant. These two factors which specifically affect the nucleophilic or the electrophilic centre are useful in the design of bifunctional catalysts.

THE concerted action of two functional groups (electrophilic and nucleophilic) is generally recognized as an important factor in enzyme catalysis.[1,2] Conceptually, the simplest model of this type of interaction can be found in the self-association of a potentially bifunctional catalyst. The factors which affect this self-association can be expected to be of some help in applications to more complex cases where the two partners of the association are different. This paper reports an i.r. study of the influence of steric and electronic effects of 4- and 5-alkyl groups on the monomer–dimer equilibrium of some Δ^4-thiazoline 2-thiones [equation (1)].

RESULTS AND DISCUSSION

I.r. spectra of Δ^4-thiazoline 2-thiones in CCl_4 feature two absorption bands in the region 3 000—3 500 cm^{-1}, a sharp peak (*ca.* 3 410 cm^{-1}) attributed to the free N–H bond stretching and a broad one (*ca.* 3 200—3 000 cm^{-1}) which corresponds to associated N–H stretching together with C–H absorption.[3] In all cases $\Delta\nu = \nu_{NH_{free}} - \nu_{NH_{ass}}$ is large enough to avoid any overlap of the two absorptions. Self-association has been followed by the change in free N–H absorbance *d* as a function of concentration C_0. The best fit of the experimental curve $C_0 = f(d)$ is obtained for the monomer–cyclic dimer model [equation (1)]. This model has been proposed previously by Griffiths *et al.* in their study of compound (1b) and two other related thioamides.[4] Furthermore, it has been often used to account for the self-association of compounds such as diketopiperazine,[5] 2-pyridone,[6]

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pyridine-2-thione,[7] maleimide,[8] amides,[9] and carboxylic acids.[10] The use of other models (see Experimental section), does not lead to a good fit.

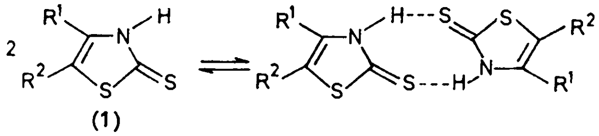
TABLE 1

Self-association constants for the monomer–cyclic dimer equilibrium for (1a—j) in CCl_4

Compound	ν_{NH}/cm^{-1}	10^3C_0 [a]/M	Number [b]	10^2A [c]	10^2B [c]	K[d]/l mol^{-1}	$\Delta K/K$ (%)	ε [d]/ l mol^{-1} cm^{-1}
(1a)	3 417	0.1—2.8	24	0.484 7 ± 0.022 8	0.143 4 ± 0.010 9	1 200	20	230
(1b)	3 408	0.1—3	30	0.44 7 ± 0.027	0.102 3 ± 0.013 9	2 200	30	200
(1c)	3 407	0.1—2.8	33	0.632 7 ± 0.052 9	0.144 1 ± 0.022 8	1 500	40	140
(1d)	3 409	0.2—3.5	35	0.797 ± 0.081	0.153 7 ± 0.031 2	1 700	50	130
(1e)	3 415	0.1—2.9	35	0.445 5 ± 0.015 7	0.149 ± 0.007 5	1 000	13	135
(1f)	3 410	0.2—2.4	15	0.181 ± 0.016	0.116 6 ± 0.009 6	665	25	170
(1g)	3 408	0.1—2.5	30	0.554 ± 0.046	0.077 ± 0.02	4 700	50	260
(1h)	3 409	0.1—3.5	35	0.675 7 ± 0.042 7	0.108 8 ± 0.018	2 900	40	185
(1i)	3 414	0.2—2.3	28	0.322 8 ± 0.025 8	0.127 7 ± 0.012	1 000	25	160
(1j)	3 423	0.3—2.6	20	0.095 5 ± 0.021 9	0.199 ± 0.015	120	38	170

[a] Concentration range. [b] Number of experimental points, all points taken. [c] A and B are the coefficients of the equation $C_0 = Ad^2 + Bd$ where d is absorbance of the free NH. The quoted errors are random errors calculated from statistical analysis (0.95 confidence level). [d] Obtained from relation (11), $K = A\varepsilon^2l^2/_2$ and $\varepsilon = 1/Bl$.

Results are reported in Table 1 together with the number of experimental points as well as the concentration range. Statistical analysis of the variance (0.95 confidence level) gives the errors in coefficients A and B of relation (11) (see Experimental section). These values are acceptable but the error in K is rather large and we believe overestimated. Nevertheless the variation in K in the series (1a—j) is large enough to give an insight into the factors which affect the equilibrium position.



(1)

(1)

a; $R^1 = H, R^2 = H$
b; $R^1 = Me, R^2 = H$
c; $R^1 = Et, R^2 = H$
d; $R^1 = Pr^i, R^2 = H$
e; $R^1 = Bu^t, R^2 = H$
f; $R^1 = Ph, R^2 = H$
g; $R^1 = Me, R^2 = Me$
h; $R^1 = Et, R^2 = Me$
i; $R^1 = Pr^i, R^2 = Me$
j; $R^1 = Bu^t, R^2 = Me$

TABLE 2

Selected values for self-associations constants for compounds related to (1)

Compound	K [a]	T (°C)	Ref.
Acetamide	2.8 [b]	30	14*a*
Maleimide	22.0	25	8
Pyrazole [c]	47.5	18	14*b*
N-Methylacetamide [d]	160 [e,f]	25	14*c*
Thiobutyrolactam	278	25	7
Pyridine-2-thione	3 220	31.3	6
2-Pyridone	6 270	30.3	6
Acetic acid	38 000 [e,g]	37	14*d*

[a] K/l mol^{-1} are obtained by i.r. with a monomer–cyclic dimer model [relation (11)], in CCl_4. [b] Solvent $CHCl_3$. [c] Monomer–dimer–trimer model. [d] Mecke's hypothesis (monomer–dimer–polymer) [relation (8)]. [e] Molar fraction. [f] Calorimetry. [g] N.m.r.

Table 2 reports selected values of self-association constants given in the literature for some related compounds. All the reported compounds are 'tautomeric '[11] as are the thiazoline-2-thiones (1) and most of them give cyclic dimers by the formation of two hydrogen bonds. Recent molecular orbital calculations[2c] and *ab initio* studies[12,13] indicate that the double hydrogen bond is stronger than the sum of the two separate single hydrogen bonds. This confirms the trend that association constants are generally higher when cyclic dimers are involved.[14] It can be seen by comparison with the values given in Table 2 that thiazoline-2-thiones (1) are largely self-associated in an inert solvent.*

Inspection of Table 2 reveals that (a) changing hydrogen for methyl in positions 4 or 5 on the thiazole ring leads to stabilisation of the cyclic dimer form; (b) destabilisation of the dimer occurs on going from R^1 = Me to $R^1 = Bu^t$. This destabilisation is much more pronounced in the series (1g—j) in which R^2 = Me than in the series (1b—e) in which R^2 = H.

Since dimerisation involves both an electrophilic and a nucleophilic centre, the NH proton and the C=S sulphur, respectively, it was of interest to measure directly the substituent effect on the nucleophilic character of the thiocarbonyl group. We measured the substituent

(2)

(2)

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* It is worth noting that Griffiths *et al.*[4] reported a larger value for K in compound (1b). We believe that the difference might arise from the few points they used as well as the method used for experimental data fitting.

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effect on the rate of alkylation at sulphur of the model compounds (2) [equation (2) and Table 3] in acetone. The replacement of NH by NMe prevents self-association and we feel safe in assuming that this model allows a precise determination of the electronic effect of the alkyl groups in positions 4 and 5 of the thiazole ring on the nucleophilicity of the thiocarbonyl group. The kinetic results are reported in Table 3.

TABLE 3

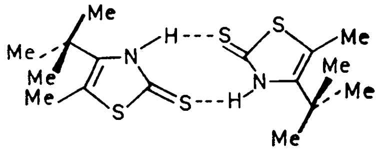
Rate constants and activation parameters for the reaction MeI + (2a—e) and (2g—j), in acetone

Compound	Number [a]	10^6k/l mol^{-1} s^{-1} 20°	25°	30°	$\Delta G^{\ddagger}_{298}$ [b]	$\Delta H^{\ddagger}$ [b]	$\Delta S^{\ddagger}$ [b]
(2a)	5	104.3	162.2	244.0	22.65	14.4 ± 0.3	−27.6 ± 1
(2b)	6	172.3	263.0	396.0	22.33	14.1 ± 0.4	−27.6 ± 1.8
(2c)	9	166.7	255.0	385.0	22.35	14.2 ± 0.3	−27.3 ± 1.5
(2d)	9	157.4	241.7	365.8	22.37	14.3 ± 0.5	−27.1 ± 2.2
(2e)	9	138.6	212.1	320.0	22.47	14.2 ± 0.5	−27.8 ± 2.3
(2g)	10	298.2	451.2	673.6	22.03	13.8 ± 0.3	−27.6 ± 1.4
(2h)	5	283.6	429.4	641.4	22.02	13.8 ± 0.25	−27.6 ± 1.2
(2i)	10	313.0	466.4	686.1	21.99	13.3 ± 0.36	−29.3 ± 2
(2j)	10	257.0	381.5	559.3	22.10	13.68 ± 0.7	−28.8 ± 2.9

[a] Number of temperatures used; the rate constants were calculated at the given temperatures from the Eyring equation. [b] $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ are in kcal mol^{-1}, $\Delta S^{\ddagger}$ is in cal mol^{-1} K^{-1}. The quoted errors are random errors calculated from statistical analysis (C. A. Bennett and N. L. Franklin, ' Statistical Analysis in Chemistry and the Chemical Industry,' Wiley, New York, 1954, p. 228).

Along the series (2a, b, and g) [*N*-methyl analogues of compounds (1a, b, and g)] the nucleophilic character of the thiocarbonyl group is increased. It can be seen from Tables 1 and 3 that the rate and association constants increase in a parallel manner. Each additional methyl group multiplies both the rate and the association constant (within the experimental error) by a factor of *ca.* 1.6.

The electronic effect of the 4-alkyl group in the series Me, Et, Pr^i, Bu^t can be anticipated from the rate constant data collected in Table 3. The nucleophilicity of the sulphur atom decreases but the observed change is small. One should expect a *K* value of *ca.* 1 700 for compound (1e) based on pure electronic effects. The observed association constant is smaller for (1e) than expected and the difference can be accounted for by the additional steric effect of the Bu^t group which affects the electrophilicity of the *ortho* NH centre. The importance of the steric contribution of the R^1 substituent is therefore more clearly evident in the series (1g—j). On going from R^1 = Me to R^1 = Bu^t, the association constant is decreased by a factor of 25, while the same change in the 5-H series results in a two-fold decrease. The electronic effect of the R^1 substituents does not change in the series 5-H and 5-Me as rate constants in Table 3 show, while the effective size of the R^1 substituent is strongly dependent upon substitution in position 5. The t-butyl group in (1j) is related to the 5-Me group in such a way that a methyl group lies in the plane of the heterocyclic skeletons and is directed towards the N–H ··· S=C bond (Scheme).[15,16] This conformational effect leads to a considerable increase in the effective steric size of the t-butyl group. This effect, which has been previously observed in alkylation studies of 4-alkyl-2,5-dimethylthiazoles by methyl iodide [17] can be used as a positive test for the occurrence of steric effects in self-association. The t-butyl group in (1e) can adopt either the same conformation or a less bulky one in which a methyl group is directed towards position 5. The conformational variation of the size of the substituents is also apparent in the Et and Pr^i cases (1h and i).



SCHEME

The behaviour of compound (1f) in which R^1 = Ph can be explained by the same two factors. The electronic effect of phenyl on the nucleophilic properties of the thiocarbonyl group is known to be of the same order as that of H; [18] on the other hand, the steric effect is not very important since the phenyl group does not lie into the plane of the heterocyclic ring.[19]

In summary, the combined effects of alkyl substitution in positions 4 and 5 lead to a large change in the self-association constants. We have shown that an increase in nucleophilicity of the thiocarbonyl group results in an increase in association while a specific decrease in electrophilicity of the NH bond through the steric hindrance of the *ortho*-substituent R^1 has the opposite effect. Thus we define a versatile way to vary both the nucleophilic and the electrophilic characters of a potentially bifunctional catalyst. This may be useful in the design of these catalysts.

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[15] An example of this locking can be found in ' stereopopulation control ' defined by S. Milstein and L. A. Cohen, *J. Amer. Chem. Soc.*, 1972, **90**, 9158; R. T. Borchardt and L. A. Cohen, *ibid.*, p. 9166.

[16] C. Roussel, R. Gallo, M. Chanon, and J. Metzger, *J.C.S. Perkin II*, 1974, 1304.

[17] A. Babadjamian, R. Gallo, M. Chanon, and J. Metzger, *J. Amer. Chem. Soc.*, 1973, **95**, 3807.

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EXPERIMENTAL

Syntheses.—Thiazoline-2-thiones (1) and (2) were prepared by general synthetic methods.[20] They were recrystallised from ethanol–water twice before use. Physical and n.m.r. data are given in Table 4.

I.r. Experiments.—All spectra were obtained with a Beckman IR9 spectrophotometer at 25°. The spectral slit width was *ca.* 1 cm^{-1}. The low solubility of the compounds in CCl_4 (Prolabo) necessitated the use of a 5 cm path length cell with CaF_2 windows. Compounds (1a and j) were studied with a 3 cm path length cell, and solutions of very low concentration were recorded in a 10 cm path length cell. For each compound, four or five solutions were prepared by weighing and dilution.

TABLE 4

Physical[a] and n.m.r.[b] [$\delta(J/\text{Hz})$] data for the compounds (1a—j) and (2a—l and g)

Compound	M.p. (°C)	N.m.r. N–R	 =C(4)–CH	 =C(4)–CMe	 5-R
(1a) [20]	79	3.32 (1 H, s)	7.3 (1 H, *d*, *J* 4.6)		6.95 (1 H, d, *J* 4.6)
(1b)	89	3.32 (1 H, s)	2.3 (3 H, d, *J* 1.6)		6.50 (1 H, d, *J* 1.6)
(1c)	80	N.r.	2.55 (2 H, m, *J* 1.3, 7.5)	1.20 (3 H, t, *J* 7.5)	6.42 (1 H, t, *J* 1.3)
(1d)	119	N.r.	2.88 (1 H, sept, *J* 7)	1.25 (6 H, d, *J* 7)	6.40 (1 H)
(1e) [20]	159	4.02 (1 H)		1.32 (9 H, s)	6.39 (1 H, s)
(1f) [c,20]	173		7.45 (5 H, m)		6.64 (1 H, s)
(1g) [20]	165	3.30 (1 H, s)	2.14 (3 H, s)		2.14 (3 H, s)
(1h) [d]	165	N.r.	2.56 (2 H, q, *J* 7.5)	1.35 (3 H, t, *J* 7.5)	2.13 (3 H, s)
(1i) [e]	171	N.r.	3.10 (1 H, sept, *J* 7)	1.26 (6 H, d, *J* 7)	2.15 (3 H, s)
(1j) [f]	163	3.10 (1 H)		1.42 (9 H, s)	2.24 (3 H, s)
(2a) [20]	46	3.58 (3 H, s)	7.33 (1 H, d, *J* 4.6)		6.76 (1 H, d, *J* 4.6)
(2b) [20]	119	3.55 (3 H, s)	2.28 (3 H, d, *J* 1.1)		6.45 (1 H, q, *J* 1.1)
(2c) [20]	59	3.57 (3 H, s)	2.62 (2 H, m, *J* 1.3, 7.5)	1.24 (3 H, t, *J* 7.5)	6.44 (1 H, t, *J* 1.3)
(2d) [20]	57	3.60 (3 H, s)	2.94 (1 H, sept, *J* 0.8, 7)	1.24 (6 H, d, *J* 7)	6.42 (1 H, d, *J* 0.8)
(2e) [20]	117	3.76 (3 H, s)		1.38 (9 H, s)	6.47 (1 H, s)
(2g) [20]	63	3.53 (3 H, s)	2.17 (3 H, s)		2.10 (3 H, s)
(2h) [g]	45	3.64 (3 H, s)	2.68 (2 H, q, *J* 7.3)	1.15 (3 H, t, *J* 7.3)	2.17 (3 H, s)
(2i) [h]	54	3.71 (3 H, s)	3.25 (1 H, sept, *J* 7.3)	1.34 (6 H, d, *J* 7.3)	2.23 (3 H, s)
(2j) [i]	118	3.83 (3 H, s)		1.53 (9 H, s)	2.33 (3 H, s)

[a] M.p.s are uncorrected. [b] All spectra were recorded for C_3D_6O solutions on a Varian HA 100 instrument at the probe temperature. [c] Recorded in $CDCl_3$ (J. P. Aune, R. Phan Tan luu, E. J. Vincent, and J. Metzger, *Bull. Soc. chim. France*, 1972, 2679). [d] Found: C, 45.1; H, 5.9; N, 8.9. $C_6H_9NS_2$ requires C, 45.3; H, 5.6; N, 8.8%. [e] Found: C, 48.3; H, 6.15; N, 8.0. $C_7H_{11}NS_2$ requires C, 48.0; H, 6.3; N, 8.1%. [f] Found: C, 50.9; H, 6.95; N, 7.6. $C_8H_{13}NS_2$ requires C, 51.3; H, 6.9; N, 7.5%. [g] Found: C, 48.15; H, 6.25; N, 8.15%. [h] Found: C, 51.4; H, 6.8; N, 7.4%. [i] Found: C, 53; H, 7.4, N, 7.0%. $\lambda_{max.}$(EtOH)/nm: (2h) 321.2 (ε 300); (2i) 320.5 (14 700); (2j) 317.3 (13 400).

Self-association Constant Determinations.—Several models of self-association are possible *e.g.* involving open polymers and cyclic oligomers. The absorbance *d* can be expressed by relations (3) or (4) assuming that each free NH bond (from open oligomer and monomer) absorbs at the same frequency and with the same molar extinction coefficient.

open aggregates

$$d = \varepsilon l(C_M + C_2 + \ldots + C_n + \ldots) \quad (3)$$

cyclic aggregates

$$d = \varepsilon l(C_M) \quad (4)$$

In relations (3) and (4), l is the path length, C_M is the monomer concentration at equilibrium, C_n the concentration in *n*mers. The association constants were evaluated for the different models assuming an ideal solution according to Prigogine.[21]

Monomer-open polymers. In the case of an equilibrium between monomer and open dimer, *K* is expressed for each initial concentration C_{0_i} by relation (5) which allows the determination of both ε and *K*. In the present study, the

$$K = \varepsilon l(C_{0_i}\varepsilon l - d_i)/(2d_i - C_{0_i}\varepsilon l)^2 \quad (5)$$

application of relation (5) led in most cases to larger variations in the calculated *K* and ε values than those obtained from the monomer–cyclic dimer model. According to Coggeshall and Saier's hypothesis (K_D, K, and $KC_M < 1$), the experimental curve $C_o = f(d)$ can be solved by relations (6) and (7) in the case of an equilibrium between monomer and open polymer.[22] The experimental curve could not be

$$d = \varepsilon lC_M(1 + K_DC_M/1 - KC_M) \quad (6)$$

$$C_o = C_M + K_DC_M/K(1 - KC_M)^2 - K_DC_M/K \quad (7)$$

accounted for by the relations (6) and (7) in the present study.

If one assumes that all the association constants are equal (Mecke's hypothesis, $K_D = K$), C_o is expressed by relation (8) in which $K = A/B^2$.[23] The experimental curve is thus

$$C_o = Ad^2 + Bd \quad (8)$$

represented by the same mathematical expression as in the monomer–cyclic dimer model.

Monomer-cyclic oligomers. *K* and C_o are given by relations (9) and (10) in the case of a monomer–cyclic dimer equilibrium. Relation (11) is deduced from (4), (9), and

$$K = C_D/C_M^2 \quad (9)$$

$$C_o = C_M + 2C_D \quad (10)$$

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(10). Relation (12) can be derived from (11) for cyclic

$$C_0 = Ad^2 + Bd \text{ and } K = A/2B^2 \qquad (11)$$

$$C_0 = Ad^n + Bd^{n-1} + Cd^{n-2} + \ldots + Zd \qquad (12)$$

polymers. Statistical treatment of the experimental curve $C_0 = f(d)$ according to equation (12) showed that in all cases the best fit was obtained for $n = 2$. The coefficients of higher degrees were not significant. It is noteworthy that the spectrometric results do not allow a choice between models defined by relations (8) and (11). We excluded the former on the following basis. (a) Equation (8) is derived when all the association constants involved in the monomer–cyclic polymer complex equilibrium are taken as equal. Such a situation seems statistically highly improbable. (b) An *X*-ray study of the crystalline form of benzothiazoline-2-thione showed that this compound exists as a cyclic dimer.[24]

Kinetics of Methylation.—We used a classical technique for the kinetic runs.[16] This method needs cell calibration by the salt. All the values obtained were within 2% of the mean value for six calibrations. Methyl iodide and acetone were freshly distilled. The given rate constants were recalculated for the given temperatures (Table 3) from the Eyring equation with data obtained from several runs at different temperatures and concentrations. The confidence level was 0.9.[16] 1% Precision was obtained. In all cases the reaction is second order. Initial rate constants were determined (salt concentration 10^{-4}M). Attempts to methylate compounds (1) showed that the obtained salts were unstable in acetone and decomposed readily to the corresponding 2-methylthiothiazoles and HI. Furthermore the reaction was complicated by the intervention of general base catalysis of the formed methylthiothiazole and acetone. The reaction is complicated by concentration and pH effects.

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