Comparison of the Ligating Properties of Disulphides and Thioethers: Dimethyl Disulphide, Dimethyl Sulphide, and Related Ligands

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The stability constants of 1 : 1 complexes between dimethyl disulphide (dmds) or dimethyl thioether (dms) and Ca^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, or Ag^+ (K_{ML} for $M^{n+} + L \rightleftharpoons [ML]^{n+}$) have been determined in aqueous solution by ^1H n.m.r. shift measurements. The results [*e.g.* log $K_{Ca(dmds)}$ *ca.* −1.4, log $K_{Cd(dmds)}$ *ca.* −1.4, log $K_{Ag(dmds)} = 2.01 \pm 0.09$; log $K_{Ca(dms)}$ *ca.* −1.6, log $K_{Cd(dms)} = -0.3 \pm 0.2$, and log $K_{Ag(dms)} = 3.7 \pm 0.3$] show that the complexes with soft metal ions are stronger than those with borderline or hard metal ions. It is also evident that the ligating properties of the thioether moiety are somewhat more pronounced towards borderline and soft metal ions than those of the disulphide group. Spectrophotometrically determined stability constants (in 50% aqueous ethanol) for the complexes between Mn^{2+}, Cu^{2+}, or one of the above metal ions and dmds, diethyl sulphide, or tetrahydrothiophen accord with this. In addition, for several complexes of tetrahydrothiophen-2-carboxylate (thtc⁻) and 1,2-dithiolan-3-carboxylate [= tetranorlipoate (tnl⁻)], the dimensionless constants for the intramolecular equilibrium between the chelated isomer (which is bonded to the metal by the sulphur atom and the carboxylate group) and the simple carboxylate-co-ordinated isomer have been calculated, together with the percentages of the chelated isomer {*e.g.* 93 ± 1 for $[Cu(thtc)]^+$ and 41 ± 7 for $[Cu(tnl)]^+$; 55 ± 5 for $[Cd(thtc)]^+$ and ⩽20% for $[Cd(tnl)]^+$; ⩽20% for both $[Mn(thtc)]^+$ and $[Mn(tnl)]^+$}. Possible biological implications of such weak interactions and the resulting intramolecular equilibria are briefly discussed.

THE disulphide group is well recognized as a potential binding site for metal ions in biological systems. This group is found in cystine,[1] an important constituent of many proteins, and in the oxidized form of glutathione,[2] as well as in lipoic acid,[3] which participates in many enzymatic reactions, especially as a protein-bound coenzyme in oxidative decarboxylations.[4]

The interactions between the disulphide moiety and hard (*e.g.* Ca^{2+} or Mn^{2+}) or borderline [5] (*e.g.* Cu^{2+} or Zn^{2+}) metal ions are certainly rather weak,[1] but they do occur, as crystal-structure determinations reveal.[6] Comparisons of stability constants have been used to suggest a Cu^{2+} interaction with the disulphide bond of L-cystine,[7] and there is spectral evidence for a possible Cu^{2+}–disulphide interaction in solutions with L-cystinediamide.[8] A copper(II) complex of oxidized glutathione has also been characterized,[9] and there is evidence that the disulphide moiety of the 1,2-dithiolan ring of α-lipoate may participate in complex formation.[10,11] However, all the determinations of stability constants have been performed with ligands containing at least one proton-basic site in addition to the disulphide moiety.[2,7,9-11]

Certainly, soft metal ions [5] like Cu^+, Ag^+, or Hg^{2+} have a greater tendency to co-ordinate with the disulphide group and crystal structures of disulphides, *e.g.* with Cu^+, are known,[12,13] although co-ordination of these metal ions often causes cleavage of the disulphide bond.[1,2] This cleavage reaction is probably one of the reasons why practically no stability data seem to exist for complexes between soft metal ions and simple disulphides, but a Ag^+–disulphide interaction has been suggested for the system Ag^+–basic bovine pancreatic trypsin inhibitor.[14]

The reasons for the complete lack of stability data on the interactions between the biologically important hard or borderline metal ions like Ca^{2+}, Mn^{2+}, Cu^{2+}, or Zn^{2+} and simple disulphides are that: (*i*) such complexes are very weak,[1,2] and (*ii*) a pH-metric determination of stability constants is not possible, as these ligands are very poor proton acceptors.[15] In fact, the disulphide group is even less basic than the sulphur of thioether [16] which is itself an extremely weak base with $pK_a = -6.8$.[17] Estimations of basicity suggested the order $Me_2S > Me_2S_2 \simeq MeSH$,[16] which indicates $pK_a < -6.8$ for the disulphide moiety. Hence, so far only disulphide complexes with ligands containing an additional binding site, like an amino- or carboxylato-group, have been studied.[1,2,7,9-11]

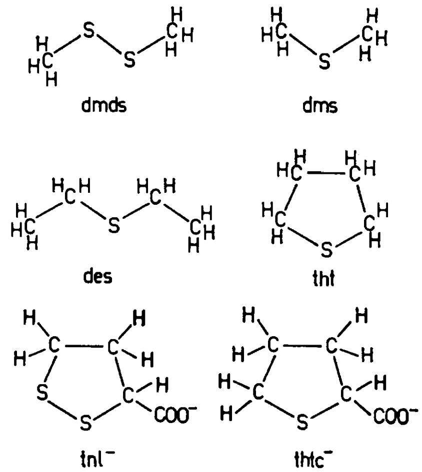

FIGURE 1 Structures of the sulphur ligands

For the thioethers, the situation is similar: the biological importance of the sulphur atom in these compounds as a potential binding site for metal ions is well recognized,[1,18,19] and indeed the *X*-ray crystal-structure analysis [20] of plastocyanin, for example, revealed a Cu^{2+}–thioether bond with a methionine residue in this ' blue ' copper protein. However, stability data have only very recently been published, based on spectrophotometric measurements,[21] for complexes between hard or borderline metal ions and simple thioether ligands like tetrahydrothiophen or diethyl sulphide.

We now compare the stability of complexes formed between Ca^{2+}, several 3*d* transition-metal ions, Zn^{2+}, Cd^{2+}, Ag^{+}, or Pb^{2+} and the ligands shown in Figure 1. First the complexes of the simple dimethyl disulphide (dmds) were studied: the stability of the $[Cu(dmds)]^{2+}$ complex was determined spectrophotometrically, while the other complexes with dimethyl disulphide and diamagnetic metal ions were investigated by ^{1}H n.m.r. shift experiments. For comparison the stabilities of some complexes with dimethyl sulphide (dms) and related thioethers were also measured, and the percentages of the chelated isomer of several M^{2+} 1 : 1 complexes of 1,2-dithiolan-3-carboxylate and tetrahydrothiophen-2-carboxylate were calculated.

EXPERIMENTAL

Materials.—The metal perchlorates (*purum* or *purissimum*) were from Fluka AG, Buchs, Switzerland, with the exception of zinc and cadmium perchlorate which were obtained from K and K Laboratories, Ohio, U.S.A. and from Ventron GmbH, Karlsruhe, Germany, respectively. The metal nitrates (*pro analysi*) were from Merck AG, Darmstadt, Germany, except silver nitrate which was from B.D.H. Chemicals Ltd., Poole.

Dimethyl disulphide (for synthesis) and tetrahydrothiophen (*pro analysi*) were obtained from Merck-Schuchardt, Hohenbrunn near Munich, Germany; both ligands were used in spectrophotometric measurements and therefore were distilled twice before use over a Raschig column under N_2 and then stored under N_2. Dimethyl sulphide (*purum*) was from Fluka AG and the solvent ethanol (for spectroscopic use) from Merck AG.

The pH was measured with a Metrohm potentiometer E 353B using a EA 121 or a micro EA 125 Metrohm glass electrode. Calibration was done with commercial aqueous buffers (pH 4 and 7, from Metrohm AG, Herisau, Switzerland) and direct readings for pH were used, except in D_2O solutions where the pD was obtained by adding 0.40 to the pH-meter reading.[22] Unless otherwise specified the pH (or pD) of the solutions was adjusted to *ca.* 2.

Spectrophotometric Measurements.—Absorbance spectra were recorded with a Beckman DB spectrophotometer connected to a Walz + Walz Electronic Hi-Speed recorder 202, or on a Varian Techtron spectrophotometer (model 635) connected to a Honeywell recorder (model 196).

The experiments with the Cu^{2+}–dimethyl disulphide system and their evaluations were done exactly as described recently [21] for Cu^{2+}–thioether systems. The conditions used in the Cu^{2+}–dmds experiments are shown in Figures 2 and 3.

The stability constants of the cadmium(II) and lead(II) complexes with tetrahydrothiophen (tht) were determined from ' competition ' experiments with the Cu^{2+}–tht system. This means that the absorption of the Cu^{2+}–tht system at 359 nm decreases in the presence of Cd^{2+} or Pb^{2+}, and from this decrease in absorption the stability of the cadmium(II) or lead(II) complexes may be calculated. The experimental conditions and the calculations were identical to those described recently for several other M^{2+}–tht systems.[21]

*Hydrogen-*1 *N.M.R. Measurements.*—For the M^{n+}–dmds systems the ^{1}H n.m.r. spectra were recorded in D_2O solutions with a Bruker WH-90 Fourier-transform spectrometer (90.025 MHz) at 27 °C or a Varian Anaspect EM-360 spectrometer (60 MHz) at 34 °C using the centre peak of the tetramethylammonium triplet as reference; all these chemical shifts were converted into a trimethylsilylpropanesulphonate reference by adding 3.188 p.p.m.[23] From a plot of these chemical shifts against the increasing concentration of the diamagnetic metal ion M^{n+} (for details see Figure 4), the curve best fitting these experimental data can be computed, using a Hewlett-Packard model 9821A, connected to a model 9862A plotter, and log $K_{M(dmds)}$ thus obtained.

The constants for the M^{n+}–dms systems were determined in exactly the same way (Figures 4 and 5), but here all spectra were recorded in aqueous solutions with the Varian Anaspect EM-360 spectrometer (60 MHz) at 34 °C.

The mentioned curve-fit is based on equation (1),[24] where δ_0 is the chemical shift of the free ligand (L) and δ_∞ the chemical shift of the complex $[ML]^{n+}$. Equation (1) together with the definition (2), which is valid for our experimental conditions where the species $[ML_m{}^{n+}]$ with $m \geqslant 2$ are negligible, gives equation (3). From the

$$\delta_{obs.} = \delta_0([L]/[L]_{tot.}) + \delta_\infty([ML]/[L]_{tot.}) \qquad (1)$$

$$[L]_{tot.} = [L] + [ML] \qquad (2)$$

$$\delta_{obs.} = \delta_0 + (\delta_\infty - \delta_0)([ML]/[L]_{tot.}) \qquad (3)$$

$$[M]_{tot.} = [M] + [ML] \qquad (4)$$

$$K_{ML} = [ML]/[M][L] \qquad (5)$$

$$[ML] = \tfrac{1}{2}([M]_{tot.} + [L]_{tot.} + K_{ML}{}^{-1} - \{([M]_{tot.} + [L]_{tot.} + K_{ML}{}^{-1})^2 - 4[M]_{tot.}[L]_{tot.}\}^{\frac{1}{2}}) \qquad (6)$$

definitions (2), (4), and (5) follows equation (6). Substitution of equation (6) in (3) gives an expression which contains only two unknown parameters, δ_∞ and K_{ML}, and these may now be determined by starting the iterative calculation with estimated values, and varying these until the standard deviation reaches a minimum (least-squares regression). In cases where δ_0 cannot be determined with a significantly greater accuracy than the other experimental points, δ_0 may also be treated as a variable parameter.

All experiments were carried out at least twice. The errors given throughout this work are twice the standard deviation, unless stated otherwise.

RESULTS

As the stability of most of the complexes to be determined was rather small, perchlorate salts were used whenever possible. Only in the few cases where these were not available or where the perchlorate salts are relatively insoluble, as with $Ag[ClO_4]$, were the nitrates used. The $[ClO_4]^-$ ion does not affect the stability constants since there is no association between this anion and the metal ions used (or an extremely small one),[25,26] while with $[NO_3]^-$ very weak complexes may form in some cases.[26,27] However, the recent results [21] for M^{2+}–thioether systems show that the influence of $[NO_3]^-$, if present at all, is very small indeed.

$$M^{n+} + L \rightleftharpoons [ML]^{n+} \qquad (7)$$

The dmds–M^{n+} *Systems.*—For the Cu^{2+}–dmds system, the stability constant K_{ML} of the 1 : 1 complex [according to equilibrium (7)] could be determined spectrophotometrically in 50% aqueous ethanol ($I = 1.0$ mol dm^{-3}, $Na[ClO_4]$; 25 °C).

Figure 2 shows how the absorption (A) of dmds decreases with increasing concentration of Cu^{2+}. Since there are two opposing factors affecting the experimental accuracy, *i.e.* increase of the concentration of Cu^{2+} leads to larger spectral differences while simultaneously the difference spectra become less accurate due to the increasing absorption of the Cu^{2+} solution in the reference beam, the spectra were evaluated at three different wavelengths (270, 278, and 282 nm).[21,28] An example of this is shown in Figure 3 where $1/[Cu^{2+}]_{tot.}$ is plotted against $1/\Delta A$; the resulting straight lines confirm that 1 : 1 complexes are formed and that their intercepts with the y axis are identical within experimental error. The average result of three independent experiments for the stability constant of $[Cu(dmds)]^{2+}$ is $\log K_{Cu(dmds)} = 0.49 \pm 0.22$.

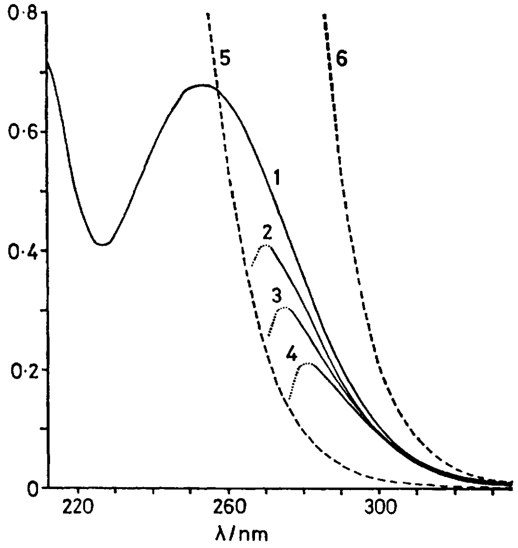

FIGURE 2 Absorption spectra (——) of dimethyl disulphide (2×10^{-3} mol dm^{-3}) alone (1) and in the presence of: 0.075 (2), 0.15 (3), and 0.30 mol dm^{-3} $Cu[ClO_4]_2$ (4); the cell in the reference beam always contained the appropriate concentration of $Cu[ClO_4]_2$. The spectra were measured in 50% aqueous ethanol (v/v) at pH *ca.* 3, $I = 1.0$ mol dm^{-3} ($Na[ClO_4]$), and 25 °C in 1-cm quartz cells. (· · · ·), Uncertainty due to the large absorption of $Cu[ClO_4]_2$; (– – – –), spectra (under the above conditions) of 0.02 (5) and 0.30 mol dm^{-3} $Cu[ClO_4]_2$ (6) solutions

The stability constants of other $[M(dmds)]^{2+}$ complexes could not be measured by the ' competition method ' used earlier,[21] since the spectral alterations were too poor to be exactly reproduceable. We therefore carried out ^1H n.m.r. experiments with some diamagnetic metal ions and measured the chemical shift of the methyl protons of dmds in D_2O solutions; under the influence of increasing amounts of

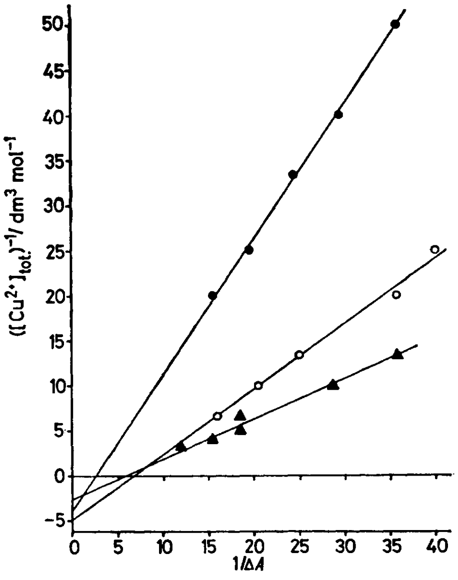

FIGURE 3 Graphical determination of the stability constant, $K_{Cu(dmds)}$ (dm^3 mol^{-1}), of the Cu^{2+}–dmds 1 : 1 complex in 50% aqueous ethanol (v/v) by plotting $1/[Cu^{2+}]_{tot.}$ against $1/\Delta A$; [dmds] $= 2 \times 10^{-3}$ mol dm^{-3}, $I = 1.0$ mol dm^{-3} ($Na[ClO_4]$); 25 °C, and pH *ca.* 3. For concentrations of $Cu[ClO_4]_2$ 0.02—0.05 mol dm^{-3} the evaluation was done at 270 nm (●), for 0.04—0.15 mol dm^{-3} at 278 nm (○), and for 0.075—0.30 mol dm^{-3} at 282 nm (▲), the intercepts with the y axis [$= -K_{Cu(dmds)}$] are -3.82 ± 0.92, -4.96 ± 1.25, and -2.59 ± 1.13 respectively. The straight lines were drawn according to the least-squares regression method

TABLE 1

Logarithms of the stability constants K_{ML} of 1 : 1 complexes of M^{n+} with dmds, dms, des, or tht [a]

	dmds		dms	des	tht
M^{n+}	D_2O	50% EtOH [b]	H_2O [c]	50% EtOH [d]	50% EtOH [d]
Ca^{2+}	-1.4 [c,e–g]		-1.6 [e–g]		-0.30 ± 0.13 [h,i]
Mn^{2+}					-0.31 ± 0.11 [h,i]
Cu^{2+}		0.49 ± 0.22 [j]		-0.47 ± 0.19 [h,i]	0.02 ± 0.04 [h,i]
Zn^{2+}	-1.4 [c,e–g,k]		-1.4 [e–g]		-0.21 ± 0.09 [h,i]
Cd^{2+}	-1.4 [c,e–g]		-0.3 ± 0.2 [g,j]		-0.26 ± 0.06 [l]
Pb^{2+}	-1.5 [c,e,f,k,m]		-1.05 ± 0.2 [e,j,m]		0.08 ± 0.05 [l]
Ag^+	2.01 ± 0.09 [b,c]		3.7 ± 0.3 [b,j]		3.51 ± 0.14 [i,l]

[a] Unless stated otherwise, the errors given are twice the standard error of the mean value. [b] $I = 0.1$ mol dm^{-3}, $Na[NO_3]$. [c] 34 °C. [d] 25 °C. [e] Estimated values with $\Delta\delta = 0.249$ and 0.334 p.p.m. for the dmds and dms systems respectively (see text). [f] The error limits for these results are estimated as follows: to see how the results depend on $\Delta\delta$ (taken from the Ag^+ systems) the calculations were repeated for dmds complexes with $\Delta\delta = 0.200$ and 0.300 p.p.m. (*i.e.* $\Delta\delta = 0.249 \pm 0.050$ p.p.m.); the results are within ± 0.1 log units, as given above, but to be on the safe side we allowed ± 0.2 log units for this error range (if $\Delta\delta$ should be out by a factor of 0.5 or of 2 the values of $\log K_{ML}$ would be out by $+0.3$ or -0.3 log units respectively). Furthermore, since the small shifts observed in the presence of M^{2+} might partly originate from the change in ionic strength from 2 to 4.5 (*i.e.* the difference calculated between δ_0 at $I = 2$ mol dm^{-3} and the shift in the presence of M^{2+} at $I = 4.5$ mol dm^{-3} might be slightly too large, as the corresponding experiments indicate), although certainly not more than by a factor of ½, the complexes might be up to 0.3 log units less stable than calculated. Hence, the lower error limit for the values given above is -0.5 and the upper limit $+0.2$ log units. [g] $I = 2.0$—4.5 mol dm^{-3}, $Na[ClO_4]$. [h] $I = 1.0$ mol dm^{-3}, $Na[ClO_4]$. [i] Value taken from ref. 21. [j] The error range is estimated (*cf.* text). [k] 27 °C. [l] $I = 1.0$ mol dm^{-3}, $Na[NO_3]$. [m] $I = 2.0$—3.0 mol dm^{-3} $Na[NO_3]$.

M^{n+} the signals are shifted downfield. These chemical-shift differences may be used to obtain the stability constants of the $[M(dmds)]^{n+}$ complexes.

An example is shown in Figure 4 for the Ag^+–dmds system ($I = 0.1$ mol dm^{-3}, $Na[NO_3]$; 34 °C), where a significant downfield shift is observed. The measured shifts were plotted against the increasing concentration of Ag^+ and the curve best fitting the experimental data was computed (see Experimental section). The resulting stability constant (the average of two experiments) of $[Ag(dmds)]^+$ is $\log K_{Ag(dmds)} = 2.01 \pm 0.09$, the chemical shifts of free dmds and $[Ag(dmds)]^+$ being $\delta_0 = 2.461 \pm 0.010$ and $\delta_\infty = 2.710 \pm 0.011$ p.p.m., respectively.

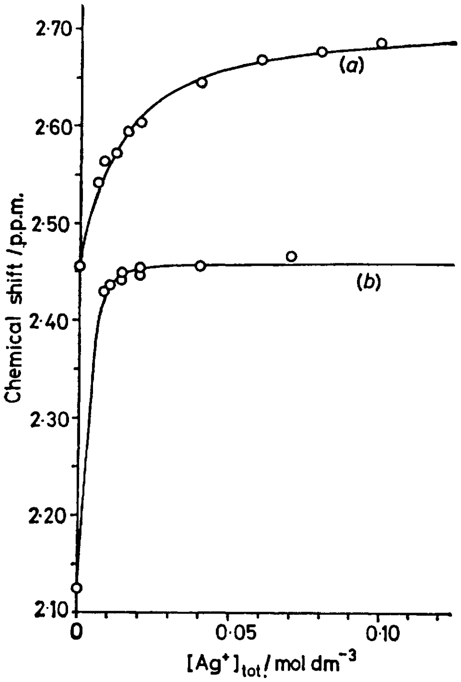

FIGURE 4 Chemical shifts of the resonance of the methyl protons of dimethyl disulphide (*a*) and of dimethyl sulphide (*b*) (each 5.7×10^{-3} mol dm^{-3}) as a function of $[Ag(NO_3)]_{tot}$. The measurements ($I = 0.1$ mol dm^{-3}, $Na[NO_3]$; 34 °C) were carried out in D_2O at pD *ca.* 2 for dmds and in H_2O at pH *ca.* 2 for dms. The curves shown are the computer-calculated best fits of the experimental data: $K_{Ag(dmds)} = 93.8 \pm 29.7$ dm^3 mol^{-1}, $\delta_0 = 2.463 \pm 0.015$ p.p.m., and $\delta_\infty = 2.708 \pm 0.016$ p.p.m.; $K_{Ag(dms)} = 2\,835 \pm 1\,066$ dm^3 mol^{-1}, $\delta_0 = 2.125$ p.p.m., and $\delta_\infty = 2.461 \pm 0.006$ p.p.m.

In these Ag^+–dmds experiments we adjusted the pD to *ca.* 2 with DNO_3 to prevent cleavage of the disulphide bond, a reaction which occurs at higher pH.[29] In fact, a Ag^+–dmds solution stored for 24 h gave the same ^1H n.m.r. spectrum as that of the freshly prepared solution. Attempts to study the Hg^{2+}–dmds system failed as a white precipitate formed; this could be the nitrate salt of a $[Hg(dmds)_x]^{2+}$ complex or the result of fission of the disulphide bond.[30] Furthermore, Hg_2^{2+} seemed to undergo disproportionation in the presence of dmds, in accordance with related observations.[31] Hence, no mercury–dmds system could be studied.

Under the influence of increasing amounts of $Ca[ClO_4]_2$, $Zn[ClO_4]_2$, $Cd[ClO_4]_2$, or $Pb[NO_3]_2$ in D_2O the signals of dmds are slightly shifted downfield indicating weak interactions, but the shift differences are far too small to allow a curve-fitting procedure ($I = 2$—4.5, $Na[ClO_4]$, or 2—3 mol dm^{-3}, $Na[NO_3]$; 27 or 34 °C). Therefore, the assumption was made that $\Delta\delta = \delta_\infty - \delta_0$ would be about the same for these systems as for the Ag^+–dmds system.* Based on $\Delta\delta = 0.249$ p.p.m. we estimated the stability constants of these $[M(dmds)]^{2+}$ complexes; the results with their approximate error limits are summarized in Table 1 together with the stability data of related thioether complexes. It is worth noting that an increase in $\Delta\delta$ leads to a slight decrease in $K_{M(dmds)}$, and *vice versa.*

Thioether–M^{n+} Systems.—Since the stability of the $[Ag(dmds)]^+$ complex is significantly lower than that of the Ag^+–thioether system,[21,32] and the same behaviour is shown by the corresponding complexes [21] with *e.g.* Cd^{2+}, we decided to study for comparison a thioether ligand under similar conditions. Hence, the chemical shifts observed for dimethyl sulphide (dms) in aqueous solution and in the presence of Ag^+, Ca^{2+}, Zn^{2+}, Cd^{2+}, or Pb^{2+} were measured. Again, Ag^+ ($I = 0.1$ mol dm^{-3}, $Na[NO_3]$; 34 °C) produced significant downfield shifts (Figure 4); in fact these were already so large at low concentrations that the stability constant could only be estimated, but the result $\log K_{Ag(dms)}$ 3.7 ± 0.3 is in excellent agreement with related data,[21] especially with the Ag^+–2,2′-thiodiethanol (tde) system studied by Widmer and Schwarzenbach: [32] $\log K_{Ag(tde)} = 3.60 \pm 0.03$ ($I = 1.0$ mol dm^{-3}, $K[NO_3]$; 20 °C); in addition the value $\log K_{Ag(tde)_2} = 2.46 \pm 0.05$ for $[Ag(tde)]^+ + tde \rightleftharpoons [Ag(tde)_2]^+$ was determined.[32]

As with dmds, the downfield shifts with dms in the presence of Ca^{2+}, Zn^{2+} ($I = 2$—4.5 mol dm^{-3}, $Na[ClO_4]$; 34 °C), or Pb^{2+} ($I = 2$—3 mol dm^{-3}, $Na[NO_3]$; 34 °C) were too small for the curve-fitting procedure, but with $\Delta\delta = 0.334$ p.p.m.† the stability constants for the corresponding $[M(dms)]^{2+}$ complexes could again be estimated in the way described for the M^{2+}–dmds systems. With the Cd^{2+}–dms system ($I = 2$—4.5 mol dm^{-3}, $Na[ClO_4]$; 34 °C) the situation is more complicated: here significant shifts were observed (Figure 5), but the plot of δ against $[Cd^{2+}]$, which is reproduceable, does not show the expected behaviour; only the measurements at $[Cd^{2+}] \leqslant 0.7$ mol dm^{-3} can be fitted by equations (3) and (6) in a satisfactory way, while the measurements at $[Cd^{2+}] \geqslant 0.75$ mol dm^{-3} deviate significantly from this calculated curve, which corresponds to $\log K_{Cd(dms)} = -0.32$. However, evaluation of the measurements at large Cd^{2+} concentrations, in the way described for Ca^{2+}–, Zn^{2+}–, or Pb^{2+}–dms, gives a very similar result: $\log K_{Cd(dms)} = -0.33$. Hence, despite the aforementioned difficulties we conclude that $\log K_{Cd(dms)} = -0.3 \pm 0.2$ and that this is a reasonable estimate for the stability of $[Cd(dms)]^{2+}$; moreover, if all experimental data shown in Figure 5 are forcefully fitted to equations (3) and (6) one still obtains a constant which is within the given error limits. The only way we see at present to explain the deviations indicated in Figure 5 would be to postulate a species $[Cd_2(dms)]^{4+}$ {which would formally correspond to a sulphone, *i.e.* O_2SR_2, while $[Cd(dms)]^{2+}$ corresponds to a sulphoxide OSR_2}, but without further evidence, which seems difficult to obtain, we are very reluctant to do so,

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* To a first approximation this assumption is certainly justified (see also footnote *c* in Table 1) and is confirmed, *e.g.* by the similar changes observed in the chemical shifts of amino-acids under the influence of protonation and Zn^{2+} complexation (B. E. Fischer and H. Sigel, *J. Amer. Chem. Soc.*, 1980, **102**, in the press).

† This value corresponds to the Ag^+–dms system where $\delta_0 = 2.125$ p.p.m. (average value) and $\delta_\infty = 2.459 \pm 0.003$ p.p.m.

although it must be said that μ-chloro- or μ-hydroxo-complexes, for example, are well known.

All the results of the M^{n+}–dms systems are summarised in Table 1, together with the stability constants of several M^{n+}–tetrahydrothiophen systems. These latter systems were studied by spectrophotometry (see Experimental section and ref. 21) in 50% aqueous ethanol which corresponds to a mol fraction of 0.24 (I = 1.0 mol dm^{-3}, Na[ClO$_4$] or Na[NO$_3$]; 25 °C). The results demonstrate again the rather high stability of the silver(I) complex compared with the listed M^{2+} complexes.

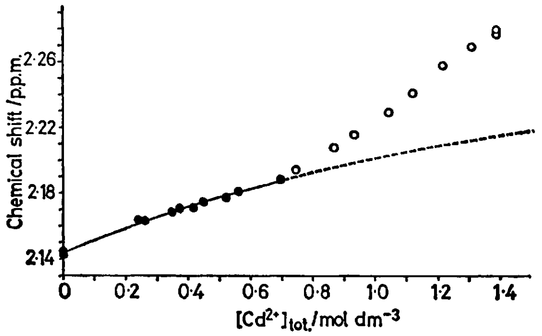

FIGURE 5 Chemical shift of the resonance of the methyl protons of dimethyl sulphide (1.5 × 10^{-2} mol dm^{-3}) as a function of [Cd(ClO$_4$)$_2$]$_{tot}$. The measurements (I = 2—4.5 mol dm^{-3}, Na[ClO$_4$]; 34 °C) were carried out in aqueous solution at pH *ca.* 2. The curve shown is the computer calculated best fit of the experimental data at [Cd^{2+}] $\leqslant$ 0.7 mol dm^{-3} (●): $K_{Cd(dms)}$ = 0.47 ± 0.25 dm^3 mol^{-1}, δ_0 = 2.143 p.p.m., and δ_∞ = 2.32 ± 0.08 p.p.m. For data (○) which deviate from the curve see text

DISCUSSION

Comparison of the Stability of Disulphide and Thioether Complexes.—A comparison of the stability constants listed in Table 1 reveals that the ligating properties of the disulphide and the thioether groups appear to be about the same for hard metal ions (*e.g.* Ca^{2+}), while for several of the borderline metal ions (*e.g.* Cd^{2+}, see refs. 1 and 21, and Pb^{2+}) they are somewhat different: this means the disulphide complexes are less stable than the corresponding thioether complexes.* With the soft Ag^+ ion these properties are even more evident: the difference in stability between the silver(I) complexes of dimethyl disulphide and dimethyl sulphide is a factor of 50. This may indicate that the S_2R_2 group is somewhat less soft than the SR_2 moiety.

All things considered, one may conclude that the results of Table 1 are in accord with what one might have predicted. Due to the formation of double bonds in a disulphide (p_π–d_π interaction) [4,34] the electrons are less available for co-ordination than at thioether sulphur,[9] hence complexes with S_2R_2 are expected to be somewhat less stable than those with SR_2. In line with this reasoning is the so-called α-effect, *i.e.* the observation that *e.g.* OH^- is a better base than OOH^-, or NH_3 than NH_2NH_2, and indeed this is also true for SMe_2 and S_2Me_2.[16]

Chelate-formation Properties of Disulphide and Thioether Moieties.—In the light of the preceding results it is interesting to compare the ligating properties of the disulphide and thioether groups in ligands which are potentially able to form chelates: this was done by comparing the tetrahydrothiophen moiety in tetrahydrothiophen-2-carboxylate (thtc$^-$) with the 1,2-dithiolan residue of 1,2-dithiolan-3-carboxylate [tetranorlipoate (tnl$^-$); see Figure 1]. It should be noted that the steric properties of both ligands are practically identical. Taking into account the suggestion [4,34] that the p_π–d_π interaction is more pronounced in simple aliphatic disulphides and that this double-bond character is somewhat diminished in the 1,2-thiolan ring, one might expect some enhanced ligating properties for the ring system compared with simple aliphatic disulphides, but this seems not to be the case. The 1,2-dithiolan moiety is also a poorer ligating group than the tetrahydrothiophen ring, *i.e.* the following results fit clearly into the picture already described for dimethyl disulphide and dimethyl thioether.

For the complexes with tetrahydrothiophen-2-carboxylate and 1,2-dithiolan-3-carboxylate (ML^+) an equilibrium is expected between a chelated isomer in which the carboxylate moiety and a sulphur atom are co-ordinated to the metal ion (depicted as ML_{OS}^+) and a simple carboxylate-co-ordinated isomer (ML_O^+). Hence, for these isomers the intramolecular equilibrium [35,36] (8a) can be

$$ML_O^+ \rightleftharpoons ML_{OS}^+ \qquad (8a)$$

$$K_{ch.} = [ML_{OS}]/[ML_O] \qquad (8b)$$

defined. The corresponding equilibrium constant $K_{chelate}$ (= K_{ch}) is dimensionless and therefore independent of the absolute concentration of ML^+. The simple equilibrium (7) may now be rewritten as equilibrium (9a)

$$M^{2+} + L^- \rightleftharpoons (ML_O^+ + ML_{OS}^+) \qquad (9a)$$

$$K_{ML} = ([ML_O] + [ML_{OS}])/[M][L] \qquad (9b)$$

In addition a constant K_{ML_O} may be defined which quantifies equilibrium (10a), *i.e.* the reaction between

$$M^{2+} + L^- \rightleftharpoons ML_O^+ \qquad (10a)$$

$$K_{ML_O} = [ML_O]/[M][L] \qquad (10b)$$

M^{2+} and L^- for the simple carboxylate co-ordination. Substitution of (8b) and (10b) into equation (9b) gives the relations (11) and (12). If one assumes that in a

$$K_{ML} = K_{ML_O} + K_{ML_O}K_{ch.} = K_{ML_O}(1 + K_{ch.}) \qquad (11)$$

$$K_{ch.} = (K_{ML}/K_{ML_O}) - 1 \qquad (12)$$

theoretical case 20% of ML^+ exists in the chelated form ML_{OS}^+, one calculates from equation (8b) $K_{ch.}$ = 0.25, and then from equation (12) the difference log Δ = logK_{ML} − logK_{ML_O} = 0.1. As a difference of 0.1 log units

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* The stabilities of [Cu(dmds)]$^{2+}$ and [Cu(des)]$^{2+}$ (des = diethyl sulphide) in 50% ethanol (see Table 1) are apparently contrary to this conclusion but one should remember that different solvents have different effects on the complex stability of ligands (probably due to steric restrictions in the solvated co-ordination sphere) [33] as was shown recently for Cu^{2+}–thioether complexes.[21] The stabilities of the copper(II) complexes of the sterically *very* similar ligands 1,2-dithiolan-3-carboxylate and tetrahydrothiophen-2-carboxylate do fit into the above picture (see below and Table 2).

corresponds approximately to the lower limit which may be determined from potentiometric pH titration data with some reliability, for the considered complex systems, this means that the lower limit of formation which may be estimated for ML_{OS}^+ is 20%; all lower values cannot be determined by this method. Furthermore, a difference of log $\Delta = 1$ means that 90% of the complex is present as the chelated isomer ML_{OS}^+, and log $\Delta = 2$ corresponds to 99% ML_{OS}^+. It must be added that the values of log Δ (Table 2) may not be directly compared with the values of log K_{ML} given in Table 1.

TABLE 2

Dimensionless equilibrium constants $K_{ch.}$ [equation (8b)] for the intramolecular equilibrium between the chelated isomer (ML_{OS}^+) and the simple carboxylate-co-ordinated isomer (ML_O^+) for several metal(II)-ion complexes of thtc⁻ and tnl⁻, together with the calculated percentages of the chelated isomer, in 50% aqueous dioxan at $I = 0.1$ mol dm^{-3} and 25 °C

L	M	log K_{ML} [a]	log K_{MLO} [b]	log Δ [c]	$K_{ch.}$	% ML_{OS}^+ [d]
thtc⁻	Mn	1.80 ± 0.05 [e]	1.88 [e]	*ca.* 0	*ca.* 0	⩽20 [f]
	Cu	4.31 ± 0.03 [e]	3.15 [e]	1.16	13.5	93 ± 1
	Zn	2.35 ± 0.03 [e]	2.20 [e]	0.15	0.4	29 ± 8
	Cd	2.68 ± 0.02 [g]	2.34 [g]	0.34	1.2	54 ± 4
	Pb	3.32 ± 0.03 [g]	2.92 [g]	0.40	1.5	60 ± 5
tnl⁻	Mn	1.87 ± 0.03 [h]	1.83 [h]	*ca.* 0	*ca.* 0	⩽20 [f]
	Cu	3.07 ± 0.03 [h]	2.84 [h]	0.23	0.7	41 ± 7
	Zn	2.14 ± 0.03 [h]	1.99 [h]	0.15	0.4	29 ± 8
	Cd	2.10 ± 0.04 [g]	2.16 [g]	*ca.* 0	*ca.* 0	⩽20 [f]
	Pb	2.76 ± 0.04 [g]	2.45 [g]	0.31	1.0	50 ± 7

[a] The errors given are *three* times the standard error of the mean value. [b] These values are expected on the grounds of the basicity of the carboxylate group (see the corresponding 'reference lines' in the original papers,[10,11,37,38] which were obtained from the complexes with formate, acetate, *etc.*). As the extrapolation of these values is based on several independent systems the error is estimated to be ⩽0.02 log units. [c] log Δ = log K_{ML} − logK_{MLO}. [d] The error limits were calculated by adding 0.02 log units to the given errors of log K_{ML}. [e] From refs. 37 and 38. [f] See text. [g] From ref. 11. [h] From ref. 10.

With this background we may now view the results listed in Table 2 which have been calculated from published data.[10,11,37,38] It is immediately evident that in all systems a considerable percentage of the simple carboxylate co-ordinated isomer ML_O^+ is still present, but also that in the M^{2+}–thtc⁻ systems the percentage of the chelated isomer ML_{OS}^+ is larger than for the M^{2+}–tnl⁻ systems, thus confirming the somewhat better ligating properties of thioethers compared with disulphides. In addition, by closer consideration, finer details are confirmed such as the similar co-ordination tendency of Zn^{2+} towards SR_2 and S_2R_2, or the tendency of Cd^{2+} to favour SR_2 (see also Table 1).

To summarize, the ligating properties of both the disulphide and the thioether [21] groups favour soft metal ions, while their tendency to co-ordinate with the biologically important hard or borderline metal ions is obviously very slight and rather unspecific (Table 1). However, it must be pointed out that these seemingly negligible co-ordinating properties may lead to enhanced complex formation with ligands which have these weakly co-ordinating moieties in addition to stronger binding sites in the appropriate steric position, as we have seen for the M^{2+}–thtc⁻ or –tnl⁻ systems (Table 2), a fact which also holds for mixed-ligand complexes.[10,38] We believe that the most important point, with regard to biological systems, is that equilibria between isomers of certain complexes may be attained rather easily. This factor could well be a key to selectivity, especially as such interactions may occur stereospecifically as was shown [18,38,39] earlier for the tetrahydrothiophen moiety of *d*-biotin with Mn^{2+} and Cu^{2+}.

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REFERENCES

[1] R. B. Martin, in 'Metal Ions in Biological Systems,' ed. H. Sigel, Marcel Dekker, New York, Basle, 1979, vol. 9, p. 1.

[2] D. L. Rabenstein, R. Guevremont, and C. A. Evans, in ref. 1, p. 103.

[3] J. C. H. Shih, P. B. Williams, L. D. Wright, and D. B. McCormick, *J. Heterocyclic Chem.*, 1974, **11**, 119.

[4] U. Schmidt, P. Grafen, and H. W. Goedde, *Angew. Chem.*, 1965, **77**, 900; *Angew. Chem. Internat. Edn.*, 1965, **4**, 846.

[5] R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581, 643.

[6] L. G. Warner, T. Ottersen, and K. Seff, *Inorg. Chem.*, 1974, **13**, 2529.

[7] C. J. Hawkins and D. D. Perrin, *Inorg. Chem.*, 1963, **2**, 843.

[8] E. W. Wilson, jun., and R. B. Martin, *Arch. Biochem. Biophys.*, 1971, **142**, 445.

[9] P. Kroneck, *J. Amer. Chem. Soc.*, 1975, **97**, 3839.

[10] H. Sigel, B. Prijs, D. B. McCormick, and J. C. H. Shih, *Arch. Biochem. Biophys.*, 1978, **187**, 208.

[11] H. Sigel, B. Prijs, and D. B. McCormick, *J. Inorg. Nuclear Chem.*, 1978, **40**, 1678.

[12] C.-I. Brändén, *Acta Chem. Scand.*, 1967, **21**, 1000.

[13] L. G. Warner, T. Ottersen, and K. Seff, *Inorg. Chem.*, 1974, **13**, 2819.

[14] K. Burger, in ref. 1, p. 213.

[15] T. L. James and R. J. Kula, *J. Phys. Chem.*, 1969, **73**, 634.

[16] P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 1973, **95**, 5960.

[17] P. Bonvicini, A. Levi, V. Lucchini, and G. Scorrano, *J.C.S. Perkin II*, 1972, 2267.

[18] D. B. McCormick, R. Griesser, and H. Sigel, in 'Metal Ions in Biological Systems,' ed. H. Sigel, Marcel Dekker, New York, Basle, 1974, vol. 1, p. 213.

[19] A. R. Amundsen, J. Whelan, and B. Bosnich, *Inorg. Chem.*, 1979, **18**, 206.

[20] P. M. Colman, H. C. Freeman, J. M. Guss, M. Murata, V. A. Norris, J. A. M. Ramshaw, and M. P. Venkatappa, *Nature*, 1978, **272**, 319.

[21] H. Sigel, V. M. Rheinberger, and B. E. Fischer, *Inorg. Chem.*, 1979, **18**, 3334.

[22] P.K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188.

[23] P. R. Mitchell and H. Sigel, *J. Amer. Chem. Soc.*, 1978, **100**, 1564.

[24] P. R. Mitchell, *J.C.S. Dalton*, 1979, 771.

[25] L. Johansson, *Co-ordination Chem. Rev.*, 1974, **12**, 241.

[26] L. G. Sillén and A. E. Martell, 'Stability Constants of Metal–Ion Complexes,' *Special Publ.*, The Chemical Society, London, 1964, no. 17; 1971, no. 25.

[27] M. H. Hutchinson and W. C. E. Higginson, *J.C.S. Dalton*, 1973, 1247.

[28] H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, 1949, **71**, 2703.

[29] R. Cecil and J. R. McPhee, *Biochem. J.*, 1957, **66**, 538; *Adv. Protein Chem.*, 1959, **14**, 255.

[30] S. Blackburn and F. Challenger, *J. Chem. Soc.*, 1938, 1872.

[31] M. M. David, R. Sperling, and I. Z. Steinberg, *Biochim. Biophys. Acta*, 1974, **359**, 101.

[32] M. Widmer, Thesis, ETH Zürich, 1972; M. Widmer and G. Schwarzenbach, *Chimia*, 1970, **24**, 447.

[33] H. B. Silber and L. U. Kromer, American Chemical Society Meeting, Honolulu (Hawaii), 1979, Abstract INOR no. 518.

[34] G. Bergson, *Arkiv. Kemi*, 1958, **12**, 233.

[35] Y. H. Mariam and R. B. Martin, *Inorg. Chim. Acta*, 1979, **35**, 23.

[36] J. B. Orenberg, B. E. Fischer, and H. Sigel, *J. Inorg. Nuclear Chem.*, 1980, in the press.

[37] H. Sigel, R. Griesser, B. Prijs, D. B. McCormick, and M. G. Joiner, *Arch. Biochem. Biophys.*, 1969, **130**, 514.

[38] H. Sigel, D. B. McCormick, R. Griesser, B. Prijs, and L. D. Wright, *Biochemistry*, 1969, **8**, 2687.

[39] R. Griesser, B. Prijs, H. Sigel, W. Föry, L. D. Wright, and D. B. McCormick, *Biochemistry*, 1970, **9**, 3285.