Synthetic, structural and kinetic studies on the binding of cyclohexane-1,2-bis(4-methyl-3-thiosemicarbazone) to divalent metal ions (Co, Ni, Cu, Zn or Cd)†

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The reactions of cyclohexane-1,2-bis(4-methyl-3-thiosemicarbazone) (CHMTSC) with MCl_2 (M = Co, Ni, Cu or Zn) and $Cd(NO_3)_2$ have been shown to produce complexes in which the thiosemicarbazone has been doubly deprotonated {[M(CHMTSC – $2H^+$)] (M = Co, Ni or Ni)}, analogous to those reported earlier with other Schiff base thiosemicarbazones. However, with $ZnCl_2$ and $Cd(NO_3)_2$, the complexes isolated are [ZnCl(CHMTSC)]Cl and $[Cd(NO_3)(CHMTSC)]NO_3$, containing the protonated forms of the ligand, which have been characterised by X-ray crystallography, as has free CHMTSC. The kinetics of the reactions between CHMTSC and all the various metal salts have been determined by stopped-flow spectrophotometry. In all cases, the reactions are complete on the seconds timescale. The reactions exhibit a first-order dependence on the concentration of metal salt and a first-order dependence on the concentration of CHMTSC. The thermodynamic and kinetic factors influencing the protonation state of the coordinated thiosemicarbazone are discussed.

Introduction

Thiosemicarbazides and their metal complexes find applications in areas as diverse as nuclear medicine, pharmacology and analytical chemistry.[1–6] In particular, Cu(II) Schiff base complexes of thiosemicarbazones have been investigated as anticancer chemotherapeutic agents and radical scavengers.[7] In addition, it is their use as agents capable of delivering radioactive copper in new copper-based radiopharmaceuticals, together with the hypoxic selectivity of certain copper thiosemicarbazone complexes, that has created much recent interest.[6–8] Furthermore, there has been an increased interest in thiosemicarbazones, particularly in the last few years, related to their range of biological properties, for example as antiviral, antibacterial and anticancer agents,[9–16] antifungal[17] and antitumour[18] properties as well as being suggested as pesticides.[19,20] These biological activities are often attributed to thiosemicarbazones chelating with metal ions. The present level of interest in metal complexes of thiosemicarbazones stems from the fact that the biological activity of the organic compound is enhanced by coordination to a transition metal.[21]

In the laboratory, the interest in thiosemicarbazone complexes relates to their applications in chemical analysis. In inorganic analysis, thiosemicarbazones have been used as reagents for the quantitative determination of a variety of metal ions, and in organic analysis for identification of aldehydes and ketones.[22,23]

The presence of amide, imine and C=S groups in thiosemicarbazides make them potentially polydentate ligands with a variety of different donor atoms possible.[24–26] Numerous complexes of thiosemicarbazones have been prepared and characterized.[27–31] In this paper, we report the synthesis, characterization and X-ray crystal structure of cyclohexane-1,2-bis(4-methyl-3-thiosemicarbazone) (CHMTSC) (Fig. 1). This molecule coordinates to a variety of divalent metal ions M^{2+} (M = Co, Ni, Cu, Zn or Cd), and two types of complexes are obtained, which differ in the protonation state of the CHMTSC ligand. With Zn or Cd, X-ray crystallography shows that the isolated products contain the $\{M(CHMTSC)\}^{2+}$ core in which CHTMSC acts as a

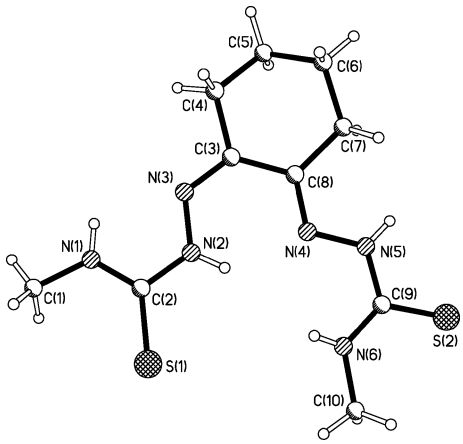

Fig. 1 The structure of CHTMSC. Selected bond lengths (Å) and angles (°): C(3)–N(3) 1.2979(17), C(2)–S(1) 1.6829(4), N(3)–N(2) 1.3585(16), C(2)–N(1) 1.3248(19), N(2)–C(2) = 1.3693(18); C(3)–N(3)–N(2) 120.44(12), N(2)–C(2)–S(1) 118.90(11), N(2)–C(2)–N(1) 115.49(12).

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† Electronic supplementary information (ESI) available: Kinetic data for the reactions between M^{2+} (M = Zn, Cd, Co, Ni or Cu) and CHMTSC in MeCN at 25 °C. CCDC reference numbers 699874–699876. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814852j

Table 1 Characterization of [M(CHMTSC – $2H^+$)] (M = Co, Ni or Cu)

			Elemental Analysis (calcd)[a]			UV-vis spectrum				IR spectrum/cm^{-1}	
M	Colour	Yield (%)	C	N	H	λ_{max}/nm	ε_{max}/dm^3 mol^{-1} cm^{-1}	Mass spectrum (M^+)	μ/BM	υ_{NH}	υ_{CN}
Co	Dark red	72	35.1 (35.0)	24.3 (24.5)	4.8 (4.7)	512 370	220 750	342	1.75	3183	1581
Ni	Green	62	35.3 (35.0)	24.1 (24.5)	4.9 (4.7)	635 405 493	160 320 240	343	—	3130	1587
Cu	Dark green	73	34.2 (34.5)	24.4 (24.2)	4.5 (4.6)	367	900	347	1.65	3196	1573

[a] Calculated values based on formulation [$M(C_{10}H_{16}N_6S_2)$].

planar quadridentate ligand. The remainder of the coordination sphere comprises anionic ligands derived from the parent metal salt. In contrast, with Co, Ni or Cu, the isolated products are the neutral [M(CHMTSC – $2H^+$)], in which the CHMTSC ligand has been deprotonated at the two hydrazide nitrogen sites. Similar complexes of Zn, Ni and Cu have been described before.[32,33] Kinetic studies on the formation of all these complexes, together with consideration of how coordination to M^{2+} would affect N–H acidity, suggests the factors that lead to formation of the two types of products.

Experimental

Elemental analyses (C, H and N) were carried out on a Carlo Erba 1108 analyzer. Electronic spectra were measured in the region 200–1100 nm for solutions in DMF at room temperature using a Shimadzu 160 UV–vis spectrophotometer. Infrared spectra were recorded by using a Thermo Electron Corporation Nicolet Avatar 370 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 using a Bruker 300 MHz spectrometer. Mass spectra were obtained using an EI (+) micro mass autospec high-resolution magnetic sector mass spectrometer.

All reagents were commercially available (Aldrich Chemical Co.) and were used without further purification. All manipulations in the synthesis of CHMTSC and the complexes were performed in air. Solvents used in the syntheses were distilled from the appropriate drying agent immediately prior to use.

Preparation of CHMTSC

To cyclohexane-1,2-dione (1.2 g, 10.7 mmol) dissolved in methanol (50 cm^3) was added 4-methyl-3-thiosemicarbazide (2.25 g, 21.4 mmol) in methanol (20 cm^3). The mixture was heated under reflux for 3 h. The clear solution was allowed to stand and then was left to cool to 0 °C. Yellow crystals formed after 48 h, and these were removed by filtration, washed with ice-cold methanol and dried under vacuum. Yield = 50%, m.p = 188–190 °C. Elemental analysis (calculated value in parentheses): C 41.69 (41.96), H 6.42 (6.29), N 29.08 (29.37). ^{1}H NMR spectrum δ/ppm: 1.7–2.4 (cyclohexane protons, m, 8H); 3.0 (CH_3, s, 6H); 8.6 ($N_{(1)}H$ and $N_{(6)}H$, s, 2H); 10.6 ($N_{(2)}H$ and $N_{(5)}H$, s, 2H). ^{13}C{^{1}H} NMR spectrum δ/ppm: 21.64–27.53 (cyclohexane carbons); 33.94 (CH_3); 138.32 (N=*C*); 179.53 (*C*=S).

Preparation of [M(CHMTSC – $2H^+$)] (M = Co, Ni or Cu)

The preparation of all these complexes is essentially the same and so a generic description of their synthesis will be presented. To a solution of the metal nitrate salt in acetonitrile was added the stoichiometric amount of CHMTSC. The solution was not stirred and a microcrystalline solid was formed immediately. The solid was removed by filtration, washed with CH_3CN, then diethyl ether and finally dried *in vacuo*. All attempts to recrystallize the samples, or to grow crystals from the reaction mixture, suitable for X-ray crystallography, were unsuccessful. Elemental analysis data, colour and yield for the complexes are given in Table 1.

Preparation [Zn(CHMTSC)Cl]Cl·CH_3CN

To a solution of anhydrous $ZnCl_2$ in CH_3CN was added the stoichiometric amount of CHMTSC. The solution was not stirred, and after leaving undisturbed for 2–3 d, yellow crystals were deposited. The crystals were removed by filtration, washed with a small amount of MeCN and dried *in vacuo*. Yield = 66%. ^{1}H NMR spectrum δ/ppm: 1.68–2.87 (cyclohexane protons, m, 8H); 2.08 (CH_3CN, s, 3H); 2.98 (CH_3, s, 6H); 8.87 ($N_{(1)}H$ and $N_{(6)}H$, s, 2H); 10.63 ($N_{(2)}H$ and $N_{(5)}H$, s, 2H). ^{13}C{^{1}H} NMR spectrum δ/ppm: 20.14–29.90 (cyclohexane carbons); 30.13 (CH_3); 32.52 (CH_3CN); 137.82 ($CH_3C{\equiv}N$); 146.15 (N=*C*); 178.67 (*C*=S).

Preparation [Cd(CHMTSC)(NO_3)]NO_3·CH_3CN

This complex was prepared by a method analogous to that described above for [Zn(CHMTSC)Cl]Cl·CH_3CN, except that $Cd(NO_3)_2{\cdot}4H_2O$ was employed. Yield = 68%. ^{1}H NMR spectrum δ/ppm: 1.75–2.87 (cyclohexane protons, m, 8H); 3.09 (CH_3, s, 6H); 8.85 ($N_{(1)}H$ and $N_{(6)}H$, s, 2H); 11.36 ($N_{(2)}H$ and $N_{(5)}H$, s, 2H). ^{13}C{^{1}H} NMR spectrum: 19.16–29.63 (cyclohexane carbons); 30.22 (CH_3); 145.22 (N=*C*); 178.53 (*C*=S).

X-Ray crystal structures of CHMTSC, [Zn(CHMTSC)Cl]Cl·CH_3CN and [Cd(CHMTSC)NO_3]NO_3·CH_3CN

Data were collected with MoKα radiation (λ = 0.71073 Å) at 150 K on a Bruker SMART 1K diffractometer.[34] Semi-empirical absorption corrections were applied, based on repeated and symmetry-equivalent reflections. Non-merohedral twinning for

Table 2 Crystal and refinement data for the structures of CHMTSC, [ZnCl(CHMTSC)]Cl·MeCN and [Cd(NO$_3$)(CHMTSC)]NO$_3$·MeCN

Compound	CHMTSC	[ZnCl(CHMTSC)]Cl·CH$_3$CN	[Cd(NO$_3$)(CHMTSC)]NO$_3$·CH$_3$CN
Formula	$C_{10}H_{18}N_6S_2$	$C_{12}H_{21}Cl_2N_7S_2Zn$	$C_{12}H_{21}CdN_9O_6S_2$
M_r/g mol^{-1}	286.4	463.8	563.9
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$
a/Å	10.1389(7)	11.9205(11)	10.0365(11)
b/Å	8.7161(6)	7.8966(7)	8.8416(9)
c/Å	15.9291(11)	20.2112(18)	24.652(3)
β/°	99.967(1)	100.084(2)	101.2411(17)
V/Å^3	1386.44(17)	1873.1(3)	2145.6(4)
Z	4	4	4
D_{calc}/g cm^{-3}	1.372	1.644	1.746
μ/mm^{-1}	0.38	1.83	1.261
Max., min. transmission	0.870, 0.895	0.678, 0.982	0.700, 0.905
Reflections measured	11 948	28 236	18 450
Unique reflections, R_{int}	3358, 0.0173		5196, 0.0287
Refined parameters	235	237	290
R (F, $F^2 > 2\sigma$)	0.0350	0.0537	0.0258
R_w (F^2, all data)	0.0925	0.1130	0.0621
Goodness of fit on F^2	1.084	1.061	1.096
Max., min. electron density/e Å^{-3}	0.39, –0.24	0.75, –0.65	0.86, –1.03

the Zn complex prevents the merging of equivalent reflections before refinement. The structures were solved by direct methods, and refined on all F^2 values. H atoms were refined freely for CHMTSC and on heteroatoms of the complexes, and were constrained with a riding model otherwise.[35] Crystal and refinement data are given in Table 2.

Kinetic studies

In the kinetic studies, the hydrated nitrate salts of Zn, Cd, Co, Ni and Cu were used. Acetonitrile (the solvent) was dried over CaH_2 and distilled under an atmosphere of dinitrogen immediately prior to use.

All kinetic studies were performed using an Applied Photophysics SX.18MV stopped-flow spectrophotometer modified to handle air-sensitive and non-aqueous solutions. The spectrophotometer was controlled *via* a RISC pc. The temperature was maintained at 25.0 ± 0.1 °C using a Grant LTD 6G thermostat tank with combined recirculating pump. The reactant solutions of metal salt and CHMTSC were prepared in CH_3CN under an atmosphere of dinitrogen and transferred to the spectrophotometer *via* gas-tight, all-glass syringes. The solutions of all reagents were prepared by dilution from freshly made stock solutions and used within 1 h of preparation.

The absorbance-time traces were fitted to exponential curves using the Applied Photophysics software. The observed rate constants (k_{obs}) presented in Fig. 6 are the average of at least three experiments. The error bars presented in the figures show a 10% reproducibility. All experiments were performed under pseudo-first-order conditions with the concentration of CHMTSC in an excess over the concentration of the metal ion.[36] The dependence on the concentration of CHMTSC was determined from plots of k_{obs} *versus* [CHMTSC], as illustrated in Fig. 6. The straight line plots were analysed by least-square fits, constrained to go through the origin.

Results and discussion

Type of complex formed

Cyclohexane-1,2-bis(4-methyl-3-thiosemicarbazone) (CHMTSC) was prepared by the condensation of cyclohexane-1,2-dione and 4-methyl-3-thiosemicarbazide. The compound was characterized by elemental analysis, IR, ^{1}H, ^{13}C NMR spectroscopy and mass spectrometry (see Experimental), as well as X-ray crystallography (Fig. 1). The UV-vis spectrum of CHMTSC exhibited two absorption peaks at 307 and 358 nm, tentatively attributable to the (π–π^*) and (n–π^*) transitions, respectively. The X-ray crystal structure reveals no unusual structural features and the bond lengths and angles are very similar to those of other Schiff bases derived from diones and thiosemicarbazides.[32,33]

Consideration of the composition of CHMTSC indicates that any of the six nitrogen atoms or two sulfur atoms could coordinate to a metal ion. Studies on the reactions of CHMTSC with a variety of divalent metal ions (M = Co, Ni, Cu, Zn or Cd), in a 1 : 1 stoichiometric ratio, showed that two types of complexes are formed. For M = Zn or Cd, well-formed crystalline salts are produced slowly from solution and the structures have been determined by X-ray crystallography. The structures clearly show that in both the Zn and Cd complexes CHMTSC acts as a quadridentate ligand with the two imine nitrogen atoms and two sulfur atoms coordinating to the metals. In both complexes, the CHMTSC ligand is effectively planar, presumably because of the inflexibility in this ligand due to the extensive multiple bonding. Furthermore, the bond lengths and angles within the ligand are essentially the same for both the Cd and Zn complexes and are very similar to those reported for other Schiff base ligands derived from diones and thiosemicarbazides.[31–33] The remainder of the Zn and Cd coordination is the anion of the metal salt used in the preparation.

In [ZnCl(CHMTSC)]Cl (Fig. 2), Zn is five-coordinate. The overall geometry is best described as square-based pyramidal,

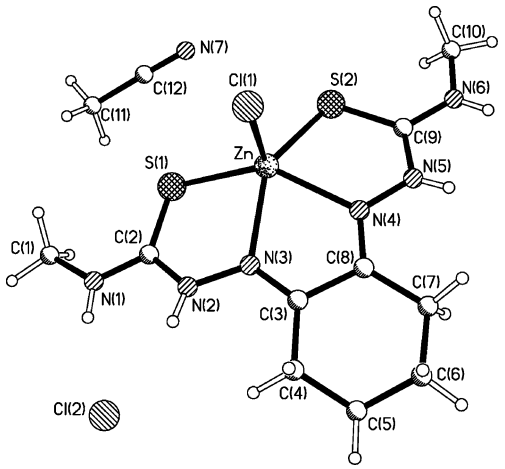


Fig. 2 Structure of $[ZnCl(CHMTSC)]Cl{\cdot}CH_3CN$. Selected bond lengths (Å) and bond angles (°) are shown in Table 3.

with the two imine nitrogen atoms and the two sulfur atoms of the CHMTSC ligand occupying the basal positions, and a chloro ligand occupying the apical site. The other chloride ion is not coordinated. The angles between the donor atoms of the Schiff base ligand and the coordinated Cl are all greater than 100°, showing that Zn sits slightly (0.40 Å) above the mean plane of the quadridentate ligand.

In $[Cd(NO_3)(CHMTSC)]NO_3$ (Fig. 3 and 4), Cd is seven-coordinate. The repeating monomeric unit comprises Cd coordinated by the planar CHTMSC ligand, and a nitrate group acting as a bidentate ligand, as shown in Fig 3. Each of these $[Cd(NO_3)(CHMTSC)]^+$ units is connected to its neighbour through one of the coordinated oxygen atoms of the bidentate nitrate. Thus, the coordination environment of each Cd atom comprises a central CHMTSC quadridentate ligand and two *trans* nitrate groups; one nitrate is a bidentate ligand to Cd whilst the other is a monodentate ligand bonded through an oxygen atom, which is also bonded to the adjacent Cd atom. The result is that the coordination sphere of the Cd is probably best described as a distorted octahedron with the CHMTSC ligand defining an equatorial plane. In contrast to the Zn complex, the Cd atom in this complex sits in the plane of the Schiff base ligand. The

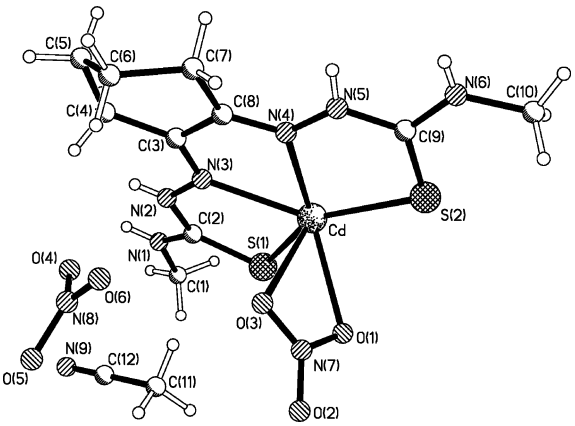


Fig. 3 Structure of the asymmetric unit of $[Cd(NO_3)(CHMTSC)]Cl{\cdot}CH_3CN$. Selected bond lengths (Å) and bond angles (°) are shown in Table 3.

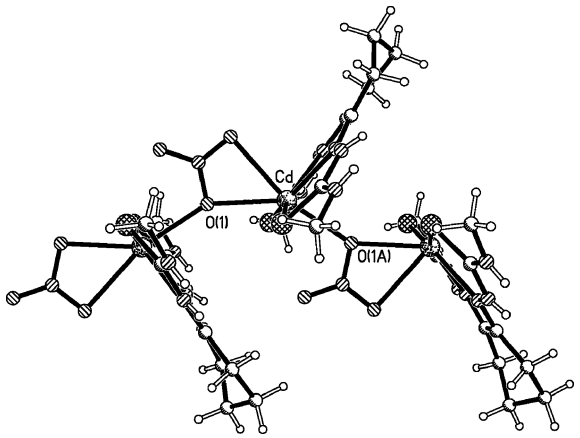


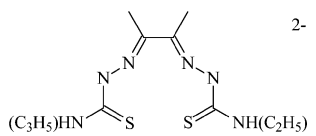
Fig. 4 The polymeric cation of $[Cd(NO_3)(CHMTSC)]NO_3{\cdot}CH_3CN$, showing the interconnection *via* bridging nitrates between adjacent $[Cd(NO_3)(CHMTSC)]^+$ units. Selected bond lengths (Å) and bond angles (°) are shown in Table 3. Symmetry operator: (A) $3/2 - x$, $1/2 + y$, $1/2 - z$.

angles between the donor atoms of the Schiff base ligand and the O(3) oxygen atom are all 90 ± 8°.

In both $[ZnCl(CHMTSC)]Cl$ and $[Cd(NO_3)(CHMTSC)]NO_3$, a CH_3CN molecule, which was indicated by the elemental analysis and spectroscopy of the complex, is evident in the crystal structure.

A comparison of the various bond lengths and angles within the CHMTSC ligands in the Zn and Cd complexes (Table 3) shows that they are very similar, and also very similar to those of uncoordinated CHMTSC (Fig. 1). Previous studies[32] on other Schiff base thiosemicarbazone complexes have reported the X-ray crystal structures of $[M(\text{thiosemicarbazone} - 2H^+)]$ (M = Zn, Ni or Cu) in which the Schiff base thiosemicarbazone ligand is deprotonated at the hydrazide atoms. Thus, in the structure of [Zn(ATSE)(MeOH)] (where ATSE has the structure shown below) the average of the two C–N (hydrazide) bond lengths is 1.325 Å and the average C–S bond length is 1.758 Å. A comparison with the analogous bond lengths for $[ZnCl(CHMTSC)]^+$ presented in Table 3 shows that the C–S distance in the CHMTSC complex is significantly shorter than in the (deprotonated) ATSE complex. Similarly, the C–N (hydrazide) bond length in the CHMTSC complex is appreciably longer than in the ATSE complex. These observations indicate that, whilst there is delocalisation in the ATSE ligand, and both the C–N and C–S bonds have partial double bond character, in the CHMTSC ligand, the C–S bond has more double bond character and the C–N (hydrazide) bond more single bond character.

ATSE =



In contrast to the type of complex obtained in the reactions between the Zn and Cd salts and CHMTSC, with the salts of Co, Ni or Cu elemental analysis and mass spectra of these materials indicate that they are neutral complexes with the formulation, $[M(CHMTSC - 2H^+)]$, analogous to those such as the ATSE complex described above. These complexes are formed by dissociation of protons from the two hydrazide nitrogen atoms

Table 3 Comparison of selected bond lengths (Å) and angles (°) in the structures of [ZnCl(CHMTSC)]Cl·CH_3CN and [Cd(NO_3)-(CHMTSC)]NO_3·CH_3CN

	Zn complex	Cd complex
Ligand dimensions		
C(2)–N(2)	1.370(2)	1.359(3)
N(2)–N(3)	1.352(2)	1.364(3)
N(3)–C(3)	1.296(2)	1.287(3)
S(1)–C(2)	1.709(2)	1.692(2)
C(3)–N(3)–N(2)	122.99(16)	119.27(19)
N(3)–N(2)–C(2)	117.10(16)	120.4(2)
N(2)–C(2)–S(1)	122.61(14)	124.06(18)
N(2)–C(2)–N(1)	115.36(18)	115.2(2)
Coordination geometry	M = Zn	M = Cd
Zn–Cl(1)	2.2908(5)	—
Cd–O(1)	—	2.4387(16)
Cd–O(3)	—	2.5797(18)
Cd–O(1A)	—	2.3715(16)
M–S(1)	2.3698(5)	2.5918(6)
M–S(2)	2.3915(6)	2.5954(7)
M–N(3)	2.1539(16)	2.3954(18)
M–N(4)	2.1516(15)	2.4039(17)
S(1)–Zn–Cl(1)	111.06(2)	—
S(2)–Zn–Cl(1)	108.24(2)	—
N(3)–Zn–Cl(1)	100.70(4)	—
N(4)–Zn–Cl(1)	100.81(4)	—
S(1)–Cd–O(3)	—	97.73(4)
S(2)–Cd–O(3)	—	94.55(4)
N(3)–Cd–O(3)	—	83.09(6)
N(4)–Cd–O(3)	—	83.59(6)
S(1)–Cd–O(1)	—	81.96(4)
S(2)–Cd–O(1)	—	81.01(4)
N(3)–Cd–O(1)	—	124.03(6)
N(4)–Cd–O(1)	—	125.51(5)
S(1)–M–N(3)	80.37(4)	74.15(5)
S(1)–M–S(2)	109.23(2)	145.25(2)
N(3)–M–N(4)	71.55(6)	65.79(6)
S(2)–M–N(4)	80.42(4)	74.09(5)

of CHMTSC (Fig. 5). There are two sources of ionizable protons in CHMTSC: N–H on the hydrazide residue and N–H on the NHMe group. Despite numerous attempts, we have been unable to produce crystals of suitable quality for X-ray structural analysis.

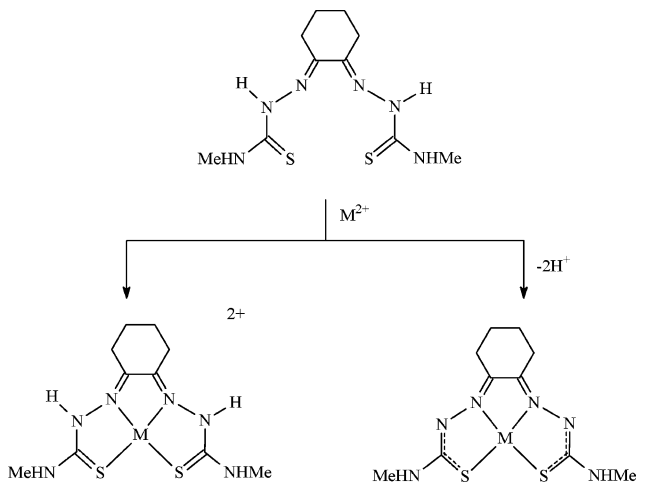


Fig. 5 Product types formed in the reactions of MX_2 salts with CHMTSC.

The poor solubility of the Ni complex precluded measuring the ^{1}H NMR spectrum.

Kinetics and mechanism of complex formation

We have investigated the kinetics of the reactions of CHMTSC with M^{2+} (M = Co, Ni, Cu, Zn and Cd) in CH_3CN, using stopped-flow spectrophotometry to see if there is a difference in the kinetics for the formation of the complexes where CHMTSC is coordinated (M = Zn or Cd) or where the deprotonated ligand, CHMTSC – $2H^+$ is coordinated (M = Co, Ni or Cu).

The reactions were studied under pseudo-first-order conditions with [CHMTSC] ≥ 10[M^{2+}]. In all cases, the stopped-flow absorbance-time traces can be fitted to a single exponential curve (Fig. 6), indicating that the reaction exhibits a first-order dependence on the concentration of M^{2+}. This conclusion is confirmed in studies where the concentration of M^{2+} was varied in the range 0.2–1.0 mmol dm^{-3} with [CHMTSC] = 10 mmol dm^{-3}, but the values of the observed rate constants (k_{obs}) for each reaction did not change (see ESI†).

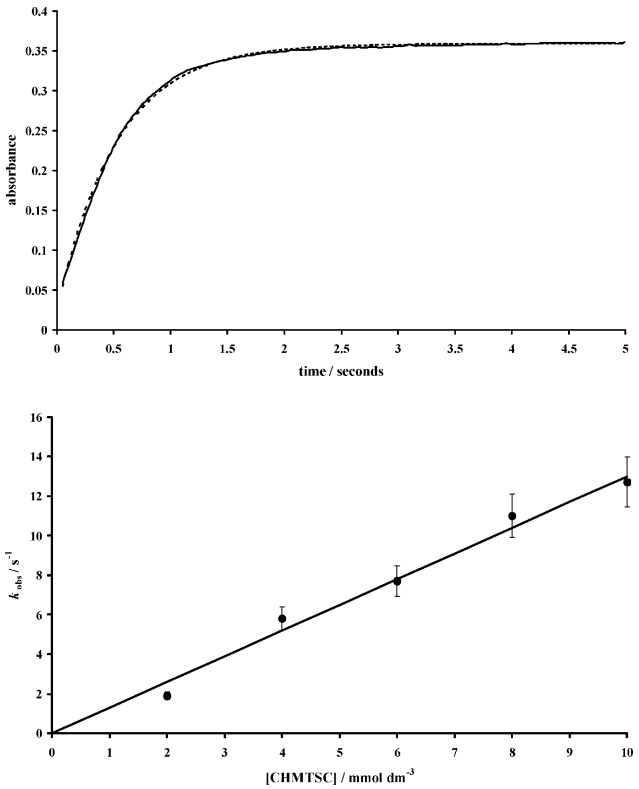


Fig. 6 Typical kinetic data for the reactions of M^{2+} with CHMTSC in MeCN at 25 °C. The example shown is for the reaction with Co^{2+}. Top shows a typical stopped-flow absorbance-time curve when [Co^{2+}] = 0.2 mmol dm^{-3} and [CHMTSC] = 2 mmol dm^{-3}. The solid black curve is the experimental data and the grey dashed curve is the fit. The fit is defined by the equation $A_t = 0.359–0.335e^{-1.9t}$. Bottom shows the first-order dependence of k_{obs} on the concentration of CHMTSC. Error bars show 10% reproducibility. Straight line fit to the data is that defined by the equation $k_{obs} = 1.3 \times 10^3$[CHMTSC].

For each different metal ion, the dependence of k_{obs} on the concentration of CHMTSC was the same, with all reactions exhibiting a first-order dependence on the concentration of CHMTSC, as

typified by the plot shown in Fig. 6 and the corresponding rate law in eqn (1). The reactions could only be studied up to a maximum concentration of [CHMTSC] = 10 mmol dm^{-3} because of the limited solubility of the thiosemicarbazone in CH_3CN. A mechanism consistent with the observed kinetics is shown in Fig. 7.

$$\frac{-\mathrm{d}\left[\mathrm{M}^{2+}\right]}{\mathrm{dt}} = k_{\mathrm{a}}{}^{\mathrm{M}}\left[\mathrm{CHMTSC}\right]\left[\mathrm{M}^{2+}\right] \quad (1)$$

$$\frac{-\mathrm{d}\left[\mathrm{M}^{2+}\right]}{\mathrm{dt}} = \frac{k_1{}^{\mathrm{M}}k_2{}^{\mathrm{M}}\left[\mathrm{CHMTSC}\right]\left[\mathrm{M}^{2+}\right]}{k_{-1}{}^{\mathrm{M}}\left[\mathrm{CH_3CN}\right] + k_2\mathrm{M}\left[\mathrm{CHMTSC}\right]} \quad (2)$$

$$\frac{-\mathrm{d}\left[\mathrm{M}^{2+}\right]}{\mathrm{dt}} = \frac{k_1{}^{\mathrm{M}}k_2{}^{\mathrm{M}}\left[\mathrm{CHMTSC}\right]\left[\mathrm{M}^{2+}\right]}{k_{-1}{}^{\mathrm{M}}\left[\mathrm{CH_3CN}\right]} \quad (3)$$

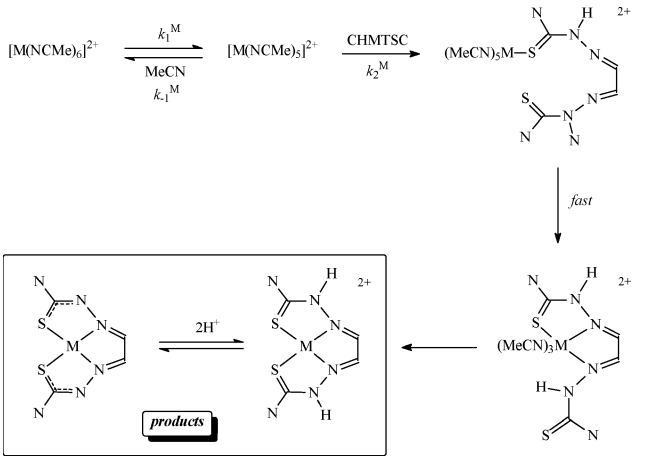


Fig. 7 Proposed mechanism for the formation of complexes containing the {M(CHMTSC)}$^{2+}$ and {M(CHMTSC – 2H$^+$)} cores in the reactions of M^{2+} with CHMTSC in MeCN.

In line with other studies on chelate formation,[37] we propose that the rate-limiting step of the chelate formation is the initial binding of CHMTSC to [M(NCMe)$_n$]$^{2+}$ by replacement of one of the coordinated CH_3CN molecules. The usual intimate mechanism for such a reaction is dissociative and involves initial dissociation of a coordinated solvent from [M(NCMe)$_n$]$^{2+}$, generating [M(NCMe)$_{(n-1)}$]$^{2+}$ containing a vacant site at which CHMTSC can bind (we suggest initially through a sulfur) as shown in Fig. 7. The full rate law for this mechanism is shown in eqn (2) and indicates that, over a large concentration range of CHMTSC, the kinetics would exhibit a non-linear dependence on concentration of CHMTSC. However, when the concentration of CHMTSC is small, $k_{-1}{}^{\mathrm{M}}$[MeCN] > $k_2{}^{\mathrm{M}}$[CHMTSC] the rate law would simplify to that shown in eqn (3), which is of the same form as observed experimentally in eqn (1). For each of the reactions studied, the values of $k_{\mathrm{a}}{}^{\mathrm{M}} = k_1{}^{\mathrm{M}}k_2{}^{\mathrm{M}}/k_{-1}{}^{\mathrm{M}}$[MeCN] are presented in Table 4.

Inspection of the rate constants in Table 4 reveals some interesting trends. In particular, the values of $k_{\mathrm{a}}{}^{\mathrm{M}}$ are rather insensitive to the nature of M^{2+}. Interestingly though, $k_{\mathrm{a}}{}^{\mathrm{M}}$ increases with the metal in the sequence Cu > Co > Ni, which is the same order as the solvent exchange rates of the corresponding [M(NCMe)$_6$]$^{2+}$ and reflects the relative dissociative lability of these metal ions.[38]

Table 4 Summary of rate constants for the reactions of CHMTSC with M^{2+} (M = Co, Ni, Cu, Zn or Cd) in MeCN at 25.0 °C

Metal ion M^{2+}	$k_{\mathrm{a}}{}^{\mathrm{M}}$/dm^3 mol^{-1} s^{-1}
Co	$1.3 \pm 0.1 \times 10^3$
Ni	$6.0 \pm 0.5 \times 10^2$
Cu	$2.0 \pm 0.2 \times 10^3$
Zn	$6.4 \pm 0.5 \times 10^2$
Cd	$6.2 \pm 0.5 \times 10^2$

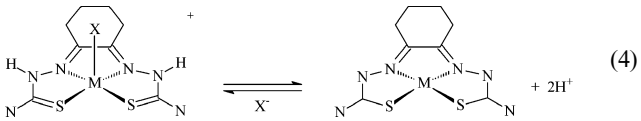
The rates of the reactions between [M(NCMe)$_n$]$^{2+}$ (M = Co, Ni or Cu) and CHMTSC are 10–1000 times slower than the rates of solvent exchange of the cations in acetonitrile.[38] This observation is consistent with the Eigen–Wilkins mechanism[39] in which outer-sphere association of CHMTSC with [M(NCMe)$_n$]$^{2+}$ precedes rate-limiting dissociation of a coordinated solvent, but the CHMTSC does not always bind to the vacant site on the metal complex. Most of the time another solvent molecule will bind to the coordinatively-unsaturated intermediate. Consequently, the rate of solvent exchange is faster than the rate of substitution.

Conclusions

In this paper, we have described two types of complexes formed in the reactions between CHMTSC and divalent metal ions; the difference in the two types of complex is that with M = Zn or Cd the isolated products contain the {M(CHMTSC)}$^{2+}$ core whilst with M = Co, Ni or Cu the products contain {M(CHMTSC – 2H$^+$)} in which the CHMTSC ligand has been deprotonated, presumably at both hydrazide nitrogen atoms. It is clearly of importance to understand the factors that control which type of complex is formed: kinetic or thermodynamic.

Our kinetic studies on the reactions between M^{2+} and CHMTSC show that for all systems, both the rate laws and values of the rate constants are very similar. There is no obvious difference in the kinetics between formation of products containing a {M(CHMTSC)}$^{2+}$ or a {M(CHMTSC – 2H$^+$)} core. This observation indicates that the protonation state of the ligand is controlled by factors, which occur after the steps monitored in the kinetic studies. It seems likely, therefore, that the protonation state of the CHMTSC ligand is controlled principally by thermodynamic factors defined by the metal site (metal and its co-ligands).

It would be anticipated that coordination of a hard Lewis acid (M^{2+}) to the Schiff base thiosemicarbazide will make the N–H groups on CHMTSC more acidic through the electron-withdrawing ability of the metal ion. However, the electron-withdrawing capability of the metal ion would be expected to be tempered by the coordination of an anion to the metal site. This proposal rationalizes why we isolate complexes containing the protonated CHMTSC ligands at Zn–Cl and Cd–NO_3. If such an argument is valid, then the protonation state of the thiosemicarbazide quadridentate ligand is coupled to, and can be controlled by, the coordination of anions (X$^-$) to the metal, as illustrated in eqn (4). Whilst this is an attractive, and reasonable proposition, it is difficult to test because of the poor solubility of [M(CHMTSC – 2H$^+$)], which complicates any analysis.



(4)

However, all of the divalent metal ions studied in this paper are labile centres and it would be anticipated that all of them would be capable of binding anions present in solution, presumably with the anions having similar residence times on the metal. It would be anticipated therefore that all the systems reported in this paper could produce complexes of the type $[MX(CHMTSC)]^+$ and $[M(CHMTSC - 2H^+)]$. The observation that when M = Co, Ni or Cu we only isolate complexes of the type $[M(CHMTSC - 2H^+)]$ indicates what controls the type of product isolated is the relative solubilities of $[MX(CHMTSC)]^+$ and $[M(CHMTSC - 2H^+)]$. The very poor solubility of $[M(CHMTSC - 2H^+)]$ (M = Co, Ni or Cu) results in these species being the only products isolated in the reactions. Attempts to protonate these complexes with strong acids (HCl or HNO_3) did not produce any tractable product, only decomposition of the complex.

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