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Metal-Induced Cyclization of Thiosemicarbazones Derived from β-Keto Amides and β-Keto Esters: Open-Chain and Cyclized Ligands in Zinc(II) Complexes

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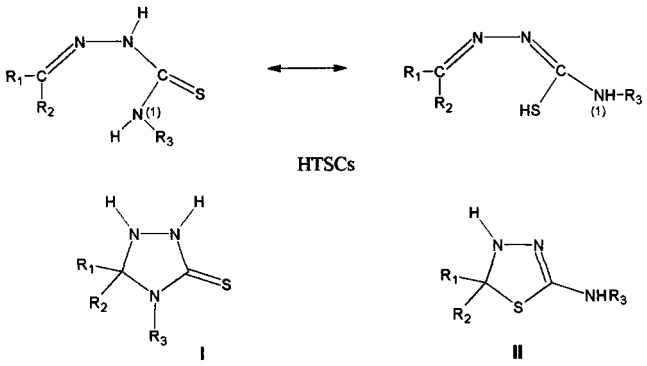
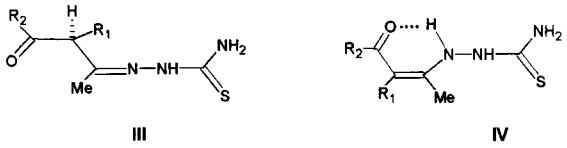
The reactions of $Zn(OAc)_2$ with acetoacetanilide, methyl acetoacetate, *o*-acetoacetanisidide, and ethyl 2-methyl-acetoacetate thiosemicarbazones ($HTSC^1$, $HTSC^2$, $HTSC^3$, and $HTSC^4$, respectively) were explored in methanol. With $HTSC^1$, $HTSC^2$, and $HTSC^3$, following isolation of the corresponding zinc(II) thiosemicarbazonates $[Zn(TSC^x)_2]$ ($x = 1, 2, 3$), the mother liquors afforded pyrazolonate complexes $[ZnL^1{}_2(H_2O)]$ (HL^1 = 2,5-dihydro-3-methyl-5-oxo-1*H*-pyrazole-1-carbothioamide) that had been formed by cyclization of the corresponding TSC^-. The reaction of $HTSC^4$ with zinc(II) acetate gave only the pyrazolonate complex $[ZnL^2{}_2(H_2O)]$ (HL^2 = 2,5-dihydro-3,4-dimethyl-5-oxo-1*H*-pyrazole-1-carbothioamide). All compounds were studied by IR and NMR spectroscopy, and $HTSC^3$, $[Zn(TSC^3)_2]\cdot$DMSO, $[ZnL^1{}_2(H_2O)]\cdot$2DMSO, and $[ZnL^2{}_2(H_2O)]\cdot$2DMSO were also studied by X-ray diffractometry, giving a thorough picture of the cyclization process. In preliminary tests of the effects of HL^1 and $[ZnL^1{}_2(H_2O)]$ on rat paw inflammatory edema induced by carrageenan, HL^1 showed antiinflammatory activity.

Introduction

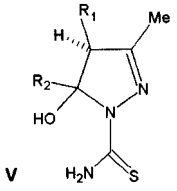
Ring−chain tautomerization in thiosemicarbazones was first postulated by Karabatsos et al.[2] Because thiosemicarbazones (HTSCs) usually possess two nucleophilic centers [N(1)−H and S−H] and a polar double bond (C═N), two rings are possible a priori: 1,2,4-triazolidine-3-thione (**I**), formed by intramolecular addition of N(1)−H to C═N; and 1,3,4-thiadiazoline-2-amine (**II**) when it is the S−H that is added to C═N:



Monothiosemicarbazones derived from 1,3-dicarbonyl compounds such as those of Scheme 1 are more complex systems.[3] In the first place, the open-chain compound can adopt either the hydrazone form **III** or the ene−hydrazine form **IV**:



Second, the existence of a C═O group that can undergo addition to the electrophilic group N(2)−H allows the formation of an additional type of ring, 1-[amino(thioxo)-methyl]-5-hydroxypyrazoline (**V**):



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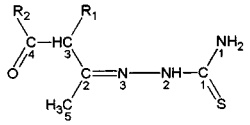
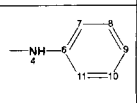
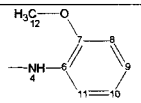
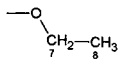
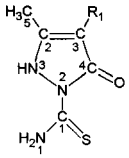
Scheme 1 The Thiosemicarbazones HTSC^x and 3-Pyrazolones (HL^1, R_1 = H; HL^2, R_1 = Me) Used or Produced in This Work, with the Atom-Numbering Convention



	HTSC^1	HTSC^2	HTSC^3	HTSC^4
R_1	H	H	H	$-CH_3$ (6)
R_2		$-OCH_3$ (6)		



The tautomeric equilibria among the above forms in solution are very sensitive to pH and the nature of the solvent.[3] Furthermore, tautomer **V** can lose HR_2 to give 3-pyrazolones. Although this latter cyclization−elimination reaction can take days or even months, depending on the pH of the solution,[4] in previous work[5] we found that the formation of 3-pyrazolones is much faster when $Cd(OAc)_2$ reacts with the thiosemicarbazones of acetoacetanilide and methyl acetoacetate (HTSC^1 and HTSC^2, respectively): in both cases, elimination of HR_2 (aniline in HTSC^1, methanol in HTSC^2) left complexes containing deprotonated 2,5-dihydro-3-methyl-5-oxo-1*H*-pyrazole-1-carbothioamide (HL^1).[6]

We report here the results of the reactions between $Zn(OAc)_2$ and HTSC^1, HTSC^2, *o*-acetoacetanisidide thiosemicarbazone (HTSC^3), and ethyl 2-methylacetoacetate thiosemicarbazone (HTSC^4) (see Scheme 1). The cyclization−elimination reactions were slower with Zn(II) than with Cd(II), allowing isolation of both complexes containing cyclized ligands and complexes containing uncyclized ligands. Thanks to this, in the case of HTSC^3 it was possible for the first time to follow step by step the structural changes leading to cyclization in the presence of a metal cation. Since the cyclization afforded derivatives of pyrazolones, a class of compounds that includes some widely used analgesic and nonsteroidal antiinflammatory drugs (NSAIDs),[7] we also carried out preliminary tests of the antiinflammatory activities of HL^1 and the zinc complex $[ZnL^1_2(H_2O)]$.

Experimental Section

Materials and Methods. Elemental analyses were performed with a Fisons EA1108 CHNS-O microanalyzer. Melting points were determined with a Büchi apparatus. IR spectra were recorded using KBr pellets on a Bruker IFS66V FT-IR spectrometer and are reported in cm^{-1} using the following abbreviations: vs = very strong, s = strong, m = medium, w = weak, sh = shoulder, br = broad. Mass spectra were recorded on Hewlett-Packard model 1100 MSD (electrospray), Hewlett-Packard model HT5988A (EI), and Micromass model Autospec (FAB) spectrometers. The quoted masses of the metaled ions (vide infra) are based on the isotope ^{64}Zn. The ^1H and ^{13}C NMR spectra of DMSO solutions were recorded on Bruker Advance 250, AMX-300, or AMX-500 apparatuses, using 5 mm o.d. tubes; chemical shifts (δ) are expressed in ppm, with the atoms numbered as in Scheme 1. Solid-state ^{13}C NMR spectra were run on a Bruker AMX 300 at 75.47 MHz with single cross-polarization contacts of 1 ms and magic angle spinning at 4.0 kHz in 7 mm zirconia rotors. The spectral width was 25 kHz, the acquisition time 41 ms, and the recycle time 5 s, using a CP/TOSS pulse program. Chemical shifts are referred to the downfield resonance of external glycine (176.1 ppm).

Thiosemicarbazide (Merck), acetoacetanilide (Merck), methylacetoacetate (Aldrich), *o*-acetoacetanisidide (Aldrich), ethyl 2-methylacetoacetate (Aldrich), and zinc acetate (Aldrich) were used as received. The HTSCs were obtained by the method of Jayasree and Aravindakshan.[8] Physical and analytical properties of HTSC^1, HTSC^2, and HL^1 have been published previously.[5] HL^2 was obtained by adding a 0.1 M aqueous solution of NaOH to a solution of HTSC^4 (0.25 g, 1.15 mmol) in MeOH (75 mL) until a pH of ca. 8 was reached. After 10 days' stirring, concentration of the solution to one-quarter of the initial volume gave a solid, which was filtered out and dried.

HTSC^1. IR: 3428s, 3268vs, b, 3155s, ν(N−H); 1655s, ν(C═O); 1595vs, ν(C═N); 1545s, 1248m, ν(NH−Ph); 1090s, 872m, ν(C═S). ^1H NMR: δ[N(2)H] = 10.17s(1); δ[N(4)H] = 10.05s(1); δ[N(1)H_2] = 8.16s(1), 7.62s(1); δ[C(7, 11)H] = 7.57 d (2); δ[C(8, 10)H] = 7.28t(2); δ[C(9)H] = 7.03t(1); δ[C(3)H_2] = 3.32s(2); δ[C(5)H_3] = 1.98s(3). ^{13}C NMR: δ[C(1)] = 178.8; δ[C(4)] = 167.3; δ[C(2)] = 148.8; δ[C(6)] = 139.0; δ[C(8, 10)] = 128.8; δ[C(9)] = 123.4; δ[C(7,11)] = 119.2; δ[C(3)] = 46.5; δ[C(5)] = 16.8.

HTSC^2. IR: 3402vs, 3277vs, 3169s, ν(N−H); 1719vs, ν(C═O); 1599vs, ν(C═N); 1440m, $\delta(OCH_3)$; 1246s, ν(C−O); 1090s, 853m, ν(C═S). ^1H NMR: δ[N(2)H] = 10.15s(1); δ [N(1)H_2] = 8.54s(1), 7.60s(1); δ[C(6)H_3] = 3.63s(3); δ[C(3)H_2] = 3.33s(2); δ[C(5)H_3] = 1.94s(3). ^{13}C NMR: δ[C(1)] = 178.9; δ[C(4)] = 170.1; δ[C(2)] = 147.2; δ[C(6)] = 51.9; δ[C(3)] = 43.7; δ[C(5)] = 16.8.

HTSC^3. Mp: 150 °C. Anal. Calcd for $C_{12}H_{16}N_4O_2S$: C, 51.4; H, 5.8; N, 20.0; S, 11.4. Found: C, 51.2; H, 6.1; N, 19.9; S, 11.4. MS(EI), *m*/*z* (%): 280(16.7) [M], 158(14.3) [M − NHPh(OCH_3)], 123(100.0) [NH_2Ph(OCH_3)]. IR: 3447s, 3414m, 3324s, 3298s, 3185m, ν(N−H); 1674s, ν(C═O); 1610vs, ν(C═N); 1542vs, 1260m, br, ν(NH−Ph(OCH_3)); 1437m, δ(O−CH_3); 1260m, br, 1048m, ν(C−O); 1100m, 820m, ν(C═S). ^1H NMR: δ[N(2)H] = 10.15s(1); δ[N(4)H] = 9.28s(1); δ[N(1)H_2] = 8.15s(1), 7.59s(1);

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(6) In our earlier paper[5] this ligand was named 2-[amino(thioxo)methyl]-5-methyl-2,3-dihydro-1H-3-pyrazolone (and referred to as HL). In the present paper we adopt the CAS nomenclature.

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δ[C(8−11)H] = 7.87m(1), 7.07m(2), 6.89m(1); δ[C(12)H_3] = 3.81s(3); δ[C(3)H_2] = 3.39s(2); δ[C(5)H_3] = 1.96. ^{13}C NMR: δ[C(1)] = 178.8; δ[C(4)] = 167.2; δ[C(6−11)] = 149.7, 126.9, 124.6, 122.1, 120.2, 111.2; δ[C(2)] = 149.4; δ[C(12)] = 55.6; δ[C(3)] = 46.6; δ[C(5)] = 16.8. Recrystallyzation from DMSO afforded crystals suitable for X-ray analysis.

HTSC^4. Mp: 80 °C. Anal. Calcd for $C_8H_{15}N_3O_2S$: C, 44.2; H, 7.0; N, 19.3; S, 14.8. Found: C, 44.2; H, 7.0; N, 19.4; S, 16.5. MS(EI), *m*/*z* (%): 217(3.5) [M], 172(1.0) [M − OEt], 144(3.0) [M − (COOEt)], 116(100.0) [M − (CH(CH_3)COOEt)]. IR: 3486s, 3354s, 3220s, ν(N−H); 1723s, ν(C═O); 1582s, ν(C═N); 1475m, δ(O−CH_2), 1182s, ν(C−O); 1085m, 852m, ν(C═S). ^{1}H NMR: δ[N(2)H] = 10.11s(1); δ[N(1)H_2] = 8.19s(1), 7.50s(1); δ[C(7)H_2] = 4.09c(2); δ[C(3)H] = 3.39c(1); δ[C(6)H_3] = 1.88s(3); δ[C(6)-H_3] = 1.21d(3); δ[C(8)H_3] = 1.15t(3). ^{13}C NMR: δ[C(1)] = 178.9; δ[C(4)] = 172.0; δ[C(2)] = 150.8; δ[C(7)] = 60.4; δ[C(3)] = 47.7; δ[C(6)] = 14.8; δ[C(5)] = 14.1; δ[C(8)] = 13.9.

HL^1. IR: 3269vs, 3164vs, ν(N−H); 1654vs, br, ν(C═O); 1592vs, 1550vs, 1507m, ν(ring); 1336s, ν(C−N) (see Results and Discussion); 1093s, 875m, ν(C═S). ^{1}H NMR: δ[N(3)H] = 11.98s-(1); δ[N(1)H_2] = 10.36s(1), 9.66s(1); δ[C(3)H] = 5.16s(1); δ[C(5)-H_3] = 2.17s(3). ^{13}C NMR: δ[C(1)] = 175.8; δ[C(4)] = 163.3; δ[C(2)] = 152.7; δ[C(3)] = 91.4; δ[C(5)] = 12.1.

HL^2. Mp: 160 °C. Anal. Calcd for $C_6H_9N_3OS$: C, 42.1; H, 5.3; N, 24.5; S, 18.7. Found: C, 42.2; H, 5.8; N, 24.6; S, 18.9. MS-(EI), *m*/*z* (%): 171(75) [M], 111(100) [M − C(S)NH_2], 97(42) [M − NC(S)NH_2]. IR: 3275vs, 3228s, ν(N−H); 1664vs, ν(C═O); 1600sh, 1581vs, br, 1512m, ν(ring); 1331s, ν(C−N) (see Results and Discussion); 1105s, 902m, ν(C═S). ^{1}H NMR: δ[N(3)H] = 10.50s(1); δ[N(1)H_2] = 10.39s(1); 9.63s(1); δ[C(5)H_3] = 2.13s-(3); δ[C(6)H_3] = 1.65s(3). ^{13}C NMR: δ[C(1)] = 175.9; δ[C(4)] = 163.1; δ[C(2)] = 149.9; δ[C(3)] = 98.7; δ[C(5)] = 10.7; δ-[C(6)] = 6.0.

Synthesis of Complexes. [Zn(TSC^1)$_2$(H_2O)]. A solution of Zn-(OAc)$_2$·2H_2O (0.09 g, 0.40 mmol) in methanol (3 mL) was added to a stirred solution of HTSC^1 (0.2 g, 0.80 mmol) in the same solvent (25 mL). After 24 h of stirring at room temperature, the solid formed was filtered out and dried under reduced pressure.Yield: 70%. Mp: 170 °C. Anal. Calcd for $C_{22}H_{28}N_8O_3S_2Zn$: C, 45.4; H, 4.8; N, 19.2; S, 11.0. Found: C, 45.5; H, 4.5; N, 19.2; S, 10.2. MS (electrospray), *m*/*z* (%): 563 (66.7) [M + H], 470 (5.8) [M − NHPh], 313 (28.8) [Zn(TSC^1)], 251 (12.4) [(HTSC^1) + H], 158 (100.0) [HTSC^1 − NHPh]. IR: 3456m, 3399m, 3334s, 3185m, ν(N−H) + ν(O−H); 1684vs, ν(C═O); 1599vs, ν(C═N); 1542s, 1268m, ν(NH−Ph); 1080w, 837w, ν(C═S). ^{1}H NMR: δ-[N(4)H] = 10.11s, 10.08s(1); δ [N(1)H_2] = 6.78s, 6.76s, 6.70s, 6.67s (2); δ[C(7, 11)H] = 7.54m(2); δ[C(8, 10)H] = 7.28m(2); δ[C(9)H] = 7.03m(1); δ[C(3)H_2] = 3.79s, 3.55s (2); δ[C(5)H_3] = 2.15s, 2.11s, 2.05s, 2.04s (3). ^{13}C NMR: δ[C(1)] = 171.1; δ[C(4)] = 165.8; δ[C(2)] = 159.6; δ[C(6)] = 138.9; δ[C(7, 11)] = 128.7; δ[C(9)] = 123.3; δ[C(8,10)] = 119.1; δ[C(3)] = 41.9; δ[C(5)] = 23.4.

[Zn(TSC^2)$_2$]. A solution of Zn(OAc)$_2$·2H_2O (0.06 g, 0.26 mmol) in methanol (2 mL) was added to a stirred solution of HTSC^2 (0.1 g, 0.53 mmol) in the same solvent (10 mL). After 5 h of stirring, the solid formed was filtered out and dried under reduced pressure. Yield: 73%. Mp: 150 °C. Anal. Calcd for $C_{12}H_{20}N_6O_4S_2Zn$: C, 32.7; H, 4.6; N, 19.1; S, 14.5. Found: C, 32.5; H, 4.5; N, 18.4; S, 13.8. MS (electrospray), *m*/*z* (%): 441 (12.3) [M + H], 409 (10.5) [M − OCH_3], 252 (55.0) [Zn(TSC^2)], 190 (13.5) [(HTSC^2) + H]. IR: 3467s, 3294s, 3177m, ν(N−H); 1730vs, ν(C═O); 1602vs, ν-(C═N); 1429m, δ(O−CH_3); 1262m, br, ν(C−O); 832w, ν(C═S). ^{1}H NMR: δ[N(1)H_2] = 6.77s (1), 6.66s (1); δ[C(6)H_3] = 3.60s-(3); δ[C(3)H_2] = 3.76s, vbr(2); δ[C(5)H_3] = 2.15s, 2.03s, 2.0s(3). ^{13}C NMR: δ[C(1)] = 171.1 (169.9 in ^{13}C CP/TOSS spectrum); δ[C(4)] = 168.7; δ[C(2)] = 156.8; δ[C(6)] = 51.8; δ[C(3)] = 38.6; δ[C(5)] = 23.2.

[ZnL$^1_2$(H_2O)]. Once [Zn(TSC^2)$_2$] had been isolated as above, the mother liquor afforded a second precipitate identified as [ZnL$^1_2$-(H_2O)]. Mp: 155 °C. Anal. Calcd for $C_{10}H_{14}N_6O_3S_2Zn$: C, 30.4; H, 3.6; N, 21.2; S, 16.2. Found: C, 30.4; H, 3.4; N, 21.0; S, 16.4. MS (FAB, nitrobenzyl alcohol), *m*/*z* (%): 377 (16.5) [M + H]. IR: 3440m, 3165s, br, 3032s, br, ν(N−H) + ν(O−H); 1616vs, ν(C═O); 1600sh, 1582sh, 1497s, ν(ring); 804m, ν(C═S). ^{1}H NMR: δ[N(1)H_2] = 11.34s(1), 10.2s(1); δ[C(3)H] = 4.80s(1); δ-[C(5)H_3] = 2.06s(3). ^{13}C NMR: δ[C(1)] = 174.0 (176.7 in ^{13}C CP/TOSS spectrum); δ[C(4)] = 165.7; δ[C(2)] = 157.0; δ[C(3)] = 86.5; δ[C(5)] = 14.5. Recrystallization from DMSO afforded single crystals of **[ZnL$^1_2$(H_2O)]·2DMSO** suitable for X-ray analysis. [ZnL$^1_2$(H_2O)]·2DMSO crystals were also obtained after recrystallization of [Zn(TSC^2)$_2$] from DMSO.

[Zn(TSC^3)$_2$]. A solution of Zn(OAc)$_2$·2H_2O (0.06 g, 0.27 mmol) in methanol (5 mL) was added to HTSC^3 (0.15 g, 0.53 mmol) in the same solvent (35 mL). After 4 days of stirring, the solid formed was filtered out and dried under reduced pressure. Yield: 71%. Mp: 190 °C. Anal. Calcd for $C_{24}H_{30}N_8O_4S_2Zn$: C, 46.2; H, 4.9; N, 18.0; S, 10.3. Found: C, 46.3; H, 5.5; N, 18.2; S, 10.8. MS (electrospray), *m*/*z* (%): 623 (100) [M + H], 343 (12) [Zn(TSC^3)], 281 (72) [(HTSC^3 + H)], 158 (39) [HTSC^3 − NHPh(OCH_3)]. IR: 3412s, 3312s, 3201s, ν(N−H); 1678m, ν(C═O); 1615s, ν(C═N); 1547s, 1253m, br, ν(NH−Ph); 1436m, δ(O−CH_3); 1253m, br, 1049m, ν(C−O); 790w, ν(C═S). ^{1}H NMR: δ[N(4)H] = 9.69s(1); δ[N(1)H_2] = 7.00s(2); δ[C(Ph)H] = 8.00d(1), 6.98m(1), 6.85 td-(1); δ[C(12)H_3] = 3.76s(3); δ[C(3)H_2] = 3.6s, vbr(2); δ[C(5)H_3] = 1.95s(3). ^{13}C NMR: δ[C(1)] = 172.5; δ[C(4)] = 165.3; δ[C(2)] = 157.5; δ[C(Ph)] = 148.5, 127.4, 123.9, 120.2, 110.6; δ[C(12)] = 55.7; δ[C(3)] = 43.2; δ[C(5)] = 23.1. Recrystallization from DMSO afforded colorless prismatic crystals of **[Zn(TSC^3)$_2$]·DMSO** suitable for X-ray analysis.

[ZnL$^2_2$(H_2O)]. A solution of Zn(OAc)$_2$·2H_2O (0.15 g, 0.35 mmol) in methanol (5 mL) was added to a solution of HTSC^4 (0.15 g, 0.69 mmol) in the same solvent (25 mL). After 6 h of stirring, concentration of the solution to one-quarter of its initial volume gave a solid that was filtered out, dried under reduced pressure, and identified as [ZnL$^2_2$(H_2O)]. Yield: 78%. Mp: 180 °C. Anal. Calcd for $C_{12}H_{18}N_6O_3S_2Zn$: C, 34.0; H, 4.3; N, 19.8; S, 15.1. Found: C, 34.0; H, 4.5; N, 19.3; S 15.8. MS (FAB, nitrobenzyl alcohol), *m*/*z* (%): 405 (15.0) [M + H]. IR: 3470 sh, 3291 m, 3067 m, ν(N−H) + ν(O−H); 1615vs, br, ν(C═O); 1615vs, br, 1524vs, br, ν(ring); 800m, ν(C═S). ^{1}H NMR: δ[N(1)H_2] = 11.40s-(1), 10.17s(1); δ[C(5)H_3] = 1.89s(3); δ[C(6)H_3] = 1.62s(3). ^{13}C NMR: δ[C(1)] = 173.5; δ[C(4)] = 164.0; δ[C(2)] = 155.5; δ-[C(3)] = 92.2; δ[C(5)] = 12.6; δ[C(6)] = 6.3. Recrystallization from DMSO afforded single crystals of **[ZnL$^2_2$(H_2O)]·2DMSO**.

X-ray Crystallography. Data were collected on an Enraf-Nonius CAD-4 diffractometer. The structures were solved using direct methods for HTSC^3 and the Patterson method for the complexes, followed by normal difference Fourier techniques. In [ZnL$^1_2$(H_2O)]·2DMSO all H atoms except those of a DMSO methyl group were located in the Fourier difference map and refined isotropically, while in HTSC^3, [Zn(TSC^3)$_2$]·DMSO, and [ZnL$^2_2$(H_2O)]·2DMSO the H atoms were introduced in calculated positions with fixed C−H distances and isotropic thermal parameters (C−H = 0.95 Å, B_{iso} = 4 Å^2). The program used was SHELX 97[9] except for [ZnL$^1_2$-(H_2O)]·2DMSO, the structure of which was solved using SHELX

Table 1. Selected Crystallographic Data for $HTSC^3$, $[Zn(TSC^3)_2]\cdot DMSO$, $[ZnL^1{}_2(H_2O)]\cdot 2DMSO$, and $[ZnL^2{}_2(H_2O)]\cdot 2DMSO$

	$HTSC^3$	$[Zn(TSC^3)_2]\cdot DMSO$	$[ZnL^1{}_2(H_2O)]\cdot 2DMSO$	$[ZnL^2{}_2(H_2O)]\cdot 2DMSO$
empirical formula	$C_{12}H_{16}N_4O_2S$	$C_{26}H_{36}N_8O_5S_3Zn$	$C_{14}H_{26}N_6O_5S_4Zn$	$C_{16}H_{30}N_6O_5S_4Zn$
fw	280.35	702.18	552.02	580.07
cryst syst	monoclinic	monoclinic	monoclinic	monoclinic
space group	*C*2/*c* (No. 15)	*C*2/*c* (No. 15)	*C*2/*c* (No. 15)	*C*2/*m* (No. 12)
color	colorless	yellow	colorless	colorless
a (Å)	23.950(7)	12.781(3)	10.7100(3)	15.266(9)
b (Å)	8.679(1)	12.311(3)	18.8440(6)	20.072(5)
c (Å)	13.778(3)	21.147(3)	12.1070(4)	8.277(1)
β (deg)	109.43(2)	92.00(2)	97.485(3)	100.17(3)
T (K)	293(2)	293(2)	293(2)	293(2)
Z	8	4	4	4
R_1	0.0532	0.0391	0.0482	0.0442
R_w	0.1533	0.1087	0.1385	0.1209
GOF on F^2	1.020	1.029	1.063	1.045

Table 2. Selected Bond Lengths (Å) and Angles (deg)[a]

atom 1	atom 2	atom 3	$HTSC^3$	$[Zn(TSC^3)_2]\cdot DMSO$	$[ZnL^1{}_2(H_2O)]\cdot 2DMSO$	$[ZnL^2{}_2(H_2O)]\cdot 2DMSO$
Zn	S(1)			2.2630(8)	2.3657(8)	2.4072(11)
Zn	N(3)			2.0529(18)	2.116(2)	2.077(3)
Zn	O(w)				2.017(4)	2.092(3)
S(1)	C(1)		1.677(2)	1.746(2)	1.697(3)	1.701(3)
N(1)	C(1)		1.321(3)	1.340(3)	1.307(4)	1.306(4)
C(1)	N(2)		1.349(3)	1.312(3)	1.364(3)	1.370(4)
N(2)	N(3)		1.380(3)	1.391(3)	1.396(3)	1.389(3)
N(3)	C(2)		1.279(3)	1.289(3)	1.317(3)	1.334(4)
C(2)	C(3)		1.495(4)	1.499(3)	1.405(4)	1.392(4)
C(3)	C(4)		1.512(3)	1.504(4)	1.383(4)	1.385(4)
C(4)	O(1)		1.231(3)	1.224(3)	1.271(3)	1.273(4)
C(4)	N(4)		1.342(3)	1.343(3)		
C(4)	N(2)				1.422(3)	1.437(4)
C(1)	N(2)	N(3)	119.35(18)	115.34(18)	120.2(2)	119.9(2)
N(2)	N(3)	C(2)	117.52(19)	115.33(18)	105.5(2)	105.1(2)
N(3)	C(2)	C(3)	118.9(2)	122.8(2)	111.9(3)	112.9(3)
S(1)	Zn	$S(1)^i$		126.45(5)	126.98(6)	
N(3)	Zn	$N(3)^i$		102.99(10)	176.13(13)	
S(1)	Zn	$S(1)^{ii}$				119.13(6)
N(3)	Zn	$N(3)^{ii}$				178.11(15)
O(w)	Zn	N(3)			91.92(6)	89.06(7)
O(w)	Zn	S(1)			116.48(3)	120.44(3)

[a] Symmetry operations: (i) $1 - x, y, 0.5 - z$; (ii) $-x, y, 1 - z$.

86[10] and refined with SHELX 93.[11] Molecular graphics were obtained with ORTEP.[12] Crystal and refinement data are listed in Table 1, and selected bond lengths and angles are included in Tables 2 and 3.

In Vivo Antiinflammatory Experiments. Animals. Sprague−Dawley rats weighing 175−200 g were used. For 1 week before the experiments, the animals were maintained in a soundproofed room thermostated at 22 ± 1 °C, with an artificial 12 h:12 h light: dark cycle. Food and sterile water were supplied ad libitum.

Paw Edema Tests (Antiinflammatory Activity). Solutions of the compound under test in 2:3 water:poly(ethylene glycol), or vehicle alone, were administered intraperitoneally 30 min before edema was induced by injection of 0.05 mL of a 1% suspension of carrageenan in 0.9% sterile saline into the right hind plantar aponeurosis.[13] Paw volume was measured with a Ugo Basile 7140 plethysmometer before and 4 h after injection of carrageenan. Antiinflammatory activity is expressed as percentage reduction of edema in treated rats by comparison with controls. Results are shown in Table 4.

Table 3. Hydrogen Bond Lengths (Å) and Angles (deg) in $HTSC^3$, $[Zn(TSC^3)_2]\cdot DMSO$, $[ZnL^1{}_2(H_2O)]\cdot 2DMSO$, and $[ZnL^2{}_2(H_2O)]\cdot 2DMSO$[a]

D−H ···A	*d*(D−H)	*d*(H···A)	*d*(D···A)	∠DHA
	$HTSC^3$			
N(1)−H(11)···N(3)	0.86	2.28	2.634(3)	104.8
N(4)−H(14)···N(3)	0.86	2.19	2.877(3)	136.6
N(4)−H(14)···O(2)	0.86	2.24	2.631(2)	107.5
N(1)−H(12)···$O(1)^i$	0.86	2.02	2.871(3)	169.0
	$[Zn(TSC^3)_2]\cdot DMSO$			
N(4)−H(14)···N(2)	0.86	2.11	2.891(3)	150.0
N(1)−H(11)···$O(1)^{ii}$	0.86	2.28	3.122(3)	165.2
N(1)−H(12)···$O(1)^{iii}$	0.86	2.15	2.910(3)	146.5
	$[ZnL^1{}_2(H_2O)]\cdot 2DMSO$			
N(1)−H(11)···O(1)	0.77(5)	2.01(5)	2.696(4)	149(5)
N(1)−H(11)···O(1s)	0.77(5)	2.57(5)	2.842(3)	103(4)
N(1)−H(12) ··· $O(1s)^{iv}$	0.73(4)	2.11(4)	2.837(4)	175(4)
O(1w)-H(1w)···$O(1)^v$	0.77(5)	1.93(5)	2.678(3)	168(6)
	$[ZnL^2{}_2(H_2O)]\cdot 2DMSO$			
N(1)−H(11)···O(1)	0.86	2.06	2.741(4)	135.0
N(1)−H(11)···$O(1s)^{vi}$	0.86	2.44	2.905(4)	115.0
N(1)−H(12)···$O(2s)^{vi}$	0.8611	2.12	2.960(4)	165.5
O(1w)-H(10)···$O(1)^{vi}$	0.92	1.91	2.810(3)	165.2

[a] Symmetry operations: (i) $x, y - 1, z$; (ii) $-x, -y, 1 - z$; (iii) $x - 0.5, y + 0.5, z$; (iv) $1 - x, y, 1.5 - z$; (v) $1.5 - x, 1.5 - y, 1 - z$; (vi) $0.5 - x, 0.5 - y, 1 - z$.

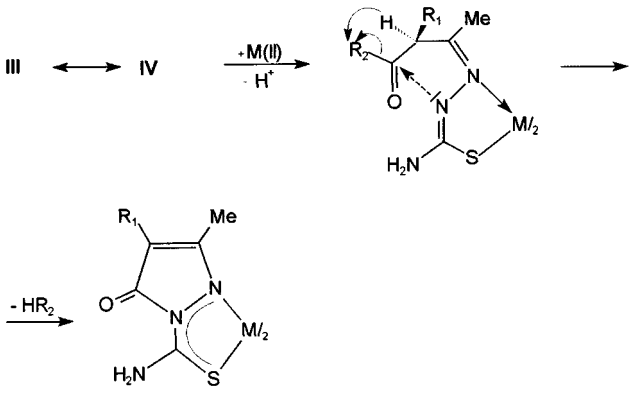
(9) Sheldrick, G. M. *SHELX-97, An integrated system for solving and refining crystal structures from diffraction data*; University of Göttingen: Göttingen, Germany, 1997.
(10) Sheldrick, G. M. *SHELX-86, Program for Crystal Structure Determination*; University of Cambridge: Cambridge, U.K., 1986.
(11) Sheldrick, G. M. *SHELX-93, Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, Germany, 1993.
(12) Johnson, C. K. ORTEP; Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN, 1965.

Table 4. Antiinflammatory Effects of HL^1 and $[ZnL^1_2(H_2O)]$ on Carrageenan-Induced Paw Edema in Rats[a]

tested substance	dose (mg/kg)	inflammation (% of paw vol)	inhibition (%)
control		40.83 ± 5.06	
HL^1	5	30.07 ± 4.2	26.85 ± 9.7
HL^1	10	0.92 ± 2.8*	97.47 ± 7.5
$[ZnL^1_2(H_2O)]$	5	35.48 ± 2.9	13.07 ± 7.2
$[ZnL^1_2(H_2O)]$	10	44.68 ± 2.8	−9.44 ± 6.9

[a] Each value indicates the mean ± SE of 5−10 rats. Significance (*) $p < 0.001$

Scheme 2



Results and Discussion

Synthesis of the Complexes. The reactions of $Zn(OAc)_2$ with $HTSC^1$, $HTSC^2$, and $HTSC^3$ in a 1:2 mole ratio in methanol at room temperature initially afforded complexes with the general formula $[Zn(TSC)_2]$. Subsequently the mother liquor also yielded precipitates of stoichiometry $[ZnL^1_2(H_2O)]$ containing pyrazolonate ligands formed by cyclization. Scheme 2 shows a plausible path for these reactions.

This scheme is supported by the fact that, as noted in the Experimental Section, $[ZnL^1_2(H_2O)]\cdot 2DMSO$ was also obtained following recrystallization of $[Zn(TSC^2)_2]$ from DMSO; and when $[Zn(TSC^2)_2]$ is dissolved in DMSO-d_6 the ^1H NMR spectrum obtained after 24 h shows signals for $[ZnL^1_2]$ along with signals for the original compound.

When the starting ligand was $HTSC^4$ it was not possible to isolate the thiosemicarbazonate complex, the reaction directly giving the complex with the cyclic ligand.

These results differ significantly from those obtained previously for the reactions of Cd(II) with $HTSC^1$ and $HTSC^2$,[5] which because they were faster had only allowed isolation of the pyrazolonate complex. Qualitative analysis of the ^1H NMR spectrum of a DMSO-d_6 solution containing $HTSC^2$ and $Zn(OAc)_2$ or $Cd(OAc)_2$ in a 2:1 mole ratio confirmed that cyclization is quicker with Cd(II), but also showed that, with both metal ions, the solution is a complex mixture containing free ligand and both the thiosemicarbazonate and pyrazolonate complexes. The faster cyclization of $HTSC^4$ highlights the influence of the leaving group bound to C(4) and also, probably, that of the substituent on C(3).

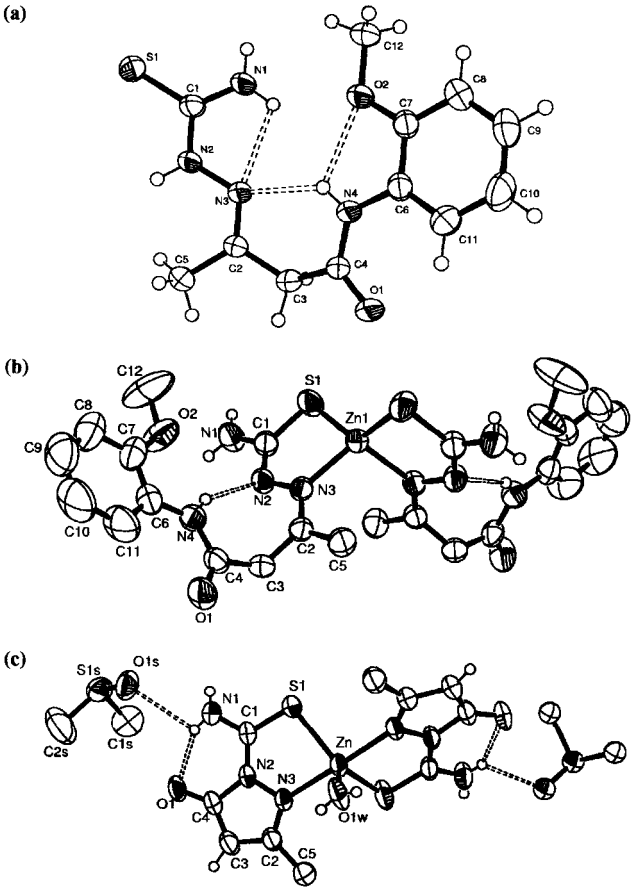


Figure 1. ORTEP diagrams of (a) $HTSC^3$, (b) $[Zn(TSC^3)_2]\cdot DMSO$, and (c) $[ZnL^1_2(H_2O)]\cdot 2DMSO$, showing intramolecular hydrogen bonds.

Like $[CdL^1_2]$,[5] the complexes $[ZnL^x_2(H_2O)]$ release HL^x when treated with $F_3CCOOH(aq)$.

X-ray Structures. a. $HTSC^3$. Figure 1a shows the atomic numbering scheme for $HTSC^3$, and selected bond lengths and angles are listed in Tables 2 and 3. Whichever tautomer may predominate in solution (vide infra), in the solid state the length of the C(2)−N(3) bond, 1.28 Å, corresponds, as in $HTSC^1$ and $HTSC^2$ (1.27−1.29 Å),[5] to the hydrazone form **III**; for the ene−hydrazine form **IV** a bond length near $d_{C-N} = 1.47$ Å[14] is expected. Also, enolization of the carbonyl group is ruled out by the C(4)−O(1) distance, 1.19−1.23 Å ($d_{C=O} = 1.20$ Å[14]). The atoms of the molecule are distributed around two planes, one defined by the thiosemicarbazone chain and the C(2) methyl group [S(1)N(1)C(1)N(2)N(3)C(2)C(5), rms = 0.090] and the other by the rest of the molecule [C(3)C(4)O(1)N(4)C(6)C(7)C(8)C(9)C(10)C(11)O(2)C(12), rms = 0.089]; the interplanar angle is 35.56°. As is usual for free thiosemicarbazone molecules, the thiosemicarbazone chain has the *E* configuration with respect to both the C(1)−N(2) and C(2)−N(3) bonds. The N(4)C(6)C(7)O(2)C(12) fragment folds back toward the thiosemicarbazone moiety so as almost to close a ring, forming a structure that differs widely from the extended arrangements of $HTSC^1$ and $HTSC^2$.[5] Since $HTSC^3$ only differs chemically from $HTSC^1$ in possessing its methoxy group, it is bonding and/

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or packing forces associated with this group that must be responsible for the structural differences between the two molecules. In particular $HTSC^3$ has an N(4)−H···O(2) bond that is not possible in $HTSC^1$ (Table 3), and the distance between N(1) and O(2), 3.212 Å, suggests the existence of another secondary bond that can only be present in $HTSC^3$. Additionally, the folded structure of $HTSC^3$ results in the N(4)−H···O(1)^i bond found[5] in $HTSC^1$ (i = $x - 1$, y, z) being replaced by an intramolecular N(4)−H···N(3) bond and an intermolecular N(1)−H···O(1)^i bond (i = x, $y - 1$, z) (Table 3).

b. $[Zn(TSC^3)_2]$·DMSO. Figure 1b shows the molecule and numbering scheme of the zinc thiosemicarbazonate of $HTSC^3$. Selected bond lengths and angles are listed in Tables 2 and 3. As is usual in thiosemicarbazonates, the ligands coordinate to the Zn(II) cation via their N(3) and S atoms, giving rise to a distorted tetrahedral coordination polyhedron. The distortion is due mainly to the constraints imposed by the bite of the ligand, which makes the S−Zn−N angle narrower than 109° (87°). Few mononuclear thiosemicarbazonates of zinc(II) that have been studied by X-ray diffraction have a coordination number of only 4.[15,16] In the present compound this unusually low coordination number is probably a consequence of the bulk of the acetoacetanisidide fragment bound to the thiosemicarbazone chain. In accordance with this low coordination number, the distances N−Zn and S−Zn [2.0529(8) and 2.2630(8) Å, respectively] are very short, even shorter, in fact, than in the tetracoordinate Zn(II) complex with $DAPTSC^{2-}$ [d_{N-Zn} = 2.07(1), d_{S-Zn} = 2.317(3), 2.327(4) Å[15]], and very close to the sums of the covalent radii of N and Zn (1.95 Å[14]) and S and Zn (2.22 Å[14]). There is no evidence of keto-to-enol evolution of the C(4)═O(1) group, the C(4)−O(1) distance remaining practically unchanged upon formation of the complex (Table 2), nor of O(1) interacting with the metal (as was proposed for $[Zn(TSC^1)(H_2O)_2]$ and $[Zn(TSC)(H_2O)]$ (TSC^{2-} = *N*-methyl or *N*-ethylacetoacetanilide thiosemicarbazonate) on the basis of IR and NMR data[8]).

As in the case of most HTSCs, deprotonation and metalation causes the initial configuration of $(TSC^3)^-$ about the C(1)−N(2) bond to change from *E* to *Z* to facilitate N(3),S-chelation (see Figure 1a,b). However, if this were the only change in $(TSC^3)^-$, it would place the chelating groups facing the center of the U formed by the TSC chain and the acetoacetanisidide moiety, thus making any chelated metal almost inaccessible to the second $(TSC^3)^-$ anion that is necessary for electrical neutrality. The ligand therefore also undergoes a second change, replacing the initial *E* configuration about the C(2)−N(3) bond by the *Z* configuration; this places the U on the other side of the C(1)-to-C(2) chain, allowing the metal to be chelated "outside" the U where there is room for a second anion. This behavior contrasts with that exhibited, according to spectroscopic evidence,[8] by $[Zn(TSC^1)(H_2O)_2]$ and $[Zn(TSC)(H_2O)]$, in which it is the C(4)═O(1) group that changes its orientation from "outside" to "inside" the U, where it evolves to the enol form, restores neutrality by losing a proton, and coordinates to the metal, thus making a second ligand unnecessary.

As in $HTSC^3$, the atoms of the ligand are arranged around two planes, C(3)C(4)O(1)N(4)C(6)C(7)C(8)C(9)C(10)C(11)O(2)C(12) (rms = 0.034) and S(1)N(1)C(1)N(2)N(3)C(2)C(5) (rms = 0.036); the interplanar angle, 64°, is wider than in the free ligand. The main changes in TSC chain bond lengths that are induced by deprotonation and metalation [lengthening of C(1)−S(1) and shortening of C(1)−N(2)] show, as expected, the thione-to-thiol evolution of the thioamide group. The intramolecular hydrogen bonds of the free ligand are replaced by a single N(4)−H···N(2) bond due to the configurational changes discussed above (Table 3). Two intermolecular hydrogen bonds, N(1)−H(11)···O(1)^{ii} and N(1)−H(12)···O(1)^{iii}, connect the molecules in a three-dimensional network. The DMSO molecule is occluded in the lattice, with no bonding interactions with the complex.

c. $[ZnL^1_2(H_2O)]$·2DMSO and $[ZnL^2_2(H_2O)]$·2DMSO. Figure 1c shows the structure and atomic numbering scheme for $[ZnL^1_2(H_2O)]$·2DMSO; selected bond lengths and angles are listed in Tables 2 and 3. The structure of $[ZnL^2_2(H_2O)]$·2DMSO is very similar (see Table 2 for bond lengths and angles). Like $(TSC^3)^-$ in $[Zn(TSC^3)_2]$·DMSO, the cyclized ligands $(L^1)^-$ and $(L^2)^-$ are N(3),S-coordinated to the Zn(II). The metal is now also coordinated to a water molecule, which increases the N−Zn and S−Zn bond lengths to values similar to those found in pentacoordinate Zn(II) thiosemicarbazonates with water as one of the ligands (e.g., $[Zn(KTSC)(H_2O)]$ and $[Zn(Bcy)(H_2O)]$·DMF,[15] where $KTSC^{2-}$ and Bcy^{2-} are bis(thiosemicarbazonato) ligands). There are nevertheless some differences between the $(L^1)^-$ and $(L^2)^-$ complexes: in particular, the latter has longer S−Zn and O−Zn bonds but a significantly shorter N−Zn bond than $(L^1)^-$. Also, although the coordination polyhedra of both complexes can be described as distorted trigonal bipyramids with the N atoms in apical positions, the distortion is clearly greater in $[ZnL^1_2(H_2O)]$·2DMSO than in $[ZnL^2_2(H_2O)]$·2DMSO, the value of the parameter τ defined by Addison et al.[17] being 0.82 for the former and 0.97 for the latter (τ = 1 for a regular trigonal bipyramid). The pyrazolonate rings are planar [rms = 0.024 in $(L^1)^-$ and 0.0617 in $(L^2)^-$], and the dihedral angle between the planes of the two ligands is 51.54° in $[ZnL^1_2(H_2O)]$·2DMSO and 56.80° in $[ZnL^2_2(H_2O)]$·2DMSO. The changes in the HL^x ring bond lengths with respect to free HL^x are similar to those described previously, although the intramolecular $-NH_2\cdots O(1)$ hydrogen bonds are in both cases longer than in free HL^1 or $[CdL^1_2Py]$.[5]

Note that, as comparison of parts b and c of Figure 1 shows, neither the TSC chain nor the metal−ligand bonds of $[Zn(TSC^3)_2]$·DMSO need to undergo significant configurational changes in order to give $[ZnL^1_2(H_2O)]$·2DMSO:

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cyclization only involves replacing the C(4)−N(4) and N(4)−H···N(2) bonds of the thiosemicarbazonate with the C(4)−N(2) and N(1)−H···O(1) bonds of the pyrazolonate (which requires no large atomic displacements) and then (or simultaneously) losing *o*-anisidine.

The water molecule forms hydrogen bonds with the O(1) atoms of neighboring molecules, giving rise to supramolecular chains, and the DMSO molecules bridge between these chains by means of hydrogen bonds with the −N(1)-H_2 groups (Table 3).

IR Spectroscopy. The IR bands of the thiosemicarbazones HTSC[1]−HTSC[4] were identified on the basis of previous data.[5,8] Comparison of the IR spectrum of [Zn(TSC[3])$_2$]·DMSO (in which the X-ray study showed the TSC^- ligand to be S,N-coordinated) with that of free HTSC[3] shows that S,N-coordination shifts ν(C═N) to slightly higher wavenumbers, eliminates the 1100 cm^{-1} band, and weakens the 820 cm^{-1} band while shifting it to lower wavenumbers. The position of ν(C═O) is practically the same in the complex as in the free ligand, in accordance with the noncoordination of this group, and the ν(N−H) bands undergo slight shifts attributable to the hydrogen bond of the NH_2 group in the free ligand differing from those of the complex.

Deprotonation of HTSC[1] and HTSC[2], and their coordination to form [Zn(TSC[1])$_2$(H_2O)] and [Zn(TSC[2])$_2$], causes changes in the ν(C═N) and ν(C═S) bands paralleling those found for HTSC[3], suggesting a similar S,N-coordination mode. The ν(C═O) bands shift to higher wavenumbers, suggesting that this group is neither coordinated nor heavily involved in hydrogen bonding as it is in the free ligands.[5] As in the case of HTSC[3], the observed shifts in the ν(N−H) bands are attributable to differences in hydrogen bonding by the NH_2 group.

When HL^1 and HL^2 are formed, the parent HTSCs of HL^1 lose −NH−Ph, $-OCH_3$, or −NH−Ph(OCH_3) fragments and HTSC[4] loses $-OCH_2CH_3$. This latter loss shows up the best in the IR spectra because the bands belonging to the lost fragment do not overlap the other bands of the ligand. As previously found for HL^1 in [CdL^1_2Py],[5] deprotonation of HL^1 and HL^2 and N,S-coordination to the zinc cation does not significantly alter the positions of the ring bands but eliminates the high-energy ν(C═S) band at 1093 cm^{-1} in HL^1 and 1105 cm^{-1} in HL^2, and shifts the low-energy ν-(C═S) band to lower wavenumbers (from 875 to 804 cm^{-1} in $(L^1)^-$ and from 902 to 800 cm^{-1} in $(L^2)^-$). Although the C═O group is not coordinated, it is heavily involved in hydrogen bonding, which together with the electronic rearrangement due to deprotonation and N-metalation shifts ν-(C═O) to lower wavenumbers [1616 cm^{-1} in $(L^1)^-$, 1615 cm^{-1} in $(L^2)^-$]. The spectra of both free ligands have a strong band close to the $\delta(CH_3)$ band, at 1336 cm^{-1} in that of HL^1 and 1331 cm^{-1} in that of HL^2. Because of its intensity, this band, which is attributed to the thioamide ν(C−N) vibration[18] (although it is probably also contributed to by ring vibrations[19]), may prove useful for diagnosing the cyclization of HTSCs to pyrazolones bearing a carbothioamide group. Upon deprotonation and N,S-coordination it shifts to higher wavenumbers (1406 cm^{-1} in [ZnL^1_2(H_2O)] and 1385 cm^{-1} in [ZnL^2_2(H_2O)]) in accordance with the slight reinforcement of the double-bond character of C−N.

NMR Spectroscopy. In the ^{1}H NMR spectrum of HTSC[3], as in those of HTSC[1] and HTSC[2],[5] the N(2/4)H, N(1)H_2, C(5)H_3, and C(3)H_2 groups are each represented by two sets of signals, indicating an equilibrium between two different conformers in DMSO solution (only the signals of the major conformer are listed in the Experimental Section[20]). This duplicity is almost inappreciable in the spectrum of HTSC[4]. The ^{1}H NMR spectrum of HL^2 is, as expected, similar[5] to that of HL^1.

The main modifications of the ^{1}H NMR spectra of the HTSC^x ligands upon formation of [Zn(TSC^x)$_2$] are the loss of the N(2)H signal, the shielding of the N(1)H_2 signals, and the deshielding of the C(3)H_2 signals. The spectra of the complexes also suggest the presence of more than one tautomer, since more than one signal or very broad signals are obtained for groups such as CH_2 or CH_3. In particular, in the spectrum of [Zn(TSC[1])$_2$], the most complex, all the signals are split and there are four signals for the CH_3 group, but this spectrum is simplified when the temperature is raised.[20]

The ^{1}H NMR spectra of [ZnL^x_2(H_2O)] (x = 1, 2) are similar. As expected, in these spectra the N(3)H signals of HL^1 and HL^2 are missing due to deprotonation. Also, in the spectrum of [ZnL^1_2(H_2O)] the difference between the chemical shifts of the two N(1)H_2 protons is greater than in that of the free ligand,[5] possibly due to increased C(1)−N(1) bond order making rotation around this bond more difficult and/or to the strong intramolecular N(1)−H···O(1) hydrogen bond (vide supra) perduring in solution. Although the molecular structure of HL^2 is still unknown, these arguments probably also apply to HL^2 and [ZnL^2_2(H_2O)], since the N(1)-H_2 signals of HL^2 are in positions similar to those of HL^1, the C(1)−N(1) bond distance is the same in both the complexes, and the N(1)−H···O(1) bond is also present in [ZnL^2_2(H_2O)] (Table 3).

The ^{13}C NMR signals of the HTSC^x ligands and [Zn(TSC^x)$_2$] complexes were identified on the basis of previous work[5] (only signals for the major isomer are listed in the Experimental Section[20]). As in their ^{1}H NMR spectra, in the ^{13}C NMR spectrum of HTSC[3] there are two signals for each of the key groups, whereas in that of HTSC[4] there is just one. Among the ^{13}C NMR spectra of the complexes that of [Zn(TSC[1])$_2$(H_2O)] is again the most complicated [two signals each for CH_3 and CH_2, three signals each for C(1) and C(4), and four for C(2); see Scheme 1]. The ^{13}C NMR spectrum of [Zn(TSC[2])$_2$] is simpler, although some signals are weakly duplicated. That of [Zn(HTSC[3])$_2$] has just one signal for each type of carbon.

The main changes in the ^{13}C NMR spectrum of HTSC[3] upon coordination affect C(1), which is shielded by about 6

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ppm due to thione-to-thiol evolution followed by sulfur−metal coordination, and C(2) and C(5), which are deshielded by about 8 and 6 ppm, respectively, due to coordination via N(3). Similar modifications are observed for $[Zn(TSC^1)_2]$ and $[Zn(TSC^2)_2]$, suggesting that, as in the solid state, N,S-coordination probably holds in all three thiosemicarbazonate complexes (at least in the major tautomers). In the case of $[Zn(TSC^2)_2]$, for which a solid-state CP/TOSS spectrum was recorded, the hypothesis that the major coordination mode is the same in both states is corroborated by the fact that the position of the C(1) signal in DMSO-d_6, 171.1 ppm, is close to its position in the CP/TOSS spectrum, 169.9 ppm.

The ^{13}C NMR spectrum of HL^2 (see Experimental Section) was interpreted on the basis of the previous work on HL^1.[5] Replacement of the H atom on C(3) by a CH_3 group deshields C(3) by 7.3 ppm and slightly shields C(2) and C(5), while the C(1) and C(4) signals remain unaltered. Deprotonation of N(3)H and N(3)-coordination to Zn lead to similar modifications in the ^{13}C NMR spectra of HL^1 and HL^2. These modifications mainly affect C(2) and C(3), which are respectively deshielded and shielded by about 5 ppm; C(1), which is shielded by about 2 ppm; and C(3) and C(5), which are both deshielded by about 2 ppm. These changes are similar to those observed when HL^1 is deprotonated and coordinates to Cd(II) to form $[CdL^1_2]\cdot 3H_2O$,[5] except that in the cadmium complex C(1) is more deshielded than in the free ligand [despite $(L^1)^-$ showing almost the same evolution to the thiol form as in the Zn complexes, which ought to induce shielding]. The deshielding of C(1) in the Cd(II) complex may possibly be due to the inductive effect of the Cd−L^1 bonds, which therefore appears to be greater than that of the Zn−L^1 bonds in the zinc complex. The solid-state CP/TOSS spectrum of $[ZnL^1_2(H_2O)]$, in which the C(1) signal lies at 176.7 ppm (only 2.7 ppm downfield from its position in DMSO-d_6) suggests that S-coordination is also common to the two states.

The C(3) signal is very valuable for diagnosis of cyclization, shifting from 44 to 48 ppm in the free thiosemicarbazones (in which C(3) belongs to a $-CH_2$ group) to 91−99 ppm in the pyrazolones (in which C(3) is part of a −CH group). Similar deshielding is observed in the spectra of the corresponding metal complexes, in which the signal shifts from 39 to 43 ppm in the thiosemicarbazonates to 87−92 ppm in the pyrazolonates.

Antiinflammatory Activity. In preliminary screening tests of HL^1 and $[ZnL^1_2(H_2O)]$ for antiinflammatory activity, the zinc complex had no significant effect at either of the doses used (5 and 10 mg/kg), but the higher dose of HL^1 strongly inhibited inflammation (Table 4). The inactivity of the complex may be due to the interaction of HL^1 with cyclooxygenase-2 (COX-2)[21] being prevented by the persistence of Zn−L bonds in the biological medium.

Conclusions. Thiosemicarbazones derived from β-keto amides and β-keto esters can be cyclized to pyrazolones in the presence of $M(OAc)_2$ (M = Zn, Cd). This process, which is easily detected using IR or ^{13}C NMR spectroscopy, is faster with cadmium(II) acetate than with zinc(II) acetate, with which pyrazolonates were in most cases obtained only after prior isolation of thiosemicarbazonate complexes. The influence of the metal cation on the cyclization process is probably due to both inductive and stereochemical effects. The substituents on the β-keto group also affect the rate of the cyclization significantly, as may likewise be expected for the solvent and the counterion of the metal. Preliminary experiments showed promising antiinflammatory activity to be possessed by HL^1 but not by its Zn(II) complex. More experimental work is necessary in order to confirm the NSAID behavior of HL^1.

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Supporting Information Available: X-ray crystallographic files (CIF format) for $HTSC^3$, $[Zn(TSC^3)_2]\cdot$DMSO, $[ZnL^1_2(H_2O)]\cdot$2DMSO, and $[ZnL^2_2(H_2O)]\cdot$2DMSO. This material is available free of charge via the Internet at http://pubs.acs.org.

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