Inorg. Chem. **2004**, *43*, 3038–3047

Using Model Complexes To Augment and Advance Metalloproteinase Inhibitor Design

Faith E. Jacobsen and Seth M. Cohen*

Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093-0358

Received December 2, 2003

The tetrahedral zinc complex [($Tp^{Ph,Me}$)ZnOH] ($Tp^{Ph,Me}$ = hydrotris(3,5-phenylmethylpyrazolyl)borate) was combined with 2-thenylmercaptan, ethyl 4,4,4-trifluoroacetoacetate, salicylic acid, salicylamide, thiosalicylic acid, thiosalicylamide, methyl salicylate, methyl thiosalicyliate, and 2-hydroxyacetophenone to form the corresponding [($Tp^{Ph,Me}$)Zn(ZBG)] complexes (ZBG = zinc-binding group). X-ray crystal structures of these complexes were obtained to determine the mode of binding for each ZBG, several of which had been previously studied with SAR by NMR (structure–activity relationship by nuclear magnetic resonance) as potential ligands for use in matrix metalloproteinase inhibitors. The [($Tp^{Ph,Me}$)Zn(ZBG)] complexes show that hydrogen bonding and donor atom acidity have a pronounced effect on the mode of binding for this series of ligands. The results of these studies give valuable insight into how ligand protonation state and intramolecular hydrogen bonds can influence the coordination mode of metal-binding proteinase inhibitors. The findings here suggest that model-based approaches can be used to augment drug discovery methods applied to metalloproteins and can aid second-generation drug design.

Introduction

Matrix metalloproteinases (MMPs) are a zinc(II)-dependent class of hydrolytic enzymes required for the breakdown of connective tissue.[1−4] MMPs can act on a range of substrates such as collagen, elastin, laminin, and other components of the extracellular matrix. The hydrolytic activity of these metalloproteins occurs at a zinc(II) ion bound by three nitrogen ligands in a highly conserved tris(histidine) motif. The remaining sites in the zinc(II) ion are open for coordinating substrate and aquo/hydroxo nucleophiles that perform amide bond cleavage.[5,6] MMPs are required for a variety of normal biological functions such as growth, development, and wound healing; however, misregulated MMP activity has been associated with a number of pathologies including cancer, arthritis, heart disease, and inflammatory disease. The wide-ranging importance of MMPs in these illnesses has prompted the development of a large number of MMP inhibitors (MPIs) as potential chemotherapeutics.[1,7−9] MPIs can be generally described as consisting of two major components: a peptidomimetic backbone for generating noncovalent interactions within the MMP active site pocket and a zinc-binding group (ZBG) that forms coordinate bonds to the catalytic zinc(II) ion. In MMP inhibitors, a variety of ligands including carboxylates, phosphinates, thiolates, and hydroxamates have been used as ZBGs,[1,7−9] but the overwhelming majority of MPIs employ hydroxamic acids as the ZBG.

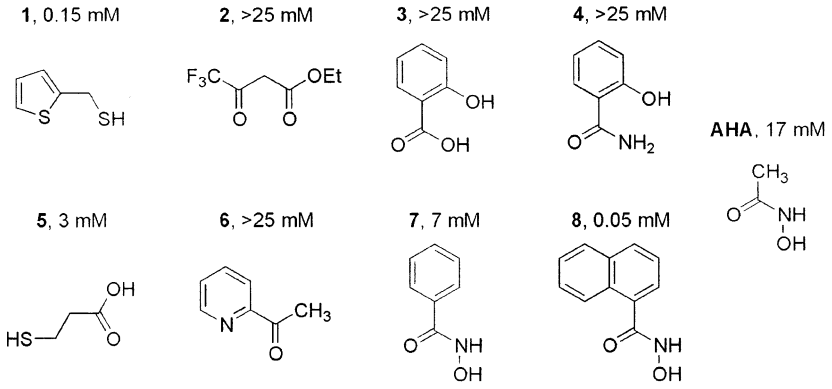
Although hydroxamic acids have produced numerous high-affinity MMP inhibitors, none of these compounds have successfully completed clinical trials.[1,10] The inability of these compounds to produce clinically useful drugs has been attributed to a number of problems, most notably unwanted side effects such as musculoskeletal pain.[10,11] In addition,

* Author to whom correspondence should be addressed. Phone: (858) 822-5596. Fax: (858) 822-5598. E-mail: scohen@ucsd.edu.

(1) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735−2776.
(2) Shapiro, S. D. *Curr. Opin. Cell Biol.* **1998**, *10*, 602−608.
(3) Matrisian, L. M. *Trends Gen.* **1990**, *6*, 121−125.
(4) Massova, I.; Kotra, L. P.; Fridman, R.; Mobashery, S. *FASEB J.* **1998**, *12*, 1075−1095.
(5) Babine, R. E.; Bender, S. L. *Chem. Rev.* **1997**, *97*, 1359−1472.
(6) Bertini, I.; Calderone, V.; Fragai, M.; Luchinat, C.; Mangani, S.; Terni, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2673−2676.
(7) Brinckerhoff, C. E.; Matrisian, L. M. *Nat. Rev. Mol. Cell. Biol.* **2002**, *3*, 207−214.
(8) Skiles, J. W.; Gonnella, N. C.; Jeng, A. Y. *Curr. Med. Chem.* **2001**, *8*, 425−474.
(9) Schwartz, M. A.; Van Wart, H. E. *Prog. Med. Chem.* **1992**, *29*, 271−334.
(10) Coussens, L. M.; Fingleton, B.; Matrisian, L. M. *Science* **2002**, *295*, 2387−2392.
(11) Hutchinson, J. W.; Tierney, G. M.; Parsons, S. L.; Davis, T. R. C. *J. Bone Jt. Surg., Br.* **1998**, *80-B*, 907−908.

10.1021/ic035388o CCC: $27.50
Published on Web 03/16/2004

Chart 1. Compounds Examined with SAR by NMR for the Ability To Bind to the MMP Active Site



the hydroxamic acid moiety suffers from other drawbacks including poor pharmokinetics and low oral availability. The limitations of hydroxamates are perhaps best exemplified by the fact that the only clinically approved MPI is a tetracycline antiobiotic,[12] which does not contain a hydroxamic acid moiety. The liabilities of hydroxamate-based compounds have, in part, motivated the search for other functional groups that can serve as effective ZBGs in these inhibitors. A recent report has employed structure−activity relationship by nuclear magnetic resonance (SAR by NMR)[13,14] to systematically explore an assortment of small molecules to function as ZBGs.[15] Chart 1 shows some of the molecules that were examined and the affinity, as measured with SAR by NMR, reported for each compound. Ultimately, a hydroxamic acid derivative, naphthylhydroxamic acid (**8**), was selected as a useful lead due to its increased binding affinity for MMP-3 and improved pharmokinetics.[15] SAR by NMR proved to be an effective tool for screening new ZBGs; however, without more comprehensive NMR experiments this method does not reveal the precise mode of zinc binding for each ligand, which can limit further development of other promising lead compounds.

Another approach for evaluating new ZBGs involves the use of small-molecule model complexes of the MMP active site zinc(II) ion.[16−18] This technique can rapidly produce high-resolution structural data that reveal the coordination mode for a prospective ligand. The use of tris(pyrazolyl)-borate or tris(pyrazolyl)methane ligands and their derivatives as model complexes for a variety of metalloenzyme active sites is well established in the literature.[19−24] The complex [(Tp^{Ph,Me})ZnOH] has been shown to be a helpful model for revealing how a ZBG will bind to the zinc(II) ion in the active site of matrix metalloproteinases.[16−18] By augmenting SAR by NMR studies with structural model studies, it is proposed that a more comprehensive understanding of both the affinity and binding conformation of new ZBGs can be obtained. To test this hypothesis, the experiments described here detail the structural characterization of four ligands that were previously examined by using SAR by NMR.[15] The results obtained from these model studies prompted the synthesis and characterization of several additional complexes to better understand how small changes in the ZBG structure affect the binding mode. These experiments reveal that ligand acidity and intramolecular hydrogen bonding in these compounds have a substantial influence on the mode of coordination. The results provide further insight into the design and development of MMP inhibitors based on novel ZBGs.

Experimental Section

General Procedure. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. [(Tp^{Ph,Me})ZnOH] was synthesized as previously described.[16,25] Methyl thiosalicylate was synthesized according to literature procedures.[26] Salicylthioamide was synthesized by using the thionation method described by Curphey;[27] NMR spectra and mass spectrometry analysis were consistent with literature data on this compound.[28] Elemental analysis was performed either at the University of California, Berkeley, Analytical Facility or at NuMega Resonance Labs, San Diego, CA. ^{1}H/^{13}C NMR spectra were recorded on a Varian FT-NMR spectrometer running at 400 MHz at the Department of Chemistry and Biochemistry, University of California, San Diego. Infrared spectra were collected on a Nicolet

(12) Golub, L. M.; Lee, H.-M.; Ryan, M. E.; Giannobile, W. V.; Payne, J.; Sorsa, T. *Adv. Dent. Res.* **1998**, *12*, 12−26.
(13) Hajduk, P. J.; Sheppard, G.; Nettesheim, D. G.; Olejniczak, E. T.; Shuker, S. B.; Meadows, R. P.; Steinman, D. H.; Carrera Jr., G. M.; Marcotte, P. A.; Severin, J.; Walter, K.; Smith, H.; Gubbins, E.; Simmer, R.; Holzman, T. F.; Morgan, D. W.; Davidsen, S. K.; Summers, J. B.; Fesik, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 5818−5827.
(14) Hajduk, P. J.; Meadows, R. P.; Fesik, S. W. *Q. Rev. Biophys.* **1999**, *32*, 211−240.
(15) Hajduk, P. J.; Shuker, S. B.; Nettesheim, D. G.; Craig, R.; Augeri, D. J.; Betebenner, D.; Albert, D. H.; Guo, Y.; Meadows, R. P.; Xu, L.; Michaelides, M.; Davidsen, S. K.; Fesik, S. W. *J. Med. Chem.* **2002**, *45*, 5628−5639.
(16) Puerta, D. T.; Cohen, S. M. *Inorg. Chem.* **2002**, *41*, 5075−5082.
(17) Puerta, D. T.; Cohen, S. M. *Inorg. Chem.* **2003**, *42*, 3423−3430.
(18) Puerta, D. T.; Schames, J. R.; Henchman, R. H.; McCammon, J. A.; Cohen, S. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3772−3774.
(19) Hammes, B. S.; Carrano, C. J. *Inorg. Chem.* **2001**, *40*, 919−927.
(20) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943−980.
(21) Trofimenko, S.; Rheingold, A. L.; Liable Sands, L. M. *Inorg. Chem.* **2002**, *41*, 1889−1896.
(22) Vahrenkamp, H. *Acc. Chem. Res.* **1999**, *32*, 589−596.
(23) Tesmer, M.; Shu, M.; Vahrenkamp, H. *Inorg. Chem.* **2001**, *40*, 4022−4029.
(24) Bridgewater, B. M.; Parkin, G. *J. Am. Chem. Soc.* **2000**, *122*, 7140−7141.
(25) Puerta, D. T.; Cohen, S. M. *Inorg. Chim. Acta* **2002**, *337*, 459−462.
(26) Sasaki, K.; Tashima, Y.; Nakayama, T.; Hirota, T. *J. Heterocycl. Chem.* **1991**, *28*, 269−272.
(27) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461−6473.
(28) Banerjee, K.; Raychaudhury, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3621−3624.

AVATAR 320 FT-IR instrument at the Department of Chemistry and Biochemistry, University of California, San Diego.

Caution! Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of these materials should be prepared, and they should be handled with great care.

[(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. In a 100 mL round-bottom flask, [(Tp^{Ph,Me})ZnOH] (100 mg, 0.18 mmol) was dissolved in 15 mL of CH_2Cl_2. To this solution was added 1.0 equiv of 2-thenylmercaptan (**1**) (14.6 μL, 0.18 mmol) dissolved in 10 mL of MeOH. The mixture was stirred at room temperature overnight under a nitrogen atmosphere. After stirring, the turbid solution was evaporated to dryness on a rotary evaporator to give a white solid. The solid was dissolved in a minimum amount of benzene ($\sim$1 mL) and filtered to remove any insoluble material, and the filtrate was recrystallized by diffusion of the solution with pentane. Yield: 72.5%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.38 (s, 2H, $-CH_2-$), 2.59 (s, 9H, pyrazole CH_3), 6.16 (d, J = 3.0 Hz, 1H, thiophene H), 6.24 (s, 3H, pyrazole H), 6.69 (dd, J = 3.0 Hz, J = 5.2 Hz, 1H, thiophene H), 6.97 (dd, J = 1.3 Hz, J = 5.1 Hz, 1H, thiophene H), 7.39 (m, 3H, phenyl H), 7.46 (m, 6H, phenyl H), 7.81 (d, J = 8.1 Hz, 6H, phenyl H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.4, 23.5, 105.8, 123.0, 124.1, 125.7, 128.2, 128.9, 129.1, 129.4, 131.6, 145.6, 148.8, 154.5. IR (film from CH_2Cl_2): ν 1176, 1369, 1415, 1438, 1546, 2549 (B−H), 2919, 3062 cm^{-1}. Anal. Calcd for $C_{35}H_{33}N_6S_2BZn$: C, 62.00; H, 4.91; N, 12.40. Found: C, 62.34; H, 5.06; N, 12.60.

[(Tp^{Ph,Me})Zn(ethyl 4,4,4-trifluoroacetoacetate)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 70.5%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 0.58 (t, J = 7.27, 3H, $-CH_3$), 2.58 (s, 9H, pyrazole CH_3), 2.91 (q, J = 7.5 Hz, 2H, $-CH_2-$), 4.66 (s, 1H, acac), 6.19 (s, 3H, pyrazole H), 7.27 (m, 9H, phenyl H), 7.52 (dd, J = 1.5 Hz, J = 7.5 Hz, 6H, phenyl H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.3, 14.0, 59.2, 85.3, 85.4, 104.9, 127.2, 127.7, 128.4, 132.9, 145.2, 153.0, 171.9. IR (film from CH_2Cl_2): ν 1172, 1285, 1436, 1572, 1658, 2547 (B−H), 2935, 2959, 3060 cm^{-1}. Anal. Calcd for $C_{36}H_{34}N_6O_3F_3BZn$: C, 59.08; H, 4.68; N, 11.48. Found: C, 58.74; H, 4.81; N, 11.33.

[(Tp^{Ph,Me})Zn(salicylic acid)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 79.3%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.62 (s, 9H, pyrazole CH_3), 6.31 (s, 3H, pyrazole H), 6.80 (m, 2H, salicyl H), 7.25 (m, 9H, phenyl H), 7.36 (br t, 1H, salicyl H), 7.67 (d, J = 7.2 Hz, 6H, phenyl H), 7.71 (d, J = 7.9 Hz, 1H, salicyl H), 11.12 (s, 1H, salicyl OH). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.3, 105.0, 116.3, 117.9, 127.4, 128.4, 128.7, 131.3, 131.9, 133.6, 146.2, 153.6, 161.1, 170.9. IR (film from CH_2Cl_2): ν 1064, 1172, 1369, 1438, 1596, 2549 (B−H), 3051 cm^{-1}. Anal. Calcd for $C_{37}H_{33}N_6O_3BZn$: C, 64.79; H, 4.84; N, 12.25. Found: C, 64.68; H, 5.16; N, 12.34.

[(Tp^{Ph,Me})Zn(salicylamide)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 79.7%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.58 (s, 9H, pyrazole CH_3), 6.26 (s, 3H, pyrazole H), 6.84 (br t, 1H, salicyl H), 7.01 (d, J = 8 Hz, 1H, salicyl H), 7.11 (m, J = 7.3 Hz, 6H, phenyl H), 7.24 (m, J = 8.9 Hz, 1H, salicyl H), 7.37 (m, 3H, phenyl H), 7.55 (d, J = 7.8 Hz, 6H, phenyl H), 7.63 (d, J = 7.2 Hz, 1H, salicyl H), 8.82 (s, 2H, amide H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.3, 105.2, 114.9, 118.5, 121.0, 127.2, 128.6, 128.7, 129.9, 131.4, 131.7, 134.7, 146.5, 153.8, 170.5. IR (film from CH_2Cl_2): ν 1375, 1546, 1635, 2552 (B−H), 3351 cm^{-1}. Anal. Calcd for $C_{37}H_{34}N_7O_2BZn\cdot$0.5pentane: C, 65.80; H, 5.59; N, 13.59. Found: C, 65.58; H, 5.27; N, 13.90.

[(Tp^{Ph,Me})Zn(thiosalicylic acid)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. This complex was poorly soluble in most solvents, and therefore, a ^{13}C NMR spectrum could not be obtained. Yield: 79.5%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 2.60 (s, 9H, pyrazole CH_3), 6.31 (s, 3H, pyrazole H), 7.11 (d, 2H, salicyl H), 7.36 (m, 9H, phenyl H), 7.52 (d, 2H, salicyl H), 7.70 (m, 6H, phenyl H). IR (KBr): ν 1055, 1403, 1528, 1568, 2550 (B−H), 3053 cm^{-1}. Anal. Calcd for $C_{37}H_{33}N_6O_2SBZn\cdot H_2O\cdot CH_2Cl_2$: C, 56.70; H, 4.63; N, 10.44. Found C, 56.75; H, 4.91; N, 10.37.

[(Tp^{Ph,Me})Zn(salicylthioamide)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 81.2%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.59 (s, 9H, pyrazole CH_3), 6.25 (s, 3H, pyrazole H), 7.13 (m, 9H, phenyl H), 7.36 (m, 4H, salicyl H), 7.47 (m, 6H, phenyl H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.3, 105.3, 115.7, 120.7, 127.1, 127.9, 128.4, 128.7, 129.0, 131.2, 132.7, 135.4, 146.7, 153.9. IR (film from CH_2Cl_2): ν 1064, 1172, 1234, 1467, 1553, 2547 (B−H), 3056, 3152, 3281, 3448 cm^{-1}. Anal. Calcd for $C_{37}H_{34}N_7OSBZn\cdot$benzene: C, 66.29; H, 5.17; N, 12.58. Found: C, 66.16; H, 5.37; N, 12.76.

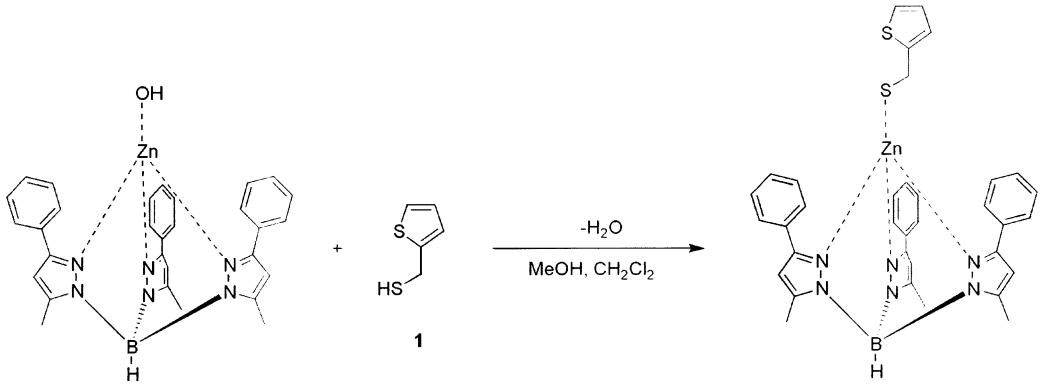
[(Tp^{Ph,Me})Zn(methyl salicylate)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 88.2%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.45 (s, 9H, pyrazole CH_3), 2.48 (s, 3H, $-OCH_3$), 6.11 (s, 3H, pyrazole H), 6.31 (t, J = 8.2 Hz, 1H, phenyl H), 6.91 (s, 1H, phenyl H), 7.01 (m, 9H, phenyl H), 7.13 (t, J = 6.4 Hz, 1H, phenyl H), 7.19 (d, J = 8.0 Hz, 1H, phenyl H), 7.57 (d, J = 6.5 Hz, 6H, phenyl H). ^{13}CNMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.1, 50.7, 104.5, 104.6, 113.2, 127.5, 127.7, 127.9 128.0, 130.3, 132.8, 134.3, 144.9, 152.9, 170.7, 171.1. IR (film from CH_2Cl_2): ν 1060, 1172, 1223, 1332, 1448, 1541, 1654, 2539 (B−H), 2951, 3052 cm^{-1}. Anal. Calcd for $C_{38}H_{35}N_6O_3BZn$: C, 65.21; H, 5.04; N, 12.01. Found: C, 65.46; H, 5.13; N, 12.28.

[(Tp^{Ph,Me})Zn(methyl thiosalicylate)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 82.2%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 2.58 (s, 9H, pyrazole CH_3), 3.19 (s, 3H, $-OCH_3$), 6.18 (s, 3H, pyrazole H), 6.54 (m, 2H, phenyl H), 6.75 (m, 1H, phenyl H), 7.08 (m, 10H, phenyl H), 7.65 (d, J = 5.7 Hz, 6H, phenyl H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.0, 51.6, 105.2, 120.6, 127.6, 127.8, 128.0, 129.4, 129.7, 131.7, 135.0, 145.4, 153.8, 162.9, 172.1. IR (film from CH_2Cl_2): ν 1067, 1180, 1283, 1433, 1549, 1677, 2539 (B−H), 2947, 3056 cm^{-1}. Anal. Calcd for $C_{38}H_{35}N_6O_2SBZn$: C, 63.75; H, 4.93; N, 11.74. Found: C, 63.77; H, 5.10; N, 11.88.

[(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)]. The same procedure was used as in the synthesis of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Yield: 90.6%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 1.22 (s, 3H, acetophenone CH_3), 2.56 (s, 9H, pyrazole CH_3), 6.22 (s, 3H, pyrazole H), 7.08 (m, 9H, phenyl H), 7.19 (br t, 1H, acetophenone H), 7.26 (s, 1H, acetophenone H), 7.37 (m, 2H, acetophenone H), 7.60 (d, J = 7.3 Hz, 6H, phenyl H). ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 13.4, 25.9, 104.8, 112.6, 121.7, 125.6, 127.5, 127.8, 128.0, 128.5, 131.8, 132.9, 135.2, 145.2, 152.9, 201.9. IR (film from CH_2Cl_2): ν 1076, 1177, 1363, 1437, 1619, 2548 (B−H), 3056 cm^{-1}. Anal. Calcd for $C_{38}H_{35}N_6O_2BZn\cdot$0.5benzene$\cdot$0.5pentane: C, 68.83; H, 5.84; N, 11.07. Found: C, 68.95; H, 5.95; N, 11.12.

X-ray Crystallographic Analysis. Single crystals of each compound suitable for X-ray diffraction structural determination were mounted onto quartz capillaries by using Paratone oil and were cooled in a nitrogen stream on the diffractometer. Data were collected on either a Bruker AXS or a Bruker P4 diffractometer both equipped with area detectors. Peak integrations were performed with the Siemens SAINT software package. Absorption corrections were applied using the program SADABS. Space group determina-

Scheme 1. General Synthesis (Compound **1** Shown) for [(Tp^{Ph,Me})Zn(ZBG)] Complexes



tions were performed by the program XPREP. The structures were solved by either Patterson or direct methods and refined with the SHELXTL software package.[29] All hydrogen atoms were fixed at calculated positions with isotropic thermal parameters, and all non-hydrogen atoms were refined anisotropically unless otherwise noted.

Structure of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atom on the boron atom was found in the difference map, and its position was refined.

Structure of [(Tp^{Ph,Me})Zn(ethyl-4,4,4-trifluoroacetoacetate)]. Large colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atom on the boron atom was found in the difference map, and the position was refined.

Structure of [(Tp^{Ph,Me})Zn(salicylic acid)]. Colorless rods were grown out of a solution of the complex in benzene diffused with pentane. The asymmetric unit contains two molecules of the complex, each having a different binding mode. In both independent molecules the phenol proton was hydrogen-bonded to the carboxylate group. The phenol oxygen atom in one complex had a 50:50 occupancy disorder over two positions; this was found in the complex having binding intermediate between monodentate and bidentate to the zinc(II) center. The hydrogen atoms on the boron atoms were found in the difference map, and their positions were refined. The complex cocrystallized with a distorted half-molecule of pentane in the asymmetric unit. No hydrogen atoms were calculated or refined for the disordered pentane solvent molecule.

Structure of [(Tp^{Ph,Me})Zn(salicylamide)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The amide oxygen atom in the complex had a ~70:30 occupancy disorder over two adjacent positions. The asymmetric unit contained a molecule of highly disordered pentane. It was treated as a diffuse contribution using the program SQUEEZE (A. Spek, Platon Library). Electron count per unit cell: 68 (found), 84 (expected). The determined and calculated intensive properties include the solvent molecule, but individual atoms do not appear in the atom lists. The hydrogen atom on the boron atom was found in the difference map, and the position was refined.

Structure of [(Tp^{Ph,Me})Zn(thiosaliyclic acid)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atoms on the boron atom and on the thiol were found in the difference map, and their positions were refined. The complex cocrystallized with a half-molecule of benzene in the asymmetric unit.

Structure of [(Tp^{Ph,Me})Zn(salicylthioamide)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atom on the boron atom was found in the difference map, and the position was refined. The complex cocrystallized with one molecule of benzene in the asymmetric unit.

Structure of [(Tp^{Ph,Me})Zn(methyl salicylate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atom on the boron atom was found in the difference map, and the position was refined.

Structure of [(Tp^{Ph,Me})Zn(methyl thiosalicylate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The hydrogen atom on the boron atom was found in the difference map, and the position was refined.

Structure of [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)]. Colorless rods were grown out of a solution of the complex in benzene diffused with pentane. The crystals were extremely thin and of low quality, resulting in a substandard data set; however, the structure is sufficient to show connectivity and geometry despite the high final *R* value. The asymmetric unit contains two molecules of the complex, having nearly identical bidentate binding modes. The complex cocrystallized with $1^1/_2$ molecules of benzene in the asymmetric unit. The hydrogen atoms on the boron atoms were found in the difference map, and their positions were refined.

Results and Discussion

The immediate goal of this study was to elucidate the mode of binding of several compounds that had been examined by using SAR by NMR as potential zinc-binding groups for MMP inhibitors (Chart 1).[15] SAR by NMR shows that most of these ligands, with the exception of **1** and **8** (0.15 and 0.05 mM, respectively), have mediocre IC_{50} values greater than 25 mM.[15] The following questions then arise: What is the binding mode of these ligands, and how does the coordination geometry relate to or explain the large IC_{50} value? To answer these questions, compounds **1**−**4** were combined with [(Tp^{Ph,Me})ZnOH][16,25] in a mixture of CH_2Cl_2 and MeOH to generate the resulting [(Tp^{Ph,Me})Zn(ZBG)] complexes (Scheme 1), which were recrystallized by diffusing pentane into a solution of benzene containing the metal complex. The structures of each complex were determined by single-crystal X-ray diffraction (Table 1). In addition, all of the [(Tp^{Ph,Me})Zn(ZBG)] complexes have also been characterized by $^1H/^{13}C$ NMR, IR, and elemental analysis.

The complex [(Tp^{Ph,Me})Zn(2-thenylmercaptan)] shows the ligand bound in a monodentate fashion to the zinc(II) ion with a Zn−S distance of 2.23 Å (Figure 1). The coordination geometry is tetrahedral with no interactions between the zinc-

(29) Sheldrick, G. M. *SHELXTL vers. 5.1 Software Reference Manual*; Brucker AXS: Madison, WI, 1997.

Table 1. X-ray Structure Data for the Complexes [(Tp^{Ph,Me})Zn(2-thenylmercaptan)], [(Tp^{Ph,Me})Zn(ethyl 4,4,4-trifluoroacetoacetate)], [(Tp^{Ph,Me})Zn(salicylic acid)], and [(Tp^{Ph,Me})Zn(salicylamide)]

	[(Tp^{Ph,Me})Zn(2-thenylmercaptan)]	[(Tp^{Ph,Me})Zn(ethyl 4,4,4-trifluoroacetoacetate)]	[(Tp^{Ph,Me})Zn(salicylic acid)]	[(Tp^{Ph,Me})Zn(salicylamide)]
empirical formula	$C_{35}H_{33}BN_6S_2Zn$	$C_{36}H_{34}BN_6O_3F_3Zn$	$C_{38.25}H_{36}BN_6O_3Zn$	$C_{42}H_{46}BN_7O_2Zn$
cryst syst	monoclinic	triclinic	triclinic	triclinic
space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
unit cell dimens	$a = 17.9294(10)$ Å	$a = 11.8958(7)$ Å	$a = 11.3476(8)$ Å	$a = 11.7605(8)$ Å
	$b = 16.9188(9)$ Å	$b = 11.9100(7)$ Å	$b = 17.3815(13)$ Å	$b = 12.2087(9)$ Å
	$c = 10.6776(6)$ Å	$c = 12.2087(7)$ Å	$c = 17.7829(13)$ Å	$c = 15.0694(11)$ Å
	$\alpha = 90°$	$\alpha = 91.678(1)°$	$\alpha = 90.550(1)°$	$\alpha = 94.884(1)°$
	$\beta = 102.251(1)°$	$\beta = 94.673(1)°$	$\beta = 103.822(1)°$	$\beta = 111.004(1)°$
	$\gamma = 90°$	$\gamma = 95.525(1)°$	$\gamma = 95.085(1)°$	$\gamma = 112.972(1)°$
vol, Z	3165.2(3) Å^3, 4	1714.7(2) Å^3, 2	3390.8(4) Å^3, 4	1794.9(2) Å^3, 2
cryst size	$0.50 \times 0.44 \times 0.37$ mm^3	$0.40 \times 0.40 \times 0.38$ mm^3	$0.27 \times 0.15 \times 0.14$ mm^3	$0.40 \times 0.40 \times 0.28$ mm^3
temp (K)	100(1)	100(1)	100(1)	100(1)
no. of reflns collected	26979	10886	29563	15912
no. of independent reflns	7228 [R(int) = 0.0195]	7558 [R(int) = 0.0120]	15175 [R(int) = 0.0217]	7982 [R(int) = 0.0204]
no. of data/restraints/ params	7228/0/413	7558/0/459	15175/3/908	7982/0/458
GOF on F^2	1.045	1.083	0.974	1.103
final R indices, $I > 2\sigma(I)$[a]	R1 = 0.0398	R1 = 0.0366	R1 = 0.0379	R1 = 0.0324
	wR2 = 0.1174	wR2 = 0.1011	wR2 = 0.1004	wR2 = 0.0890
R indices (all data)[a]	R1 = 0.0442	R1 = 0.0413	R1 = 0.0478	R1 = 0.0351
	wR2 = 0.1198	wR2 = 0.1033	wR2 = 0.1032	wR2 = 0.0907

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4]\}^{1/2}$.

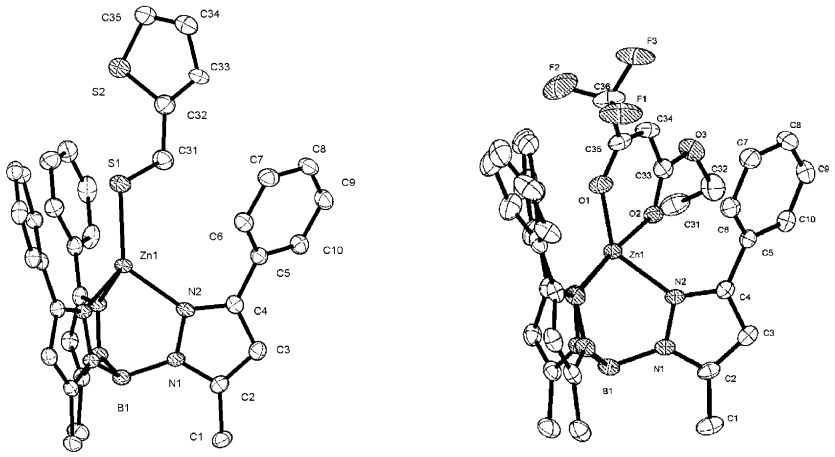


Figure 1. Structural diagram of [(Tp^{Ph,Me})Zn(2-thenylmercaptan)] (left) and [(Tp^{Ph,Me})Zn(ethyl 4,4,4-trifluoroacetoacetate)] (right) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

(II) ion and the sulfur heterocycle of this ligand (Table 1). The thiophene ring is poised away from the metal center, and the Zn−S distance for the heterocycle is 5.62 Å, clearly indicating that no bonding interaction is present. The high affinity (IC_{50} = 0.15 mM) of this ligand for the MMP zinc(II) ion is likely due, in part, to the inherent thiophilicity of the zinc(II) ion. The zinc(II) ion is known to be reasonably thiophilic although it is generally categorized as an "intermediate" ion in terms of soft/hard theory; several inhibitors have used sulfur coordination to exploit this feature.[1,30−32] In addition to strong Zn−S binding, the high affinity of 2-thenylmercaptan may be due to hydrophobic aromatic interactions with the S3 pocket of the MMP active site.[15] Such interactions were identified in multidimensional NMR experiments to explain the high affinity of naphthylhydroxamic acid for MMP-3. Although we do not have access to the structural parameters from the reported NMR experiment,[15] we hypothesize that a similar interaction may be possible for 2-thenylmercaptan, further enhancing its interaction with MMP-3. Regardless of the reasons for the high affinity of **1**, for pharmokinetic reasons (formation of disulfides with proteins)[33] free thiols such as 2-thenylmercaptan are typically considered poor candidates for clinically useful MPIs.

The structure of [(Tp^{Ph,Me})Zn(ethyl 4,4,4-trifluoroacetoacetate)] (Figure 1) shows that the ligand binds in a bidentate fashion utilizing both the keto and ester carbonyl groups. The ligand binds in an asymmetric manner with Zn−O bond distances of 1.92 and 2.14 Å. The Zn−O bond length for the keto oxygen atom is shorter than that for the ester carbonyl, indicating that the former atom retains most of the

(30) Baxter, A. D.; Bird, J.; Bhogal, R.; Massil, T.; Minton, K. J.; Montana, J.; Owen, D. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 897−902.
(31) Campbell, D. A.; Xiao, X.-Y.; Harris, D.; Ida, S.; Mortezaei, R.; Ngu, K.; Shi, L.; Tien, D.; Wang, Y.; Navre, M.; Patel, D. V.; Sharr, M. A.; DiJoseph, J. F.; Killar, L. M.; Leone, C. L.; Levin, J. I.; Skotnicki, J. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1157−1162.
(32) Levin, J. I.; DiJoseph, J. F.; Killar, L. M.; Sharr, M. A.; Skotnicki, J. S.; Patel, D. V.; Xiao, X.-Y.; Shi, L.; Navre, M.; Campbell, D. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1163−1168.
(33) Migdalof, B. H.; Antonaccio, M. J.; McKinstry, D. N.; Singhvi, S. M.; Lan, S.-J.; Egli, P.; Kripalani, K. J. *Drug Metab. Rev.* **1984**, *15*, 841−869.

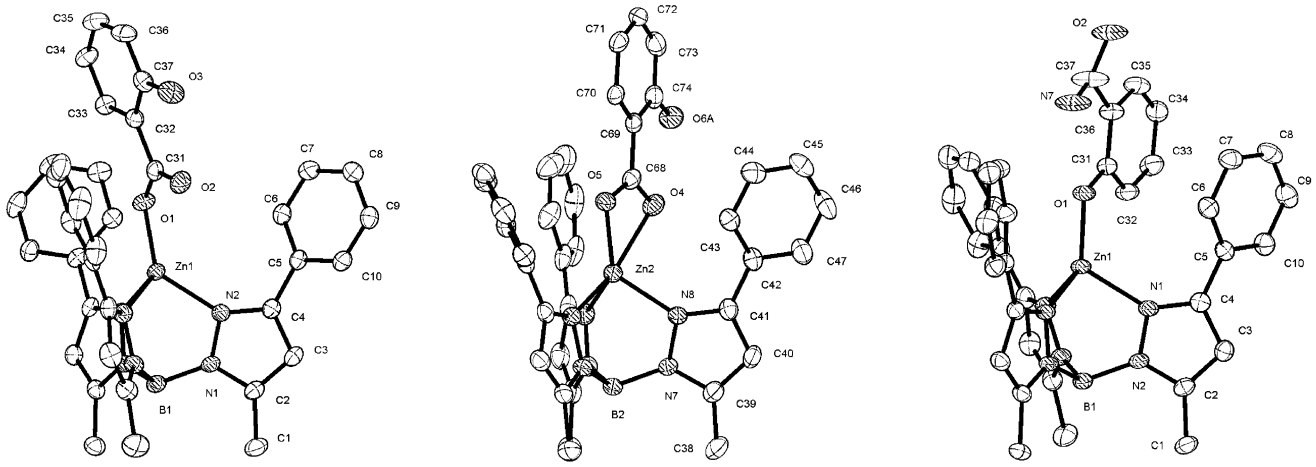
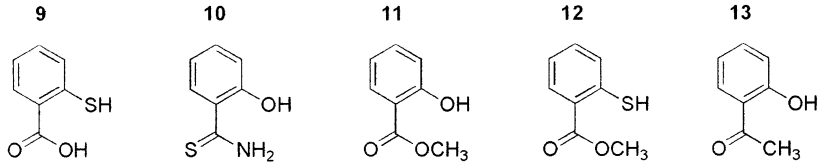


Figure 2. Structural diagram of [(Tp^{Ph,Me})Zn(salicylic acid)] (left and center, both binding modes shown) and [(Tp^{Ph,Me})Zn(salicylamide)] (right) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms, disorder, and solvent molecules have been omitted for clarity.

Chart 2. Compounds Examined To Evaluate Factors Influencing the Coordination Mode of Salicylate Derivatives



anionic charge of the deprotonated ligand. The zinc(II) center can be described as a distorted trigonal bipyramid (τ = 0.67),[34] with one of the pyrazole nitrogen atoms and the ester carbonyl occupying the axial positions of the coordination sphere. The IC_{50} obtained for this ligand using SAR by NMR was greater than 25 mM.[15] Thus, although this complex exhibits bidentate coordination, which would suggest a strong affinity for the zinc(II) ion, it does not appear to be an effective ZBG. It is possible that the six-membered ring formed upon complexation with the zinc center is not as thermodynamically stable relative to the five-membered rings formed by more effective ZBGs such as hydroxamic acids. Unfavorable electrostatic or other noncovalent interactions with the protein active site not revealed by the model complex may further lower the affinity of this ligand for binding to the MMP zinc(II) ion.

The structure of [(Tp^{Ph,Me})Zn(salicylic acid)] reveals two independent molecules in the asymmetric unit (Table 1) with two different modes of binding (Figure 2).[35] One molecule displays a binding mode intermediate between monodentate and bidentate utilizing both oxygen atoms of the carboxylic acid.[36] The Zn−O bond lengths are 1.95 and 2.46 Å for each coordinated atom, respectively. The binding mode of this structure can be best described as highly distorted trigonal bipyramidal (τ = 0.57). The asymmetry in the bond lengths indicates that the charge of this deprotonated ligand is not highly delocalized and that one of the Zn−O bonds is significantly stronger. The other molecule in the asymmetric unit is monodentate through only the acidic oxygen on the carboxylic acid with a bond length of 1.89 Å. The lack of bidentate coordination is demonstrated by the clearly tetrahedral coordination geometry of the metal center and the long Zn−O distance for the carbonyl oxygen atom of 2.95 Å. This is significantly longer than any known Zn−O bond reported in the Cambridge Crystallographic Data Bank where Zn−O bond lengths for coordinated carboxylates generally do not exceed 2.5 Å.[36−41] Thus, there are indeed two different binding modes in the asymmetric unit for [(Tp^{Ph,Me})Zn(salicylic acid)]. Notably, in both structures the phenolic oxygen atom is not bound to the metal center but is protonated and hydrogen bonded to the carboxylate oxygen atom(s). It was anticipated that the binding of salicylic acid would be bidentate through both the acidic oxygen on the carboxylic acid and the phenolic oxygen atom. It appears that hydrogen bonding and a tendency toward an electroneutral complex may dominate the binding of this ligand, thereby disfavoring coordination of the phenolic group.

Changing from the carboxylic acid group of the salicylic acid to an amide, as in the case of [(Tp^{Ph,Me})Zn(salicylamide)], demonstrates an interesting feature of these compounds. An X-ray crystal structure of [(Tp^{Ph,Me})Zn(salicylamide)] (Figure 2) shows the ZBG binds in a monodentate fashion to the zinc(II) ion. In contrast to salicylic acid, salicylamide binds to the zinc(II) ion through the phenolic oxygen atom with a Zn−O bond length of 1.89 Å. Instead

(34) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349−1356.
(35) Hartmann, U.; Vahrenkamp, H. *Chem. Ber.* **1994**, *127*, 2381−2385.
(36) Kremer-Aach, A.; Kläui, W.; Bell, R.; Strerath, A.; Wunderlich, H.; Mootz, D. *Inorg. Chem.* **1997**, *36*, 1552−1563.
(37) Darensbourg, D. J.; Wildeson, J. R.; Yarbrough, J. C. *Inorg. Chem.* **2002**, *41*, 973−980.
(38) Darensbourg, D. J.; Holtcamp, M. W.; Khandelwal, B.; Klausmeyer, K. K.; Reibenspies, J. H. *Inorg. Chem.* **1995**, *34*, 2389−2398.
(39) Looney, A.; Han, R.; Gorrell, I. B.; Cornebise, M.; Yoon, K.; Parkin, G.; Rheingold, A. L. *Organometallics* **1995**, *14*, 274−288.
(40) Hambley, T. W.; Lynch, M. J.; Zvargulis, E. S. *J. Chem. Soc., Dalton Trans.* **1996**, 4283−4286.
(41) Ruf, M.; Vahrenkamp, H. *Inorg. Chem.* **1996**, *35*, 6571−6578.

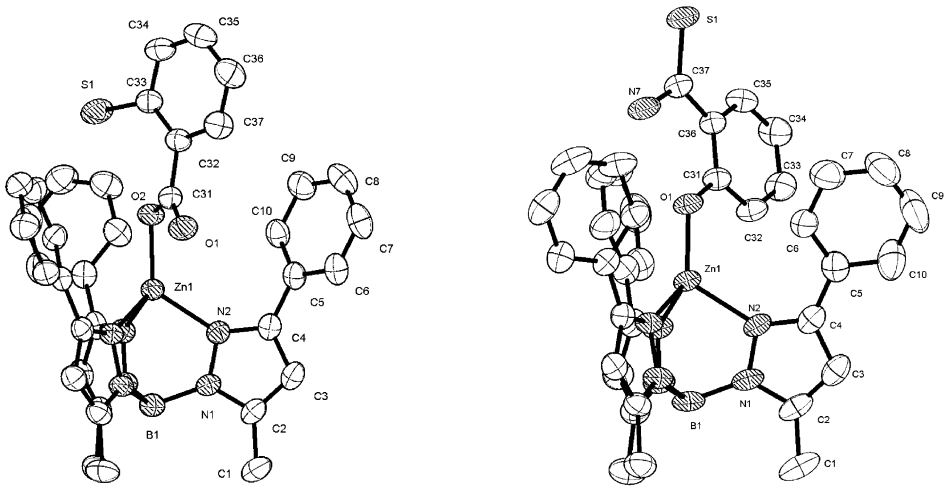


Figure 3. Structural diagram of [(Tp^{Ph,Me})Zn(thiosaliyclic acid)] (left) and [(Tp^{Ph,Me})Zn(salicylthioamide)] (right) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent molecules have been omitted for clarity.

of bidentate coordination through both the phenolic and carbonyl oxygen atoms, the complex binds in a monodentate fashion through only the phenolic oxygen atom. Furthermore, there is a hydrogen bond between the deprotonated phenolic oxygen atom and the hydrogen atom(s) of the amide nitrogen. This is similar to a related complex [(Tp^{Ph})Zn(anthranilate)] in which the anthranilate ligand binds in a mode intermediate between monodentate and bidentate through a carboxylate oxygen atom that is hydrogen bonded to an adjacent primary amine.[36] The importance of intramolecular hydrogen bonding in the reactivity of zinc model complexes has been highlighted in several recent studies.[42,43]

The observations here prompt the following questions: What is the driving force for monodentate versus bidentate coordination by these salicylate ligands? Does the internal hydrogen bonding direct the binding mode of the ZBG or is the amide carbonyl oxygen too weak a donor group to drive coordination to the zinc(II) center? The latter argument seems unlikely on the basis of the known ability of salicylamides to form six-membered chelate rings to a variety of metal ions through both phenolic and carbonyl oxygen atoms.[44−46] To explore how hydrogen bonding, pK_a of the donor groups, and the thiophilicity of the zinc(II) ion influences the binding mode of the ZBG, a number of additional complexes were prepared. Several donor groups were examined (Chart 2), and the complexes with these ligands, [(Tp^{Ph,Me})Zn(thiosalicylic acid)], [(Tp^{Ph,Me})Zn(salicylthioamide)], [(Tp^{Ph,Me})Zn(methyl salicylate)], [(Tp^{Ph,Me})Zn(methyl thiosalicylate)], and [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)], were synthesized and characterized.

The first ZBG complex of this series is [(Tp^{Ph,Me})Zn(thiosaliyclic acid)], which bound to the model complex in a monodentate manner through the acidic oxygen on the carboxylic acid (Figure 3). The Zn−O bond length of 1.93 Å (the carbonyl Zn−O distance is 2.53 Å) is very similar to that found in the monodentate binding mode of [(Tp^{Ph,Me})-Zn(saliyclic acid)]. The hydrogen on the sulfur atom was located in the difference map (S−H distance 1.18 Å) and was found to be pointing toward the acidic oxygen atom of the carboxylic acid; the H···O distance is 2.02 Å, indicating the presence of an internal hydrogen bond. In the crystal structure of free thiosalicylic acid, where the carboxylate is protonated, hydrogen bonding does not occur in this manner. Instead, there is an infinite array of S−H intermolecular hydrogen bonds.[47] However, when the carboxylic acid is deprotonated as in the structure of [(Tp^{Ph,Me})Zn(thiosaliyclic acid)], the thiol favors hydrogen bonding to the anionic deprotonated oxygen. The zinc(II) ion is known to be thiophilic, and it was anticipated that coordination through the thiol group might be favored over that through the carboxylic acid. Instead, it was found that the zinc(II) ion was bound through a deprotonated carboxylic acid, and the protonated thiol is hydrogen bonded to the coordinated carboxylate. Thus, the lower pK_a of the carboxylate combined with the formation of a six-membered hydrogen-bonding ring dominate the binding mode of this ligand in the model complex.

The importance of hydrogen bonding over thiophilicity is further supported by the crystal structure of [(Tp^{Ph,Me})Zn-(salicylthioamide)]. [(Tp^{Ph,Me})Zn(salicylthioamide)] was found to bind through the phenolic oxygen atom (Figure 3) in a monodentate fashion (Zn−O bond length of 1.88 Å) analogous to the binding mode found for [(Tp^{Ph,Me})Zn(salicylamide)]. Not surprisingly, the Zn−O bond length is nearly identical to that found for [(Tp^{Ph,Me})Zn(salicylamide)] of 1.89 Å (Table 2). There is hydrogen bonding between the coordinated oxygen atom and the amide hydrogen atoms with an NH---O distance of ∼1.9 Å. The structures of [(Tp^{Ph,Me})-Zn(thiosaliyclic acid)] and [(Tp^{Ph,Me})Zn(salicylthioamide)] strongly suggest that hydrogen bonding has a substantial

(42) Chiou, S.-J.; Riordan, C. G.; Rheingold, A. L. *Proc. Natl. Acad. Sci., U.S.A.* **2003**, *100*, 3695−3700.
(43) Smith, J. N.; Shirin, Z.; Carrano, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 868−869.
(44) Cohen, S. M.; Meyer, M.; Raymond, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 6277−6286.
(45) Cohen, S. M.; Raymond, K. N. *Inorg. Chem.* **2000**, *39*, 3624−3631.
(46) Cohen, S. M.; Petoud, S.; Raymond, K. N. *Inorg. Chem.* **1999**, *38*, 4522−4529.
(47) Steiner, T. *Acta Crystallogr., C* **2000**, *56*, 876−877.

Table 2. X-ray Structure Data for the Complexes [(Tp^{Ph,Me})Zn(thiosaliyclic acid)] and [(Tp^{Ph,Me})Zn(salicylthioamide)]

	[(Tp^{Ph,Me})Zn(thiosalicylic acid)]	[(Tp^{Ph,Me})Zn(salicylthioamide)]
empirical formula	$C_{40}H_{36}BN_6O_2SZn$	$C_{43}H_{40}BN_7OSZn$
cryst syst	triclinic	triclinic
space group	$P\bar{1}$	$P\bar{1}$
unit cell dimens	$a = 10.2483(10)$ Å	$a = 12.0248(10)$ Å
	$b = 10.4116(10)$ Å	$b = 12.0580(9)$ Å
	$c = 17.3045(17)$ Å	$c = 15.0153(12)$ Å
	$\alpha = 102.317(2)°$	$\alpha = 84.230(2)°$
	$\beta = 94.080(2)°$	$\beta = 75.737(2)°$
	$\gamma = 93.098(2)°$	$\gamma = 66.522(2)°$
vol, Z	1794.8(3) Å^3, 2	1935.3(3) Å^3, 2
cryst size	$0.40 \times 0.30 \times 0.20$ mm^3	$0.50 \times 0.40 \times 0.10$ mm^3
temp (K)	218(2)	218(2)
no. of reflns collected	13000	10859
no. of independent reflns	8023 [R(int) = 0.0220]	6050 [R(int) = 0.0297]
no. of data/restraints/params	8023/0/471	6050/0/494
GOF on F^2	1.024	1.233
final R indices, $I > 2\sigma(I)$[a]	R1 = 0.0437	R1 = 0.0686
	wR2 = 0.1087	wR2 = 0.1361
R indices (all data)[a]	R1 = 0.0523	R1 = 0.0797
	wR2 = 0.1137	wR2 = 0.1407

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]\sum[wF_o^4]\}^{1/2}$.

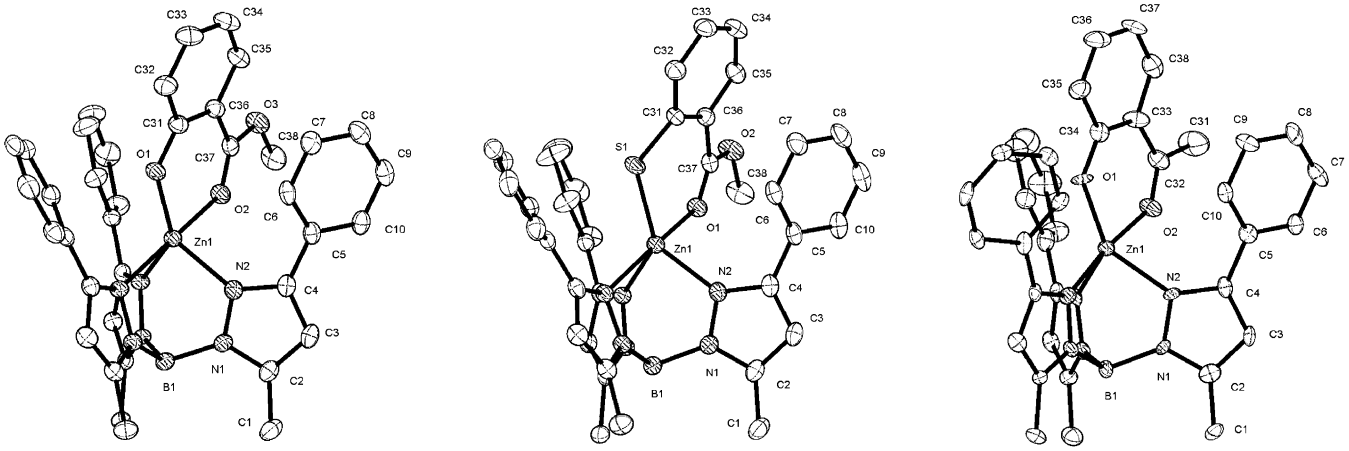


Figure 4. Structural diagram of [(Tp^{Ph,Me})Zn(methyl salicylate)] (left), [(Tp^{Ph,Me})Zn(methyl thiosalicylate)] (middle), and [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)] (right) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms have been omitted for clarity.

influence on the binding of these ZBGs and may be a more important factor than the thiophilicity of the zinc(II) center.

The crystal structure of [(Tp^{Ph,Me})Zn(methyl salicylate)] indicates that the mode of binding for this ZBG is bidentate through the phenolic oxygen atom and the carbonyl oxygen atom of the ester group (Figure 4). The Zn−O bond lengths are 1.89 and 2.18 Å, respectively (Table 3). The geometry of the complex is distorted trigonal bipyramidal ($\tau = 0.69$), with one of the pyrazole nitrogen atoms and the ester carbonyl oxygen atom occupying the axial positions of the coordination sphere. The thiol derivative of this complex, [(Tp^{Ph,Me})Zn(methyl thiosalicylate)], also has the same geometry and mode of coordination (Figure 4). It is bidentate through the thiol and ester carbonyl with bond lengths of 2.26 and 2.20 Å, respectively; the geometry is highly distorted trigonal bipyramidal ($\tau = 0.58$), with the axial ligands the same as for the methyl salicylate complex. Bidentate coordination is also observed for the binding of 2-hydroxyacetophenone in [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)]. Changing from an ester to a keto functionality does little to the mode of binding with [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)], showing a distorted trigonal bipyramidal coordination sphere ($\tau = 0.64$) and Zn−O bond lengths of ∼1.9 and ∼2.2 Å (Figure 4). [(Tp^{Ph,Me})Zn(methyl salicylate)], [(Tp^{Ph,Me})Zn(methyl thiosalicylate)], and [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)] demonstrate that bidentate coordination can be achieved in salicylate-derived ligands where no hydrogen-bonding groups are available. This supports the contention that the carbonyl group is a sufficiently strong ligand to bind the metal center, but that internal hydrogen-bonding forces in a chelator may override this preference. It is important to note that these effects are observed in the solid state and that in an aqueous solution the observed hydrogen-bonding interactions may be strongly diminished due to hydrogen bonding with the solvent.

The X-ray crystallographic information clearly demonstrates stable binding of these ligands to the [(Tp^{Ph,Me})ZnOH] model complex. NMR spectra were obtained for all of the free ligands and the resulting metal complexes to confirm that ligand binding was stable in solution. Characteristic upfield shifts were observed when the ^{1}H NMR and ^{13}C NMR spectra of free and bound ligands were compared.[16,17] For example, in the ^{13}C NMR for [(Tp^{Ph,Me})Zn(salicylic acid)], the carbonyl carbon is found at 170.9 ppm, whereas

Table 3. X-ray Structure Data for the Complexes [(Tp^{Ph,Me})Zn(methyl salicylate)], [(Tp^{Ph,Me})Zn(methyl thiosalicylate)], and [(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)]

	[(Tp^{Ph,Me})Zn(methyl salicylate)]	[(Tp^{Ph,Me})Zn(methyl thiosalicylate)]	[(Tp^{Ph,Me})Zn(2-hydroxyacetophenone)]
empirical formula	$C_{38}H_{35}BN_6O_3Zn$	$C_{38}H_{35}BN_6O_2SZn$	$C_{42.5}H_{39.5}BN_6O_2Zn$
cryst syst	monoclinic	monoclinic	triclinic
space group	$P2_1/n$	$P2_1/c$	$P\bar{1}$
unit cell dimens	$a = 11.3869(8)$ Å	$a = 11.3698(10)$ Å	$a = 10.8652(15)$ Å
	$b = 22.6123(15)$ Å	$b = 23.399(2)$ Å	$b = 16.770(2)$ Å
	$c = 13.1052(9)$ Å	$c = 12.8640(12)$ Å	$c = 20.893(3)$ Å
	$\alpha = 90°$	$\alpha = 90°$	$\alpha = 77.227(2)°$
	$\beta = 92.306(1)°$	$\beta = 90.503(2)°$	$\beta = 89.995(2)°$
	$\gamma = 90°$	$\gamma = 90°$	$\gamma = 87.780(2)°$
vol, Z	3371.6(4) Å^3, 4	3422.2(5) Å^3, 4	3709.6(9) Å^3, 4
cryst size	$0.32 \times 0.26 \times 0.17$ mm^3	$0.40 \times 0.25 \times 0.20$ mm^3	$0.28 \times 0.23 \times 0.05$ mm^3
temp (K)	100(1)	100(1)	100(1)
no. of reflns collected	20941	29276	24677
no. of independent reflns	7679 [R(int) = 0.0244]	7832 [R(int) = 0.0273]	11579 [R(int) = 0.0875]
no. of data/restraints/params	7679/0/450	7832/0/450	11579/0/962
GOF on F^2	1.038	1.043	1.128
final R indices, $I > 2\sigma(I)$[a]	R1 = 0.0338	R1 = 0.0333	R1 = 0.0948
	wR2 = 0.0848	wR2 = 0.0822	wR2 = 0.1794
R indices (all data)[a]	R1 = 0.0408	R1 = 0.0399	R1 = 0.1424
	wR2 = 0.0882	wR2 = 0.0852	wR2 = 0.1945

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$, $wR_2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^4]\}^{1/2}$.

in the free ligand it was found to be at 161.1 ppm. This is also observed in the ^{1}H NMR, with the hydrogen atom ortho to the carboxylic acid shifting from 7.92 to 7.71 ppm upon binding. A similar trend is observed in non-salicylate ligands such as 2-thenylmercaptan. In the ^{1}H NMR the methylene hydrogen atoms of 2-thenylmercaptan are found at 3.97 ppm and shift to 2.38 ppm in the complex.

Infrared analysis of carboxylate complexes has been shown to be a useful tool for determining the coordination mode of carboxylate ligands in these compounds.[48] When this analysis is applied, the difference in the asymmetric and symmetric stretching frequencies ($\Delta\nu(CO_2) = \nu_{as}(CO_2) - \nu_{sym}(CO_2)$) is used as a probe for the mode of binding. Large $\Delta\nu(CO_2)$ values (>200 cm^{-1}) are associated with monodentate carboxylate coordination, while small $\Delta\nu(CO_2)$ values (<100 cm^{-1}) are associated with bidentate coordination. For [(Tp^{Ph,Me})Zn(salicylic acid)], thin film IR spectra were obtained cast from CH_2Cl_2, and the $\Delta\nu(CO_2)$ value for this complex was found to be 179 cm^{-1}. This $\Delta\nu(CO_2)$ value is similar to the value found in the related complex [(Tp^{Ph})Zn(anthranilate)] (173 cm^{-1}), where coordination intermediate between monodentate and bidentate was also observed (Zn−O bond lengths of 1.93 and 2.46 Å).[36] The intermediate $\Delta\nu(CO_2)$ for [(Tp^{Ph,Me})Zn(salicylic acid)] is consistent with the crystal structure where both weakly bidentate and monodentate modes of coordination are found. This suggests that both binding modes are readily accessed in solution as the IR analysis of $\Delta\nu(CO_2)$ for [(Tp^{Ph,Me})Zn(salicylic acid)] does not indicate exclusively monodentate or bidentate coordination.

Conclusions

Prompted by the importance of MMPs in many human diseases, substantial efforts have been placed on identifying MPIs that can serve as useful chemotherapeutics. The vast majority of these research efforts have focused on using the hydroxamic acid moiety as the ZBG for binding the zinc(II) ion in the active site of the protein. As mentioned previously, hydroxamic acids have failed to generate clinically successful inhibitors, with the only FDA-approved MMP inhibitor being a non-hydroxamate tetracycline antibiotic.[12] This suggests that a shift in focus toward efforts to develop inhibitors that use alternative ZBGs may prove essential to developing MPIs for diseases such as cancer, arthritis, and heart disease.[1,10] SAR by NMR was applied by Fesik and co-workers to find ZBGs that bind to MMP-3 with high affinity.[15] The SAR by NMR study identified several promising ZBGs; however, it did not reveal the mode of binding for the majority of the ligands tested. Such information would be useful for both strong and weak ligands, to better understand what features of these compounds contribute to their success or failure. By using the complex [(Tp^{Ph,Me})ZnOH] as a model of the active site of MMPs, we are able to augment SAR by NMR by quickly determining a probable binding geometry for each ZBG. With this additional information, one can better ascertain the characteristics of a compound that lend it to favorable use in MPIs and allow for further study of a given class of compounds to obtain optimized metal−ligand interactions. Internal hydrogen bonding was found to play a dominant role in the coordination of salicylate-derived ligands. The thiophilicity of the zinc(II) center was found to be a less significant factor than internal hydrogen bonding or ligand acidity. These results provide new directions for the use of model complexes in metalloprotein inhibitor design. Not only must the requirements for the zinc(II) center of the enzyme be taken into account, but the functional groups on the ZBG must also be considered. As shown in this study, hydrogen bonding is an important factor that must be thoroughly considered to design effective inhibitors regardless of whether the objective is to exploit this feature or to avoid it to obtain a desired binding mode. Additional solution studies could better establish the integrity of these hydrogen bonds; nevertheless, on the basis of the data

(48) Deacon, G. B.; Phillips, R. J. *Coord. Chem. Rev.* **1980**, *33*, 227−250.

obtained here, the design of salicylate-derived MPIs can be pursued. If bidentate metal coordination is desired of a salicylate-derived MPI, amide linkages between the ZBG and the inhibitor backbone should be avoided due to the tendency to form stable internal hydrogen bonds. The results presented here suggest an ester linkage would give the desired coordination; however, these bonds are susceptible to hydrolysis in vivo. Therefore, on the basis of the [($Tp^{Ph,Me}$)-Zn(2-hydroxyacetophenone)] structure, a carbon−carbon linkage could be employed to obtain a stable inhibitor that retains bidentate metal coordination to the active site zinc(II) ion. Using this type of analysis, efforts are presently under way to develop novel MMP inhibitors based on non-hydroxamate ZBGs.

Acknowledgment. We thank Prof. Arnold L. Rheingold, Dr. Lev N. Zakharov, David T. Puerta (University of California, San Diego), and Dr. James A. Golen (University of Massachusetts, Dartmouth) for help with the X-ray structure determinations, Misha V. Golynskiy for synthetic assistance, Prof. Emmanuel A. Theodorakis (University of California, San Diego) for use of his FT-IR instrument, and Dr. Ulla Nørklit Andersen (University of California, Berkeley) for assistance with the elemental analysis. This work was supported by the University of California, San Diego, a Chris and Warren Hellman Faculty Scholar award, a Hellman Fellows award, and American Cancer Society Grant IRG-70-002-29.

Supporting Information Available: X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. X-ray crystallographic data can also be obtained from the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk). Refer to CCDC Reference Nos. 221811, 221812, 221813, 221814, 221815, 221816, 221817, 221818, and 221819.

IC035388O