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Elucidating Drug-Metalloprotein Interactions with Tris(pyrazolyl)borate Model Complexes†

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The tetrahedral zinc complex [($Tp^{Me,Ph}$)ZnOH] ($Tp^{Me,Ph}$ = hydrotris(5,3-methylphenylpyrazolyl)borate) was combined with acetohydroxamic acid, 3-mercapto-2-butanone, *N*-(methyl)mercaptoacetamide, β-mercaptoethanol, 3-mercapto-2-propanol, and 3-mercapto-2-butanol to generate the complexes [($Tp^{Me,Ph}$)Zn(ZBG)] (ZBG = zinc-binding group). These complexes were prepared to determine the mode of binding for three different types of thiol-derived matrix metalloproteinase (MMP) inhibitors. The solid-state structures of all six metal complexes were determined by X-ray crystallography. The structures reveal that while β-mercaptoketones and β-mercaptoamides bind the zinc ion in a bidentate fashion, the three β-mercaptoalcohol compounds only demonstrate monodentate coordination via the sulfur atom. Prior to this work, no experimental data were available for the binding conformation of these types of inhibitors to the zinc active site of MMPs. The results of these model studies reveal different binding modes for these ZBGs and are useful for explaining the results of inhibition assays and in second-generation drug design. This work demonstrates the utility of model complexes as a tool for revealing drug–metalloprotein interactions.

Introduction

Matrix metalloproteinases (MMPs) are an important class of hydrolytic proteins associated with a number of disease states, most notably cancer. Despite an extensive effort to develop MMP inhibitors (MPIs) as drugs, no compounds to date have successfully completed clinical trials.[1] Although there are many facets to the problem of MMP inhibition, clearly one factor that has hindered drug development is a detailed molecular understanding of how some compounds interact with the protein.[2] This task is complicated by the presence of a zinc(II) ion in the active site where the catalytic hydrolysis of substrate occurs. Understanding the drug−metalloprotein interactions in these systems is a critical issue that must be overcome to rationally develop second-generation MPIs.

Inorganic model complexes traditionally have been used to model the structure, spectroscopy, and function of metalloproteins.[3−5] Working with model complexes often offers a number of advantages when compared to studying the native protein system.[4] Model complexes are often easier to synthesize and prepare in greater quantities than the corresponding biomolecule. Model complexes are useful for stabilizing and studying intermediates that may be difficult to isolate in the biological system. The synthetic diversity of organic chemistry allows systematic modification of a model complex to evaluate the relative importance of steric and electronic effects in a given biological system. For all of these reasons, the use of model complexes has been applied to address a variety of biological questions including, but not limited to, reversible oxygen binding by hemoglobin,[5] substrate activation by oxidases,[3,6−8] and the reduction of dinitrogen by nitrogenases.[9−12] The substantial insight that

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† This paper is dedicated to the fond memory of Professor Barbara K. Burgess.

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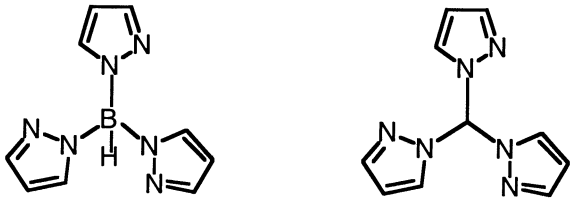
Chart 1. Homoscorpionate Ligands Tris(pyrazolyl)borate (Left) and Tris(pyrazolyl)methane (Right)



synthetic model chemistry has provided into the reactivity and mechanism of these systems is well recognized.

The essence of bioinorganic model chemistry is the design and synthesis of ligand systems that will create the desired metal coordination environment. Among the numerous ligand systems designed to model metalloprotein active sites, the use of tris(pyrazolyl)borate and tris(pyrazolyl)methane complexes and their derivatives to mimic the active site of an number of enzymes has been well established by the work of Vahrenkamp,[13,14] Parkin,[4,15] Trofimenko,[16,17] and others (Chart 1).[18−21] These systems have been applied to the modeling of several protein active sites including carbonic anhydrase,[22] liver alcohol dehydrogenase,[14] and various peptidases.[4] Because tris(pyrazolyl)borate derivatives have been successfully used to model the structural features of these metalloprotein active sites, we sought to use them in a different capacity, namely to elucidate previously unknown metalloprotein−drug interactions.[23]

Matrix metalloproteinases are hydrolytic zinc enzymes required for the breakdown of connective tissue such as collagen and elastin.[2] MMP activity has been correlated with a number of disease states, including cancer metastasis and arthritis.[1,2] The implication of MMPs in these diseases has made them promising targets for inhibition, and a number of potential drug candidates have been investigated and entered clinical trials.[2,24] All MMPs contain a common active site motif in which a zinc(II) ion is bound by three histidine residues of the protein.[25] The zinc ion then serves to bind water, whereby the Lewis acidity of the zinc center activates the water molecule sufficiently to hydrolyze amide bonds when the polypeptide substrate is present in the active site of the protein. Inhibitors of MMPs have largely relied on the use of substrate mimetics terminated with a zinc-binding group (ZBG) to shut down hydrolytic activity.[2] In these inhibitors, the ZBG coordinates the catalytic zinc ion, blocking coordination by water and anchoring the drug to the protein. Generally, hydroxamic acids have been the most successful and widely used ZBGs for incorporation into MMP inhibitors.[2] The coordination chemistry of hydroxamate binding to the MMP zinc ions has been well-characterized by X-ray structures of the inhibited proteins.[26−28] However, in addition to hydroxamates, a number of other ZBGs have been incorporated into MMP inhibitors, including carboxylic acids,[29] phosphates,[30] and thiols.[2] The interaction of several of these ZBGs with the MMP zinc ion has not been well-studied.

Previous work by Vahrenkamp and co-workers demonstrated that tris(pyrazolyl)borate complexes of zinc (Tp*Zn, where Tp* = hydrotris(3,5-cumylmethylpyrazolyl)borate) could provide an accurate model for the tris(histidine) active site of MMPs.[23] In addition, their work showed that acetohydroxamic acid formed a complex with Tp*Zn that was structurally identical to the coordination environment of hydroxamate-based drugs bound to the catalytic zinc ion in MMPs. This suggested to us that Tp*Zn complexes would be useful not only for confirming accepted drug−protein interactions, but also for predicting similar interactions with non-hydroxamate inhibitors where the coordination behavior was presently unknown. In an ongoing research effort to utilize coordination complexes to model drug−protein interactions, we have synthesized a series of zinc complexes that are structural models for the binding of thiol-based inhibitors to MMPs (Chart 2). Prior to the work presented here, the binding mode of these thiol drug candidates was not known.[31−33] The model complexes demonstrate that tris(pyrazolyl)borate complexes of zinc can be used to determine the binding mode of these inhibitors without the need for elaborate drug synthesis or protein structure determination. The data presented here establish that β-mercaptoketone and β-mercaptoamide drugs bind in a bidentate fashion; however, β-mercaptoalcohols bind exclusively in a monodentate manner, contrary to prior expectations.[32,33] By providing a facile route to characterizing these types of interactions, we show

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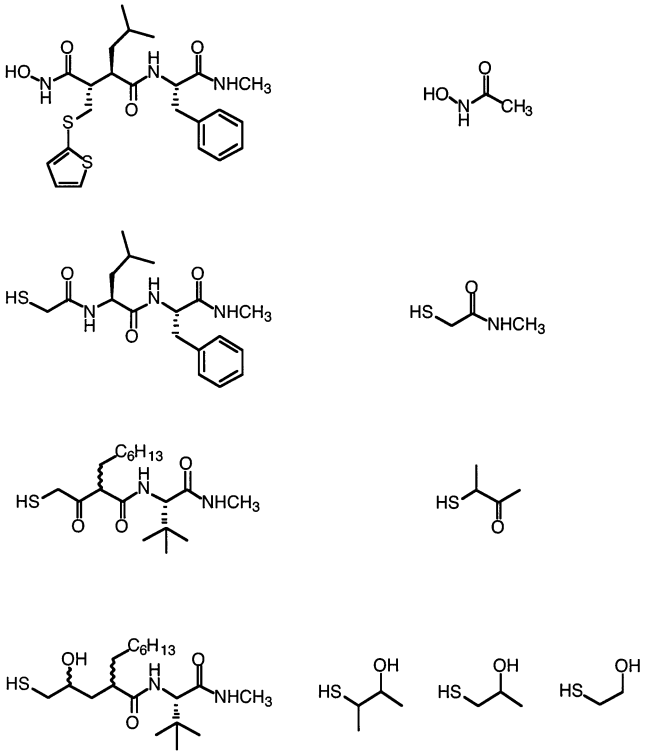
Chart 2. List of Representative MMP Inhibitors (Left) and the Corresponding Small Molecules (Right) Used to Model Zinc Binding



that certain compounds coordinate as previously predicted, while others do not. This modeling approach is expected to aid in second-generation drug design.

Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. [(Tp^{Me,Ph})K] was synthesized as previously described.[34,35] Elemental analysis was performed at the University of California, Berkeley Analytical Facility. ^{1}H/^{13}CNMR spectra were recorded on a Varian FT-NMR spectrometer running at 300 or 400 MHz at the Department of Chemistry and Biochemistry, University of California, San Diego. Isolated yields of metal complexes were ~30−75% unless noted otherwise. *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^{Me,Ph})ZnOH]. [Tp^{Me,Ph}K] (1.57 g, 3.0 mmol) was dissolved in 100 mL of CH_2Cl_2 and added to a stirring solution of $Zn(ClO_4)_2 \cdot 6H_2O$ (1.11 g, 3.0 mmol) in 20 mL of methanol. After the mixture was stirred for 2 h at room temperature under a nitrogen atmosphere, KOH (168 mg, 3.0 mmol) was added to the solution. After being stirred at room temperature overnight under a nitrogen atmosphere, the solution was filtered through a glass frit and 60 mL of methanol was added to filtrate. The filtrate was evaporated on a rotary evaporator to one-third of the original volume (40 mL). The remaining solution was left to stand at room temperature producing the title compound as a white solid. Yield: 78%. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 2.52 (s, 9H, pyrazole-CH_3), 6.23 (s, 3H, pyrazole-H), 7.28 (m, 3H, phenyl-H), 7.5 (d, J = 69 Hz, 6H, phenyl-H), 7.65 (d, J = 4.5 Hz, 6H, phenyl-H).

[(Tp^{Me,Ph})Zn(acetohydroxamate)]. In a 100-mL round-bottom flask, [(Tp^{Me,Ph})ZnOH] (100 mg, 0.18 mmol) was dissolved in 15 mL of CH_2Cl_2. To this solution was added 1.0 equiv of acetohydroxamic acid (13 mg, 0.18 mmol) dissolved in 10 mL of MeOH. The mixture was stirred at room temperature overnight under a nitrogen atmosphere. After being stirred, 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 (~3 mL) and the material was recrystallized by diffusion with pentane. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 2.14 (s, 3H, CH_3, hydroxamate-CH_3), 2.50 (s, 9H, CH_3, pyrazole-CH_3), 6.16 (s, 3H, pyrazole-H), 7.23 (m, 3H, phenyl-H), 7.34 (m, 6H, phenyl-H), 7.59 (d, J = 8.1 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 13.3, 30.9, 38.5, 104.8, 125.8, 127.8, 128.8, 133.0, 145.2, 152.8. Anal. Calcd for $C_{32}H_{32}BN_7O_2Zn \cdot 0.5$ benzene: C, 63.51; H, 5.33; N, 14.81. Found: C, 63.71; H, 5.60; N, 14.60.

[(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)]. The same procedure was used as in the synthesis of [(Tp^{Me,Ph})Zn(acetohydroxamate)]. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 0.90 (d, J = 5.7 Hz, 3H, butanonate-CH_3), 1.13 (s, 3H, butanonate-CH_3), 2.56 (s, 9H, pyrazole-CH_3), 2.77 (m, 1H, butanonate-H), 6.16 (s, 3H, pyrazole-H), 7.27 (d, J = 5.4 Hz, 3H, phenyl-H), 7.37 (m, 6H, phenyl-H), 7.69 (d,, J = 6.0 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 13.4, 23.1, 25.0, 47.5, 105.7, 128.0, 128.6, 128.9, 132.7, 145.0, 153.5, 211.9. Anal. Calcd for $C_{34}H_{35}BN_6OSZn$: C, 62.64; H, 5.41; N, 12.89. Found: C, 62.33; H, 5.62; N, 12.92.

[(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)]. The same procedure was used as in the synthesis of [(Tp^{Me,Ph})Zn(acetohydroxamate)]. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 1.2 (m, 3H, amidate-CH_3), 2.2 (s, 2H, amidate-CH_2), 2.6 (s, 9H, pyrazole-CH_3), 6.2 (s, 3H, pyrazole-H), 7.3 (m, 3H, phenyl-H), 7.4 (m, 6H, phenyl-H), 7.7 (d, J = 8.0 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 12.9, 26.3, 30.9, 105.3, 127.6, 128.0, 132.0, 145.1, 153.4, 172.8. Anal. Calcd for $C_{33}H_{34}BN_7OSZn \cdot 0.5$ benzene$\cdot H_2O$: C, 63.53; H, 5.65; N, 13.09. Found: C, 62.58; H, 5.36; N, 13.21.

[(Tp^{Me,Ph})Zn(2-mercaptoethanoate)]. The same procedure was used as in the synthesis of [(Tp^{Me,Ph})Zn(acetohydroxamate)]. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 2.1 (m, 2H, ethanoate-CH_2), 2.2 (m, 2H, ethanoate-CH_2), 2.6 (s, 9H, pyrazole-CH_3), 6.2 (s, 3H, pyrazole-H), 7.3 (m, 3H, phenyl-H), 7.4 (m, 6H, phenyl-H), 7.7 (d, J = 7.6 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 13.3, 28.8, 64.7, 105.8, 128.5, 128.6, 128.8, 131.8, 145.8, 154.1. Anal. Calcd for $C_{32}H_{33}BN_6OSZn \cdot 0.5$ benzene: C, 63.22; H, 5.46; N, 12.64 Found: C, 63.34; H, 5.69; N, 12.56.

[(Tp^{Me,Ph})Zn(3-mercapto-2-propanoate)]. The same procedure was used as in the synthesis of [(Tp^{Me,Ph})Zn(acetohydroxamate)]. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 0.49 (d, J = 4.5 Hz, 3H, propanoate-CH_3), 1.1 (m, 2H, propanate-CH_2), 1.2 (m, 1H, propanoate-CH), 2.6 (s, 9H, pyrazole-CH_3), 6.2 (s, 3H, pyrazole-H), 7.3 (m, 3H, phenyl-H), 7.4 (m, 6H, phenyl-H), 7.7 (d, J = 8.0 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 13.3, 21.8, 34.9, 69.3, 105.8, 128.6, 128.9, 129.1, 131.7, 145.8, 154.1. Anal. Calcd for $C_{36}H_{38}BN_6OSZn \cdot 0.5$ benzene: C, 63.68; H, 5.64; N, 12.38. Found: C, 63.99; H, 6.01; N, 12.40.

[(Tp^{Me,Ph})Zn(3-mercapto-2-butanoate)]. The same procedure was used as in the synthesis of [(Tp^{Me,Ph})Zn(acetohydroxamate)]. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 0.13/0.27 (d, J = 5.1/5.1 Hz, 3H, butanoate-CH_3), 0.50/0.57 (d, J = 5.1/4.2 Hz, 3H, butanoate-CH_3), 2.57 (s, 9H, pyrazole-CH_3), 6.19 (s, 3H, pyrazole-H), 7.35 (m, 3H, phenyl-H), 7.41 (m, 6H, phenyl-H), 7.66 (d, J = 7.2 Hz, 6H, phenyl-H). ^{13}C NMR ($CDCl_3$, 400 MHz, 25 °C) δ 13.4, 18.4/19.3, 21.0/24.1, 42.1/43.7, 72.2/72.8, 105.8, 128.6, 128.7,

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128.9, 131.8, 145.7, 154.1. Anal. Calcd for $C_{34}H_{37}BN_6OSZn$: C, 62.44; H, 5.70; N, 12.85. Found: C, 62.79; H, 5.96; N, 12.97.

X-ray Crystallographic Analysis. Data were collected on a Brucker AXS area detector diffractometer. Crystals were mounted on quartz capillaries by using Paratone oil and were cooled in a nitrogen stream (Kryo-flex controlled) on the diffractometer (−173 °C). Peak integrations were performed with the Siemens SAINT software package. Absorption corrections were applied by using the program SADABS. Space group determinations were performed by the program XPREP. The structures were solved by direct or Patterson methods and refined with the SHELXTL software package.[36] Unless noted otherwise, all hydrogen atoms, except for the boron hydrogen atoms, were fixed at calculated positions with isotropic thermal parameters; all non-hydrogen atoms were refined anisotropically.

[(Tp^{Me,Ph})Zn(acetohydroxamate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the monoclinic space group *C*2/*c* (No. 15, $Z = 8$, $a = 40.321$ Å, $b = 16.979$ Å, $c = 10.821$ Å, $\beta = 105.043°$). The hydrogen atom on the boron and the N−H hydrogen atom on the zinc-bound acetohydroxamate were found in the difference map and their positions were not fixed. The complex cocrystallized with one molecule of free acetohydroxamic acid and one-half of a benzene solvent molecule in the asymmetric unit.

[(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the monoclinic space group $P2_1/c$ (No. 14, $Z = 4$, $a = 10.148$ Å, $b = 10.942$ Å, $c = 28.807$ Å, $\beta = 98.793°$). The 3-mercapto-2-butanone used to prepare the complex was a combination of *R* and *S* isomers, and the crystals grown are a racemic mixture of the complexes formed with each enantiomer. The two enantiomers did not segregate in the crystal and therefore the structure was disordered with a partial occupancy (55:45) of the carbon atoms α (C11/C11B) and β (C12/C12B) to the sulfur atom (Figure S2, Supporting Information). The hydrogen atom on the boron was found in the difference map and the position was refined. No hydrogen atoms were calculated or refined for the disordered carbon atoms. No solvent molecules were found in the asymmetric unit.

[(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the triclinic space group $P\bar{1}$ (No. 2, $Z = 2$, $a = 11.944$ Å, $b = 12.241$ Å, $c = 14.909$ Å, $\alpha = 69.039°$, $\beta = 85.523°$, $\gamma = 62.603°$). The hydrogen atom on the boron was found in the difference map and the position was refined. The complex cocrystallized with one molecule of benzene in the asymmetric unit.

[(Tp^{Me,Ph})Zn(2-mercaptoethanoate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the triclinic space group $P\bar{1}$ (No. 2, $Z = 2$, $a = 11.349$ Å, $b = 12.020$ Å, $c = 14.899$ Å, $\alpha = 71.114°$, $\beta = 88.315°$, $\gamma = 62.123°$). The hydrogen atom on the boron was found in the difference map and the position was refined. The complex cocrystallized with one molecule of benzene in the asymmetric unit.

[(Tp^{Me,Ph})Zn(3-mercapto-2-propanoate)]. Colorless blocks were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the triclinic space group $P\bar{1}$ (No. 2, $Z = 2$, $a = 11.580$ Å, $b = 11.674$ Å, $c = 15.250$ Å, $\alpha = 88.252°$, $\beta = 82.245°$, $\gamma = 60.308°$). The hydrogen atom on the boron was found in the difference map and the position was refined. A severely disordered solvent molecule was found in the asymmetric unit. Despite several attempts, identification of the solvent (benzene or pentane) could not be resolved. However, there is no disorder in the metal complex.

[(Tp^{Me,Ph})Zn(3-mercapto-2-butanoate)]. Large colorless prisms were grown out of a solution of the complex in benzene diffused with pentane. The complex crystallized in the monoclinic space group $P2_1/c$ (No. 14, $Z = 4$, $a = 10.027$ Å, $b = 11.382$ Å, $c = 28.672$ Å, $\beta = 99.127°$). The 3-mercapto-2-butanol used to prepare the complex was a combination of the *R*,*R*, *S*,*S*, *R*,*S*, and *S*,*R* isomers, and the crystals grown are a mixture of the complexes formed with each stereoisomer. The two enantiomeric pairs did not segregate during crystal growth nor in the crystal lattice and therefore the structure represents a mixture of all four isomers bound to the zinc center. A disorder (partial occupancy) model of all four isomers was obtained to fit the data (Figure S3, Supporting Information). The structure clearly shows the mode of binding and indicates that all four isomers bind in a monodentate fashion to the zinc ion. The hydrogen atom on the boron was found in the difference map and the position was refined. No hydrogen atoms were calculated or refined for the disordered carbon atoms. No solvent molecules were found in the asymmetric unit.

Results

Utilizing [(Tp^{Me,Ph})ZnOH] as a starting point,[34,35] a number of complexes were synthesized that employed small molecules as exogenous donors to the zinc center. To demonstrate that the ligand, hydrotris(5,3-methylphenylpyrazolyl)-borate (Tp^{Me,Ph}) provided an adequate model for the MMP zinc active site, the zinc complex [(Tp^{Me,Ph})ZnOH] was combined with acetohydroxamic acid in a methanol/methylene chloride to obtain the complex [(Tp^{Me,Ph})Zn(acetohydroxamate)]. Like the structures of [(Tp*)Zn(acetohydroxamate)] and [(Tp*)Zn(2-hydroxamato-4-methylpentanoyl-alanyl-glycylamide)],[23,28] [(Tp^{Me,Ph})Zn(acetohydroxamate)] reveals a five-coordinate zinc center (Table 1) bound by the three nitrogen atoms of the Tp^{Me,Ph} ligand and the two oxygen atoms of the hydroxamate in what is best described as a highly distorted trigonal bipyramidal environment (Figure 1). The acetohydroxamate ligand is bound in a bidentate manner with Zn−O distances of 1.98 (N−O) and 2.10 Å (C═O), very close to the distances described in early studies.[23] An overlay of the structure of the zinc center in [(Tp^{Me,Ph})Zn(acetohydroxamate)] indicates, as found in similar complexes,[23] that the coordination geometry is very similar to that found in the structure of the zinc ion in MMPs when inhibited by hydroxamate compounds, as determined by macromolecular crystallography.[28] An overlay of all nine atoms (one zinc, two oxygen, four nitrogen, and two carbon atoms) from [(Tp^{Me,Ph})Zn(acetohydroxamate)] with that of MMP-13 (mature truncated human fibroblast collagenase) inhibited by (*N*-(2-hydroxamatemethylene-4-methyl-pentoyl)-phenylalanyl)methylamine,[28] results in a RMS deviation of 0.372 Å (Figure S1, Supporting Information). The structure of [(Tp^{Me,Ph})Zn(acetohydroxamate)] indicates, as anticipated, that [(Tp^{Me,Ph})Zn(ZBG)] complexes provide a good model for the metal-binding properties of MMP inhibitors. This encouraged us to use similar complexes to determine the

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Table 1. Crystal Data for [(Tp^{Me,Ph})Zn(acetohydroxamate)], [(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)], and [(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)]

	[(Tp^{Me,Ph})Zn-(acetohydroxamate)]	[(Tp^{Me,Ph})Zn-(3-mercapto-2-butanonate)]	[(Tp^{Me,Ph})Z-(*N*-methylmercaptoacetamidate)]
empirical formula	$C_{37}H_{40}BN_8O_4Zn$	$C_{34}H_{36}BN_6OSZn$	$C_{39}H_{40}BN_7OSZn$
cryst syst	monoclinic	monoclinic	triclinic
space group	*C*2/*c*	$P2_1/c$	$P\bar{1}$
unit cell dimens	$a = 40.321(2)$ Å	$a = 10.148(1)$ Å	$a = 11.944(2)$ Å
	$\alpha = 90°$	$\alpha = 90°$	$\alpha = 69.039°$
	$b = 16.979(1)$ Å	$b = 10.942(1)$ Å	$b = 12.241(2)$ Å
	$\beta = 105.043(1)°$	$\beta = 98.793(1)°$	$\beta = 85.523°$
	$c = 10.821(1)$ Å	$c = 28.807(1)$ Å	$c = 14.909(3)$ Å
	$\gamma = 90°$	$\gamma = 90°$	$\gamma = 62.603°$
vol, *Z*	7154.3(6) Å^3, 8	3161.0(3) Å^3, 4	1797.3(5) Å^3, 2
cryst size	$0.2 \times 0.1 \times 0.05$ mm^3	$0.3 \times 0.2 \times 0.1$ mm^3	$0.1 \times 0.04 \times 0.02$ mm^3
temp (K)	100(1)	100(1)	100(1)
reflns collected	30093	26142	15756
independent reflns	8088 (R(int) = 0.0235)	7116 (R(int) = 0.0253)	8038 (R(int) = 0.0519)
data/restraints/parameters	8088/0/478	7116/0/422	8038/0/463
goodness-of-fit on F^2	1.088	1.068	1.024
final R indicies $I > 2\sigma(I)$	$R1 = 0.0298$	$R1 = 0.0405$	$R1 = 0.0604$
	$wR2 = 0.0807$	$wR2 = 0.1063$	$wR2 = 0.1196$
R indicies (all data)	$R1 = 0.0340$	$R1 = 0.0458$	$R1 = 0.0960$
	$wR2 = 0.0870$	$wR2 = 0.1093$	$wR2 = 0.1328$
largest peak/hole diff	0.418/−0.231 e Å^{-3}	0.726/−0.754 e Å^{-3}	0.981/−0.519 e Å^{-3}

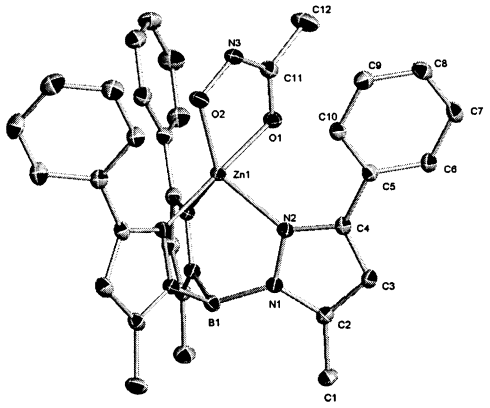

Figure 1. Structural diagram of [(Tp^{Me,Ph})Zn(acetohydroxamate)] with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent have been omitted for clarity.

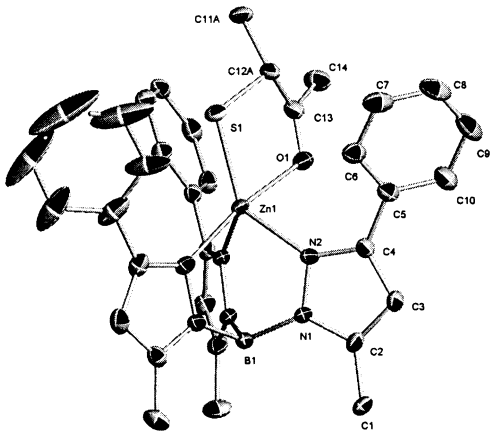

Figure 2. Structural diagram of [(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)] with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and one isomer (partial occupancy disorder, C11B/C12B) have been omitted for clarity.

interaction of inhibitors with MMPs where the mode of binding was not known.

The substantial interest in thiol and thiol-derived MMP inhibitors prompted the synthesis of a number of complexes to probe the binding mode of these compounds.[31−33] All of the complexes were prepared in an identical fashion from commercially available thiols, by combining 1 equiv of the thiol with [(Tp^{Me,Ph})Zn(OH)] in a methanol/methylene chloride mixture. After being stirred overnight at room temperature, the reaction mixture was evaporated to dryness and the resulting residue was recrystallized from a benzene solution of the complex diffused with pentane. Chart 2 shows representative examples of the inhibitors that were studied here and the thiol compounds used to model their zinc binding. All of the [(Tp^{Me,Ph})Zn(ZBG)] complexes were characterized by elemental analysis, ^{1}H/^{13}C NMR, and X-ray crystallography.

Three classes of molecules, β-mercaptoketones,[32,33] β-mercaptoamides,[31] and β-mercaptoalcohols,[32,33] were examined for elucidating the coordination mode of a number of MMP inhibitors. The interaction of β-mercaptoketone-based drugs was evaluated by using 3-mercapto-2-butanone as the ZBG. The structure of [(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)] shown in Figure 2 demonstrates that this ligand binds the zinc atom in a bidentate fashion, utilizing both the sulfur and carbonyl oxygen donor atoms. Only one isomer of the 3-mercapto-2-butanonate ligand is shown in Figure 2, although the crystal structure possessed a partial occupancy disorder with both the *R*- and *S*-isomers bound to the zinc ion. The zinc center can be described as distorted trigonal bipyramidal with the oxygen donor and one of the pyrazole rings occupying the axial positions of the coordination sphere. The Zn−S distance is 2.27 Å and the Zn−O distance is 2.33 Å, demonstrating strong bidentate coordination to the metal center. The Zn−O distance is slightly longer (0.23 Å) than the carbonyl Zn−O distance in the acetohydroxamic structure (Figure 1), suggesting that the strong sulfur coordination prohibits tighter binding by the keto-oxygen donor atom.

The interaction of β-mercaptoamide-based drugs was evaluated by using *N*-methylmercaptoacetamide as the ZBG. The structure of [(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)] shown in Figure 3 demonstrates that this ligand also binds

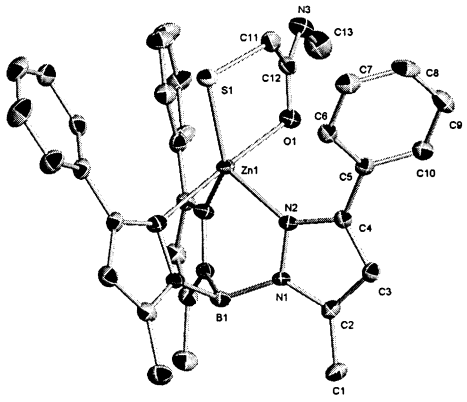

Figure 3. Structural diagram of [(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)] with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent have been omitted for clarity.

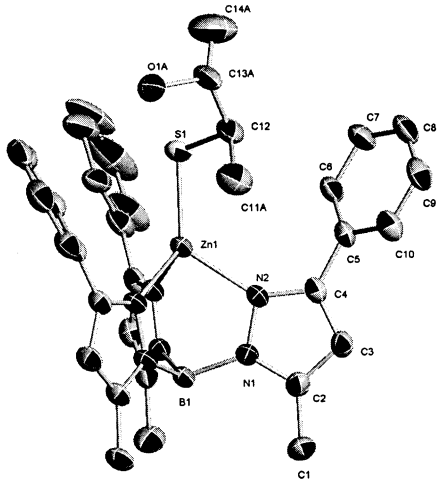

Figure 4. Structural diagram of [(Tp^{Me,Ph})Zn(3-mercapto-2-butanoate)] with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and three isomers (partial occupancy disorder) have been omitted for clarity.

the zinc atom in a bidentate fashion, utilizing the sulfur and amide oxygen atoms (Table 1). Previous work on mercaptoacyl-derived MMP inhibitors had predicted that this ZBG would bind in a bidentate fashion although no experimental evidence was provided to support this hypothesis.[31] The zinc center is very similar to that found in [(Tp^{Me,Ph})Zn(3-mercapto-2-butanonate)]: a distorted trigonal bipyramid with the oxygen donor and one pyrazole ring occupying the axial positions of the 5-coordinate environment. The Zn−S distance is 2.28 Å and the Zn−O distance is 2.26 Å, again demonstrating strong chelation to the metal center. The Zn−O distance is also longer (0.15 Å) than the carbonyl Zn−O distance in the acetohydroxamate structure (Figure 1), suggesting that the sulfur atom impedes closer coordination by the oxygen donor atom.

The interaction of β-mercaptoalcohol-based drugs[32,33] was evaluated by using β-mercaptoethanol, 3-mercapto-2-propanol, and 3-mercapto-2-butanol as the ZBGs. All three complexes, shown in Figures 4 and 5, demonstrate that these ligands bind in a monodentate fashion, only through the sulfur atom (Table 2). The binding of three different small molecules was analyzed to evaluate the interaction of β-mercaptoalcohols to unambiguously confirm the unexpected monodentate coordination mode. The zinc centers are tetrahedral, with average Zn−N bond distances of 2.07(2) Å and a Zn−S distance of 2.22(1) Å.

In contrast to 3-mercapto-2-butanone and *N*-(methyl)-mercaptoacetamide, the β-mercaptoalcohol compounds bind only in a mondentate fashion. The difference in coordination behavior is likely the result of two distinct factors. First, unlike 3-mercapto-2-butanone and *N*-(methyl)mercaptoacetamide, the β-mercaptoalcohols are not conformationally restricted at the carbon α to the oxygen donor. Because 3-mercapto-2-butanone and *N*-(methyl)mercaptoacetamide have sp^2 carbonyl carbon atoms β to the sulfur donor atoms, the ligand has less overall flexibility making it poised for bidentate coordination through the oxygen donors in a manner similar to that observed for the hydroxamate compounds. The second reason the β-mercaptoalcohols bind in a monodentate fashion is due to the reduced Lewis acidity of the zinc center upon sulfur binding. The deprotonated thiol sulfur atom is a strong Lewis base that significantly reduces the Lewis acidity of the zinc ion. Coupled with the conformational freedom of the β-mercaptoalcohols, the zinc center is not sufficiently electrophilic to deprotonate the alcohol oxygen atom thereby acquiring another strong ligand. Therefore, the conformationally unrestricted protonated alcohol donor remains a very weak ligand and does not bind to the zinc center.

These model complexes show that in the solid state some ZBGs bind in a bidentate manner while others are observed to coordinate in a monodentate fashion. To confirm the solution structure of these model systems, the free and bound ZBGs were studied by using NMR. These data confirm that the interactions seen in the crystal structures are representative of the solution interactions, further supporting the relevance of these model compounds. Comparison of the room temperature ^{13}C NMR spectrum for 3-mercapto-2-butanone to the corresponding spectrum of [(Tp^{Me,Ph})Zn(3-mercapto-2-butanoate)] shows downfield shifts in three of the four carbons on the bound ZBG. The change is greatest in the carbons adjacent to the coordinated S and O atoms. The carbon atom α to the sulfur shifts 5.0 ppm (42.5−47.5) while the binding carbonyl carbon shifts 6.5 ppm (205.4−211.9). In contrast, only small changes in chemical shift are observed for the monodentate ZBGs. The ^{13}CNMR of free 3-mercapto-2-propanol and its model complex [(Tp^{Me,Ph})Zn-(3-mercapto-2-propanoate)] illustrate this difference. The downfield shift of the carbon atom α to the sulfur moves only 1.9 ppm (32.8−34.9) while the carbon α to the hydroxyl group shifts 1.0 ppm (68.3−69.3). The strong downfield shifts of the bidentate ZBGs when compared to the smaller shifts from monodentate ZBGs suggest that the solid-state structure is maintained in solution at room temperature.

Discussion

The inhibition of MMPs is a central theme in developing antiarthritic and anticancer drugs.[1,2,24] Although a great deal of effort has gone into the design and synthesis of new inhibitors, largely based on the binding interaction between the drug and the catalytic zinc(II) center, surprisingly very

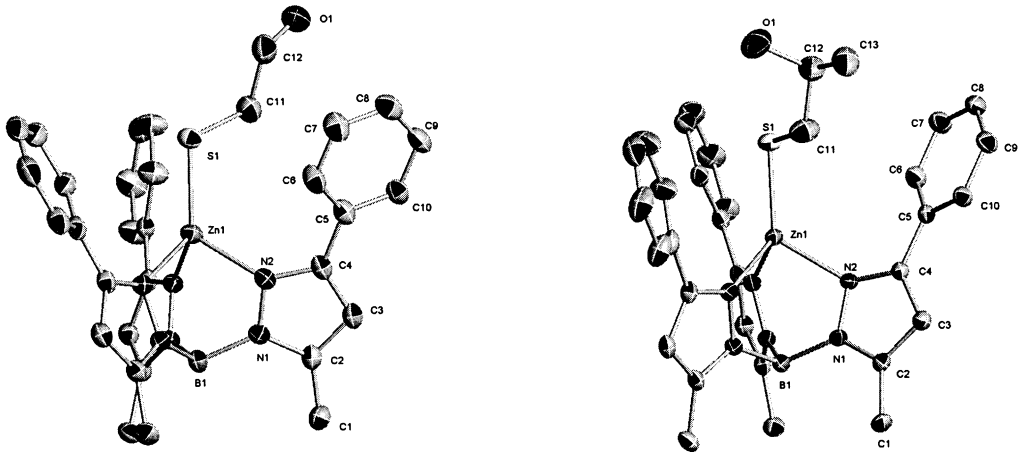

Figure 5. Structural diagrams of [(Tp^{Me,Ph})Zn(2-mercaptoethanoate)] (left) and [(Tp^{Me,Ph})Zn(3-mercapto-2-propanoate)] (right) with partial atom numbering schemes (ORTEP, 50% probability ellipsoids). Hydrogen atoms and solvent have been omitted for clarity.

Table 2. Crystal Data for [(Tp^{Me,Ph})Zn(2-mercaptoethanoate)], [(Tp^{Me,Ph})Zn(3-mercapto-2-propanoate)], and [(Tp^{Me,Ph})Zn(3-mercapto-2-butanoate)]

	[(Tp^{Me,Ph})Zn-(2-mercaptoethanoate)]	[(Tp^{Me,Ph})Zn-(3-mercapto-2-propanoate)]	[(Tp^{Me,Ph})Zn-(3-mercapto-2-butanoate)]
empirical formula	$C_{38}H_{39}BN_6OSZn$	$C_{41}H_{35}BN_6OSZn$	$C_{340}H_{37}BN_6OSZn$
cryst syst	triclinic	triclinic	monoclinic
space group	$P\bar{1}$	$P\bar{1}$	$P2_1/c$
unit cell dimens	$a = 11.349(1)$ Å	$a = 11.580(1)$ Å	$a = 10.0273(6)$ Å
	$\alpha = 71.114(2)°$	$\alpha = 88.252(1)°$	$\alpha = 90°$
	$b = 12.020(1)$ Å	$b = 11.674(1)$ Å	$b = 11.382(1)$ Å
	$\beta = 88.315(2)°$	$\beta = 82.245(1)°$	$\beta = 99.127(1)°$
	$c = 14.899(2)$ Å	$c = 15.250(1)$ Å	$c = 28.672(2)$ Å
	$\gamma = 62.123(2)°$	$\gamma = 60.308(1)°$	$\gamma = 90°$
vol, Z	1681.8(3) Å^3, 2	1772.8(2) Å^3, 2	3230.9(3) Å^3, 4
cryst size	$0.4 \times 0.2 \times 0.2$ mm^3	$0.6 \times 0.6 \times 0.3$ mm^3	$0.3 \times 0.2 \times 0.1$ mm^3
temp (K)	100(1)	100(1)	100(1)
reflns collected	14688	15239	26807
independent reflns	7541 [R(int) = 0.0192]	7843 [R(int) = 0.0159]	7299 [R(int) = 0.0297]
data/restraints/parameters	7541/0/437	7843/0/466	7299/0/468
goodness-of-fit on F^2	1.076	1.054	1.058
final R indicies $I > 2\sigma(I)$	$R1 = 0.0486$	$R1 = 0.0537$	$R1 = 0.0463$
	$wR2 = 0.1345$	$wR2 = 0.1577$	$wR2 = 0.1210$
R indicies (all data)	$R1 = 0.0589$	$R1 = 0.0556$	$R1 = 0.0558$
	$wR2 = 0.1392$	$wR2 = 0.1594$	$wR2 = 0.1270$
largest peak/hole diff	1.641/−0.586 e Å^{-3}	2.529/−0.949 e Å^{-3}	1.029/−0.373 e Å^{-3}

little information is available on the mode of binding for many of these compounds.[2] The traditional means of obtaining these data is to obtain crystal structures of the protein with different inhibitors bound in the active site.[27,28,37] Unfortunately, this requires the isolation and purification of large amounts of high-quality protein, extensive screening of crystallization conditions, and the preparation of heavy-atom derivatives (in some cases). Ultimately, this endeavor can be quite time-consuming and may never result in crystals suitable for X-ray diffraction. Nevertheless, without these data it is extremely difficult to proceed with rational drug design and explain differences in drug activity when comparing ZBGs from different compounds.

The inorganic complex [(Tp^{Me,Ph})Zn(OH)] provides an excellent structural model for the MMP active site.[13,23] In the catalytic form of MMPs, the zinc ion is held in a tetrahedral coordination environment by three histidine nitrogen atoms and an aquo/hydroxide ligand that acts as the activated nucleophile for peptide hydrolysis. In [(Tp^{Me,Ph})-Zn(OH)], the zinc ion is similarly bound by three nitrogen heterocycles and a hydroxide ligand. Inhibition of MMPs by synthetic compounds typically occurs by chelation of the zinc center by a ZBG that displaces the bound nucleophile and thereby shuts down the hydrolytic activity. It was clear from prior studies that [(Tp^{Me,Ph})Zn(OH)] could reproduce the metal-binding interaction of these inhibitors, by combining model ligands with this zinc complex.[13,23] These results were confirmed by the structure of [(Tp^{Me,Ph})Zn-(acetohydroxamate)], which demonstrates the same binding mode as found for hydroxamate-based drugs, and can be directly superimposed on the inhibited catalytic site of MMPs (Figure S1, Supporting Information) with high fidelity (root-mean-sqaure deviation of 0.372 Å).[28] These data indicated that [(Tp^{Me,Ph})Zn(OH)] could be used not only for reproducing known drug−metalloprotein interactions, but also for elucidating similarly unknown interactions. It was apparent that such data could be extremely useful for explaining trends in inhibitory activity, as well as serving as an aid for future drug design.

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As an initial attempt to implement this strategy, a number of thiol-derived drug candidates were examined. Many thiol-based drugs demonstrate significant inhibitory activity against a variety of MMP targets[2,31−33,38] and some are being pursued clinically.[1,2] Thiol derivatives are a logical diversion from the more commonly used hydroxamic acid motif, as the strong binding of sulfur groups to zinc(II) is found prevalently in biological systems.[39] Indeed, MMPs have autoinhibitory activity before excretion from cells by a "cystine-switch" mechanism,[2,40] where the reactivity of the catalytic zinc center is suppressed by a cystine side-chain of the protein, until cleavage of this residue occurs by extracellular or membrane-bound proteinases. Despite the widespread investigation of various thiol-derived drugs the binding mode of these compounds, with the exception of simple thiols, is presently not known.[31−33]

Complexation of [(Tp^{Me,Ph})Zn(OH)] with β-mercaptoketones, β-mercaptoamides, and a number of β-mercaptoalcohols quickly revealed the binding mode of these ZBGs. As previously suggested,[31−33] the structures of [(Tp^{Me,Ph})Zn-(3-mercapto-2-butanonate)] and [(Tp^{Me,Ph})Zn(*N*-methylmercaptoacetamidate)] revealed bidentate zinc coordination for β-mercaptoketone- and β-mercaptoamide-derived drugs, respectively. The binding of these compounds is much less symmetric than is found in the acetohydroxamate structures, indicating weaker binding by the oxygen donor atoms. This likely contributes to the overall lower efficacy of these compounds when compared with hydroxamic acid derivatives.

Surprisingly, the complexation of a series of β-mercaptoalcohols with [(Tp^{Me,Ph})Zn(OH)] consistently demonstrated monodentate, as opposed to bidentate, coordination of the ZBG to the metal center. This compelling result, confirmed with three independent compounds and crystal structures, leaves little doubt that β-mercaptoalcohol-derived drugs bind in a monodentate fashion to the catalytic MMP zinc ion. This is contrary to the anticipated bidentate mode of binding put forth by earlier studies.[32,33] These data facilitate interpretation of earlier reports that directly compared the inhibitory activity of β-mercaptoalcohol- and β-mercaptoketone-derived drugs. Campbell and co-workers described a series of malonyl β-mercaptoalcohols and β-mercaptoketones with good potency against a number of MMPs.[32] Of 12 compounds that contained the same backbone substituents and only varied the ZBG between a β-mercaptoalcohol and a β-mercaptoketone, 11 showed greater potency with the β-mercaptoketone functionality (the remaining compound showed equal activity for both derivatives). In more than half of these compounds the IC_{50} of the β-mercaptoketone was at least one order of magnitude lower.[32] Although the authors of the papers recognized the higher inhibitory activity of the β-mercaptoketone compounds, no explanation was provided for the increased efficacy. On the basis of the data presented here, it is probable that the difference in activity is due to a change in the mode of binding for the two classes of compounds. The β-mercaptoketones are likely to bind the catalytic zinc ion in a bidentate fashion while the β-mercaptoalcohols bind in only a monodentate fashion, dramatically weakening the interaction with the enzyme. In a separate study from the same group,[33] succinyl β-mercaptoalcohols and a β-mercaptoketones were compared and the anti isomer of the alcohols was found to have very poor activity against MMPs, while the syn isomer of the alcohol and the β-mercaptoketones demonstrated good activity. The difference in activity of the two alcohol isomers was speculated to be due to differences in the orientation of the drug backbone, resulting from the different bidentate binding conformations of the two β-mercaptoalcohol stereoisomers. Again, in light of the data presented here, this explanation is not compelling and although the stereochemistry of these compounds clearly plays a role in their inhibitory ability, it is unlikely that this originates from differences in the metal-binding conformation. Because both β-mercaptoalcohol isomers will be mondentate the differences in activity likely originate from variations in the way the backbone of these isomers lie in the MMP binding cleft and the resulting dissimilar noncovalent interactions (hydrogen-bonding, van der Waals, etc.) each isomer experiences. Evaluation of these biochemical experiments is clearly augmented by the studies presented here and demonstrates the great potential for the use of model chemistry to evaluate similar drug−biomolecule interactions.

By using a simple model complex that accurately mimics, for structural purposes, the active site in MMPs, we have rapidly and at high resolution determined the binding modes of several MMP inhibitors. The resulting structural data assist in explaining differences in the inhibitory activity of several drug candidates in development for anticancer and antiarthritic therapy. We believe that this represents an unexplored use of traditional bioinorganic model chemistry, that is, as a tool to elucidate unknown drug−protein interactions. Efforts are underway in our labs to further exploit this concept for the development of next-generation drug design.

Acknowledgment. We thank Prof. Clifford Kubiak for helpful discussions and Dr. Villa Nørklit Andersen (U.C. Berkley) for assistance with taking the elemental analysis. This work was supported by the University of California, San Diego, the Chris and Warren Hellman Faculty Scholar award (S.M.C.), and N.I.H. Grant No. GM-60202-03 (D.T.P.).

Supporting Information Available: Figures S1, S2, and S3 and X-ray crystallographic CIF files. This material is available free of charge via the Internet at http://pubs.acs.org. CIF files are available free of charge via the Internet at http://www.ccdc.cam.ac.uk. Refer to CCDC reference numbers 183881, 183882, 183883, 183884, 183885, 183886.

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