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Solvent Effects on the Structural and Formyl Substrate Reactivity Properties of a Nitrogen/Sulfur-Ligated Zinc Hydroxide Complex

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The solution structural and formyl substrate reactivity properties of a nitrogen/sulfur-ligated zinc hydroxide complex, $[(bmnpaZn)_2(\mu\text{-}OH)_2](ClO_4)_2$ (**1**, bmnpa = *N*,*N*-bis-2-(methylthio)ethyl-*N*-((6-neopentylamino-2-pyridyl)methyl)amine), in acetonitrile and methanol are reported. In CH_3CN, **1** has a binuclear cation $[(bmnpaZn)_2(\mu\text{-}OH)_2]^{2+}$ that is stabilized by secondary hydrogen bonding and CH/π interactions involving the bmnpa chelate ligand. In CH_3OH, **1** undergoes reaction with solvent to yield a zinc methoxide species, as determined by ^{1}H NMR and electrospray mass spectral analysis. Treatment of **1** with methyl formate in CH_3CN results in stoichiometric hydrolysis of the formyl ester to produce $[(bmnpa)Zn(O_2CH)]ClO_4$ (**2**) and methanol. The formate complex was identified via independent synthesis and characterization (X-ray crystallography, ^{1}H and ^{13}C NMR, FTIR, LRFAB-MS, conductance, and elemental analysis). In the solid state, $\mathbf{2}_n$ has a formate-bridged coordination polymer-type structure. However, in CH_3CN, **2** behaves as 1:1 electrolyte, indicating cleavage of the polymer structure into mononuclear $[(bmnpa)Zn(O_2CH)]ClO_4$ species. Treatment of **1** with a stoichiometric amount of formanilide in CH_3CN for 48 h at 45 °C results in decomposition of the zinc hydroxide complex to yield the free bmnpa ligand and an inorganic solid, presumably a zinc hydroxide or oxide species. Treatment of **1** with a stoichiometric amount of ethyl formate in CD_3OD results in rapid, quantitative transesterification of the formyl carboxylate ester. A control reaction indicates that this transesterification reaction does not occur on the same time scale in the absence of the catalyst. Treatment of **1** with an excess of ethyl formate in CD_3OD results in catalytic formyl carboxylate ester transesterification, with approximately 1000 turnovers in 60 min at 22(1) °C. Treatment of a CD_3OD solution of **1** (0.5 equiv) with formanilide (1 equiv) results in the formation of aniline, d_3-methyl formate, and the zinc formate complex **2**. While aniline is produced stoichiometrically, the yield of d_3-methyl formate varied from 30 to 50%, and the yield of **2** varied from 50 to 70% in repetitive experiments. Formation of both d_3-methyl formate and **2** indicates that both methanolysis and hydrolysis reactions take place.

Introduction

The structural and reactivity properties of zinc hydroxide complexes of a variety of chelate ligands have been examined in studies directed at elucidating chemistry of relevance to the role of zinc in biological systems.[1] Recently, we and others initiated investigations into how secondary hydrogen bonding interactions influence the chemical properties of zinc hydroxide complexes.[2−10] Within the realm of hydrogen bond-containing systems, we are interested in several aspects of the biologically relevant chemistry of Zn−OH species,

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(1) Parkin, G. *Chem. Rev.* **2004**, *104*, 699−768.
(2) Berreau, L. M.; Allred, R. A.; Makowska-Grzyska, M. M.; Arif, A. M. *Chem. Commun.* **2000**, 1423−1424.
(3) Garner, D. K.; Allred, R. A.; Tubbs, K. J.; Arif, A. M.; Berreau, L. M. *Inorg. Chem.* **2002**, *41*, 3533−3541.
(4) Garner, D. K.; Fitch, S. B.; McAlexander, L. H.; Bezold, L. M.; Arif, A. M.; Berreau, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 9970−9971.
(5) MacBeth, C. E.; Hammes, B. S.; Young, V. G., Jr.; Borovik, A. S. *Inorg. Chem.* **2001**, *40*, 4733−4741.
(6) Mareque-Rivas, J. C.; Prabaharan, R.; Parsons, S. *Dalton Trans.* **2004**, 1648−1655.
(7) Mareque-Rivas, J. C.; de Rosales, R. T. M.; Parsons, S. *Chem. Commun.* **2004**, 610−611.
(8) Mareque-Rivas, J. C.; Prabaharan, R.; de Rosales, R. T. M.; Metteau, L.; Parsons, S. *Dalton Trans.* **2004**, 2800−2807.
(9) Mareque-Rivas, J. C.; Prabaharan, R.; de Rosales, R. T. M. *Chem. Commun.* **2004**, 76−77.
(10) Livieri, M.; Mancin, F.; Tonellato, U.; Chin, J. *Chem. Commun.* **2004**, 2862−2863.

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including how hydrogen bonding influences the reactivity of zinc hydroxide complexes with alcohols.[3,4] This particular interest stems from that fact that within the active site of the zinc enzyme liver alcohol dehydrogenase a reactive mononuclear nitrogen/sulfur-ligated zinc alkoxide species is suggested to interact with a nearby serine (Ser48) residue via a strong hydrogen-bonding interaction.[11,12] The degree to which this hydrogen-bonding interaction influences the reactive properties of the zinc alkoxide species remains to be fully elucidated. In this regard, we have demonstrated that a N_3S-donor ligand (ebnpa = *N*,*N*-bis-2-(ethylthio)ethyl-*N*-((6-neopenylamino-2-pyridyl)methyl)amine) with two internal hydrogen-bond donors can be used to produce a mononuclear zinc methoxide complex, $[(ebnpa)Zn-OCH_3]ClO_4$.[4] This methoxide complex, in which the zinc-bound alkoxide oxygen atom participates in two moderate hydrogen-bonding interactions,[13] has enhanced hydrolytic stability compared to mononuclear zinc methoxide complexes of ligands with hydrophobic substituents surrounding the zinc methoxide moiety.[14−16]

We are also interested in the reactivity of nitrogen/sulfur-ligated zinc hydroxide species as it relates to the function of the active-site metal center in Zn(II)-containing peptide deformylase (PDF) enzymes.[17−21] Within the active site of the Zn(II)-containing PDF enzymes from *Escherichia coli* and *Arabidopsis thaliana* is a tetrahedral $(N_{His})_2(S_{Cys})Zn-OH_2$ center.[21,22] Peptide deformylase enzymes catalyze the hydrolysis of an *N*-terminal formamide moiety of nascent polypeptides.[23] Interestingly, despite the fact that PDF enzymes catalyze an amide hydrolysis reaction, substantial evidence now points to the fact that the native metal ion in *E. coli* PDF is Fe(II).[24−27] The Zn(II)-containing form of *E. coli* PDF is 100-fold less active than the Fe(II)-containing form of the enzyme.[28,29] This is interesting, as the X-ray crystallographic studies of *E. coli* PDF having Zn(II), Fe(II), Ni(II), or Co(II) within the active site are essentially identical.[19,22,26,30] Recently, Chan and co-workers reported a series of crystal structures of formate-bound *E. coli* PDF containing Zn(II), Fe(II), or Co(II).[31] In the presence of Zn(II), the formate anion is bound to the metal center in a monodentate fashion, whereas for Fe(II) and Co(II), the formate is bound bidentate. These differing coordination modes led to a proposal that Zn(II)-containing *E. coli* PDF is less active because the metal ion has only one coordination position available for the substrate or nucleophile during catalysis. This would limit the role of the metal center to either substrate or nucleophile activation, but not both, as may occur in Fe(II)- or Co(II)-containing PDF where two coordination positions are available. Biomimetic studies in which this type of proposal might be evaluated have not been reported to date. Furthermore, to our knowledge, zinc-mediated formyl substrate cleavage to yield a zinc formate complex has not yet been reported.[1] Importantly, for the *A. thaliana* PDF, the fully active form of the enzyme contains Zn(II).[20,21]

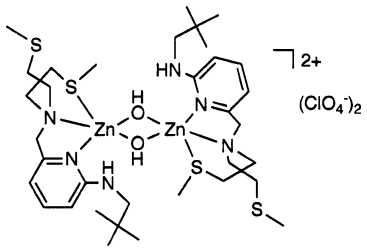

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Figure 1. Nitrogen/sulfur-ligated zinc hydroxide complex.

We have previously described the solid-state X-ray structure of the nitrogen/sulfur-ligated zinc hydroxide complex $[(bmnpaZn)_2(\mu\text{-}OH)_2](ClO_4)_2$ (**1**, *N*,*N*-bis-2-(methylthio)ethyl-*N*-((6-neopentylamino-2-pyridyl)methyl)amine).[2] This structure contains a binuclear cation in which each zinc center is five-coordinate and one thioether appendage of each bmnpa ligand is not coordinated to a zinc center (Figure 1).[2] Within the cation, the secondary amine moiety of each bmnpa ligand participates in a hydrogen-bonding interaction with a bridging hydroxyl group. Because each of these secondary interactions spans the longer Zn−O(H) bond, we rationalize that the hydrogen bonds likely contribute to the stability of the binuclear structure.

In this report, we outline the solution and formyl substrate reactivity properties of **1**.[2] In doing so, we (a) provide evidence from conductance measurements that **1** has a binuclear $Zn_2(\mu\text{-}OH)_2$ cation in CH_3CN solution, (b) define the ^1H NMR properties of $[(bmnpaZn)_2(\mu\text{-}OH)_2](ClO_4)_2$ (**1**) in CD_3CN versus CD_3OD solution, (c) use electrospray mass

(11) Ramaswamy, S.; Park, D.-H.; Plapp, B. V. *Biochemistry* **1999**, *38*, 13951−13959.
(12) Agarwal, P. K.; Webb, S. P.; Hammes-Schiffer, S. *J. Am. Chem. Soc.* **2000**, *122*, 4803−4312.
(13) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: New York, 1997.
(14) Bergquist, C.; Parkin, G. *Inorg. Chem.* **1999**, *38*, 422−423.
(15) Bergquist, C.; Storrie, H.; Koutcher, L.; Bridgewater, B. M.; Friesner, R. A.; Parkin, G. *J. Am. Chem. Soc*. **2000**, *122*, 12651−12658.
(16) Brombacher, H.; Vahrenkamp, H. *Inorg. Chem.* **2004**, *43*, 6042−6049.
(17) Meinnel, T.; Blanquet, S. *J. Bacteriol.* **1995**, *177*, 1883−1887.
(18) Meinnel, T.; Lazennec, C.; Blanquet, S. *J. Mol. Biol.* **1995**, *254*, 175−183.
(19) Meinnel, T.; Blanquet, S.; Dardel, F. *J. Mol. Biol.* **1996**, *262*, 375−386.
(20) Serero, A.; Giglione, C.; Meinnel, T. *J. Mol. Biol*. **2001**, *314*, 695−708.
(21) Fieulaine, S.; Juillan-Binard, C.; Serero, A.; Dardel, F.; Giglione, C.; Meinnel, T.; Ferrer, J.-L. *J. Biol. Chem.* **2005**, *280*, 42315−42324.
(22) Chan, M. K.; Gong, W.; Rajagopalan, P. T. R.; Hao, B.; Tsai, C. M.; Pei, D. *Biochemistry* **1997**, *36*, 13904−13909.
(23) Meinnel, T.; Mechulam, Y.; Blanquet, S. *Biochimie* **1993**, *75*, 1061−1075.
(24) Rajagopalan, P. T. R.; Yu, X. C.; Pei, D. *J. Am. Chem. Soc*. **1997**, *119*, 12418−12419.
(25) Groche, D.; Becker, A.; Schlichting, I.; Kabsch, W.; Schultz, S.; Wagner, A. F. V. *Biochem. Biophys. Res. Commun.* **1998**, *246*, 342−346.
(26) Becker, A.; Schlichting, I.; Kabsch, W.; Groche, D.; Schultz, S.; Wagner, A. F. V. *Nat. Struct. Biol.* **1998**, *5*, 1053−1058.
(27) Baldwin, E. T.; Harris, M. S.; Yem, A. W.; Wolfe, C. L.; Vosters, A. F.; Curry, K. A.; Murray, R. W.; Bock, J. H.; Marshall, V. P.; Cialdella, J. I.; Merchant, M. H.; Choi, G.; Deibel, M. R., Jr. *J. Biol. Chem.* **2002**, *277*, 31163−31171.
(28) Rajagopalan, P. T. R.; Datta, A.; Pei, D. *Biochemistry* **1997**, *36*, 13910−13918.
(29) Ragusa, S.; Blanquet, S.; Meinnel, T. *J. Mol. Biol.* **1998**, *280*, 515−523.
(30) Dardel, F.; Ragusa, S.; Lazennec, C.; Blanquet, S.; Meinnel, T. *J. Mol. Biol*. **1998**, *280*, 501−513.
(31) Jain, R.; Hao, B.; Liu, R.-P.; Chan, M. K. *J. Am. Chem. Soc*. **2005**, *127*, 4558−4559.

spectrometry to provide evidence for the formation of a zinc methoxide cation $[(bmnpa)Zn-OCH_3]^+$ in methanol solutions of **1**, and (d) probe the reactivity of **1** with formyl carboxylate ester and formanilide substrates in acetonitrile and methanol solutions. These studies provide evidence for the presence of a $Zn-OH/Zn-OCH_3$ equilibrium in methanol solutions of **1** and include the first examples of zinc-mediated formyl carboxylate ester hydrolysis and transesterification and zinc-mediated formanilide methanolysis. The combined results of this work provide insight into how the presence of an internal hydrogen-bond donor influences the solvent reactivity and, subsequently, the formyl substrate reactivity of a nitrogen/sulfur-ligated zinc hydroxide complex.

Experimental Section

General Methods. All reagents and solvents were obtained from commercial sources and were used as received unless otherwise noted. CD_3OD was dried according to a literature procedure from $Mg(OCD_3)_2$ and was distilled under vacuum prior to use.[32] The bmnpa (*N*,*N*-bis-2-(methylthio)ethyl-*N*-((6-neopentylamino-2-pyridyl)methyl)amine) ligand and the zinc complex $[(bmnpaZn)_2(\mu\text{-}OH)_2](ClO_4)_2$ (**1**) were prepared as previously reported.[2]

Physical Methods. FTIR spectra were recorded on a Shimadzu FTIR-8400 spectrometer as KBr pellets or as CH_3CN solutions (~100 mM). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 20(1) °C on a JEOL GSX-270 spectrometer or a Bruker ARX-400 spectrometer. Chemical shifts (in ppm) are referenced to the residual solvent peak(s) (CD_2HCN, ^1H 1.94 (quintet), $^{13}C\{^1H\}$ 1.39 (heptet) ppm; CD_2HOD, ^1H 3.31 (quintet) ppm). Conductance measurements were made at 22(1) °C using a YSI Model 31A conductivity bridge with a cell constant of 1.0 cm^{-1} and Me_4NClO_4 as a standard. The preparation of solvents and standard solutions for conductance measurements, as well as subsequent data analysis, was performed as previously described.[33] Fast atom bombardment (FAB) mass spectra were obtained at the University of California, Riverside, using a VG ZAB2SE high-resolution mass spectrometer in a matrix of *m*-nitrobenzyl alcohol (MNBA). Electrospray mass spectra in methanol solution were obtained at the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry, St. Louis, MO. Elemental analyses were performed by Atlantic Microlabs of Norcross, GA.

***Caution**: Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared and these should be handled with great care.*[34]

Stoichiometric Hydrolysis of Methyl Formate Mediated by 1 in CD_3CN. Excess methyl formate (~1.6 μL, 26 × 10^{-3} mmol) was added to a CD_3CN solution (~0.6 mL) of **1** (6.8 mg, 6.5 × 10^{-3} mmol), and the resulting solution was left at ambient temperature for 19 h. At that point, the formyl proton resonance of **2** (vida infra) could be identified. The tube was left for a total of 15 days at ambient temperature, which resulted in the stoichiometric formation of **2** and 2 equiv of methanol.

Independent Synthesis of $[(bmnpa)Zn(O_2CH)]ClO_4$ (2). A methanol solution (1 mL) of $Zn(ClO_4)_2\cdot 6H_2O$ (0.12 g, 0.33 mmol) was added to a methanol solution (1 mL) of bmnpa (0.11 g, 0.33 mmol). The resulting solution was stirred for ~10 min at ambient temperature and then transferred to a methanol solution (1 mL) of NaO_2CH (0.022 g, 0.33 mmol). After the mixture was rapidly stirred for 40 min, an excess of diethyl ether (~17 mL) was added and the resulting cloudy mixture was cooled to ~ −18 °C for 12 h. A white solid that had deposited was collected and carefully dried under vacuum. This solid was redissolved in CH_2Cl_2, and the solution was filtered through a Celite/glass wool plug. An excess of diethyl ether was added to the filtrate, and the resulting cloudy mixture was cooled to ~ −18 °C for 12 h. A white solid that had deposited was then collected and carefully dried under vacuum. Recrystallization of this powder by diethyl ether diffusion into a CH_3CN solution at ambient temperature yielded colorless needle-shaped crystals suitable for X-ray diffraction (0.12 g, 67%). ^1H NMR (CD_3CN, 270 MHz): δ 8.36 (s, 1H, O_2CH), 7.67 (br m, includes N-*H* proton, 2H), 6.69 (d, J = 8.6 Hz, 1H), 6.61 (d, J = 7.3 Hz, 1H), 3.92 (s, 2H), 3.09−2.74 (m, 10H), 2.15 (s, 6H), 1.02 (s, 9H). ^1H NMR (CD_3OD, 270 MHz): δ 8.40 (s, 1H, O_2CH), 7.68 (m, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 6.9 Hz, 1H), 4.01 (s, 2H), 3.18−2.71 (m, 10H), 2.14 (s, 6H), 1.05 (s, 9H). $^{13}C\{^1H\}$ NMR (CD_3CN, 67.9 MHz): δ 169.4, 160.6, 152.3, 142.7, 112.6, 108.2, 58.5, 55.3, 51.4, 32.9, 31.8, 27.7, 15.8 (13 signals expected and observed). FTIR (KBr, cm^{-1}): 3341 (br, ν_{N-H}), 1388 (ν_{OOCH}, sym stretch), 1092 (ν_{ClO4}, asym stretch), 623 (ν_{ClO4}, asym bend). FTIR (CH_3CN, ~100 mM, cm^{-1}): 1102 (ν_{ClO4}, asym stretch), 625 (ν_{ClO4}, asym bend). Anal. Calcd for $C_{18}H_{32}N_3O_6ClS_2Zn$: C, 39.34; H, 5.87; N, 7.65. Found: C, 39.46; H, 6.02; N, 7.75.

Reaction of 1 with Formanilide in CD_3CN. Formanilide (1.6 mg, 0.013 mmol) and **1** (10 mg, 0.0096 mmol) were dissolved in CD_3CN (0.5 mL). Heating of the solution for 48 h at 45 °C produced new resonances in the ^1H NMR spectrum at ~6.7−6.8 (m), 5.7 (br), and 0.94 (s) ppm. A white precipitate was also evident in the ^1H NMR tube. Thin-layer chromatography analysis of this CD_3CN solution, using ethyl acetate as the eluent, revealed one movable product with $R_f \approx 0.9$. These combined ^1H NMR and chromatographic results indicate the presence of free bmnpa ligand. Thus, the heating of a CD_3CN solution of **1** results in the decomposition of **1** to form free bmnpa and an inorganic solid, presumably a zinc hydroxide or oxide species.

Stoichiometric Transesterification of Ethyl Formate Mediated by 1 in CD_3OD. In a typical reaction, a CD_3OD solution (~0.6 mL) of **1** (5.2 mg, 5.0 × 10^{-3} mmol) was added to a slight stoichiometric excess of ethyl formate (~1 μL). Within the time necessary to obtain a ^1H NMR spectrum at ambient temperature (~10 min), the ethyl formate had been completely converted to d_3-methyl formate and ethanol.

Formyl Ester Control Reaction. Methyl formate and cyclohexane (internal standard) were distilled prior to this reaction. Methyl formate (17 μL, 0.27 mmol), dry CD_3OD (0.6 mL), and cyclohexane (internal standard, 7.5 μL) were added to a NMR tube at ambient temperature. A ^1H NMR spectrum obtained within ~25 min showed the presence of a trace amount free methanol. A second ^1H NMR spectrum, obtained after the tube was left at ambient temperature for ~4.5 h, showed that the same trace amount of protio methanol was present. Thus, transesterification of methyl formate does not occur under these conditions. A catalytic amount of **1** (1.2 mg, 1.2 × 10^{-3} mmol) was added to this tube. A ^1H NMR spectrum obtained after ~8 min indicated that ~85% of the methyl formate present had undergone transesterification to yield $HC(O)OCD_3$ and CH_3OD. After ~20 min at ambient temperature, a ^1H NMR spectrum indicated that ≳98% of the methyl formate had undergone transesterification.

Reaction of Excess Ethyl Formate with 1 in CD_3OD. Catalytic Transesterification. Complex **1** (20.7 μL of 0.0017 M CD_3OD

(32) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Boston, 1996.
(33) Allred, R. A.; McAlexander, L. H.; Arif, A. M.; Berreau, L. M. *Inorg. Chem.* **2002**, *41*, 6790−6801.
(34) Wolsey, W. C. *J. Chem. Educ.* **1973**, *50*, A335−A337.

solution) in dry CD_3OD (0.61 mL) was added to an NMR tube. Ethyl formate (10.0 μL, 0.12 mmol, 3430 equiv) was also added to this tube. A ^{1}H NMR spectrum was measured after 1 h at 22 °C at which point a 29% yield of d_3-methyl formate and ethanol (~1000 turnovers) was found. ^{1}H NMR (CD_3OD, 270 MHz): δ 8.08 (s, 0.07H, *H*C(O)OCD$_3$), 8.06 (s, 0.2H, *H*C(O)OEt), 4.20 (q, J = 7.0 Hz, 1.4H, HC(O)O*Et*), 3.60 (q, J = 7.3 Hz, 0.6H, *Et*OH), 1.27 (t, J = 7.3 Hz, 2.1H, HC(O)O*Et*), 1.17 (t, J = 7.4 Hz, 0.9H, *Et*OH).

Reaction of 1 with Formanilide in CD_3OD. Formanilide (0.0012 g, 0.010 mmol) and cyclohexane (internal standard, 1.0 μL) were added to a CD_3OD solution (0.60 mL) of [(bmnpaZn)$_2$-(μ-OH)$_2$](ClO$_4$)$_2$ (**1**) (0.0052 g, 0.050 mmol). An initial ^{1}H NMR spectrum was obtained after 10 min at room temperature (Figure 7a). The resulting solution was then heated at 45(1) °C for 1 h. At this point, another ^{1}H NMR spectrum was obtained (Figure 7b). The formation of d_3-methyl formate was identified by comparison of the chemical shift of the formyl proton (8.07 ppm) with that of an authentic sample of HC(O)OCH$_3$ in CD_3OD solution (8.08 ppm). The formation of aniline was identified by comparison of the chemical shift of aromatic resonances (7.12−7.03, 6.74−6.62 ppm; some overlap present with ligand-related pyridyl doublets at 6.72 and 6.62 ppm) with those of an authentic sample of $H_2NC_6H_5$ in CD_3OD solution (7.12−7.03, 6.74−6.62 ppm). The presence of **2** was confirmed by comparison of the formyl proton resonance (8.40 ppm) to that of an authentic sample of the complex dissolved in CD_3OD. In addition, complex **2** was crystallized from the reaction mixture. After 12 h, another ^{1}H NMR spectrum was obtained (Figure 7c) which indicated that the amounts of methyl formate, **2**, and aniline had increased, while the amount of formanilide had decreased.

Formanilide Control Reaction. A CD_3OD solution (~0.6 mL) of formanilide (0.0012 g, 0.010 mmol) was prepared. This solution was probed by ^{1}H NMR spectroscopy immediately after it was mixed (~10 min). The only resonances present were those from formanilide (8.70 (s), 8.25 (s), 7.55−7.05 (m, 5H)). This solution was heated at 45(1) °C for 27 h. After 3 h, by ^{1}H NMR, no change had taken place. After 27 h, a ^{1}H NMR spectrum indicated no change. In addition, the integrated amount of formanilide relative to the C*H*D$_2$OD multiplet at 3.30 ppm remained unchanged throughout the entire experiment.

Addition of Excess Ethyl Formate to the Final Formanilide Reaction Mixture. Identification of Formyl Ester Transesterification Reactivity. A ^{1}H NMR tube containing **1**, formanilide, cyclohexane (internal standard), and CD_3OD was prepared exactly as described above for examining the formanilide cleavage reactivity of **1** in CD_3OD solution. After the NMR tube was stored at 45(1) °C for ~1 week, the ^{1}H NMR features in the formyl proton region were identical to those shown in Figure 7d), with integration being consistent with the presence of methyl formate/**2**/aniline in a ~0.50:0.50:1 ratio. Excess ethyl formate (~5 equiv) was added to this tube at ambient temperature. Within the time necessary to obtain a ^{1}H NMR spectrum at ambient temperature (<10 min), the ethyl formate had been completely converted to d_3-methyl formate and ethanol.

Addition of Excess Ethyl Formate to 2 in CD_3OD. To determine if zinc formate complex **2** is capable of catalyzing the transesterification of ethyl formate in CD_3OD solution, we treated **2** (~6 mg, 0.01 mmol) with excess ethyl formate (5 μL, 0.06 mmol) in 0.6 mL CD_3OD. After ~10 min at ambient temperature, resonances consistent with the presence of ethyl formate, d_3-methyl formate, and ethanol were clearly identifiable. This mixture was monitored by ^{1}H NMR, and after ~20 min, >90% of the ethyl formate had been converted to ethanol and methyl formate.

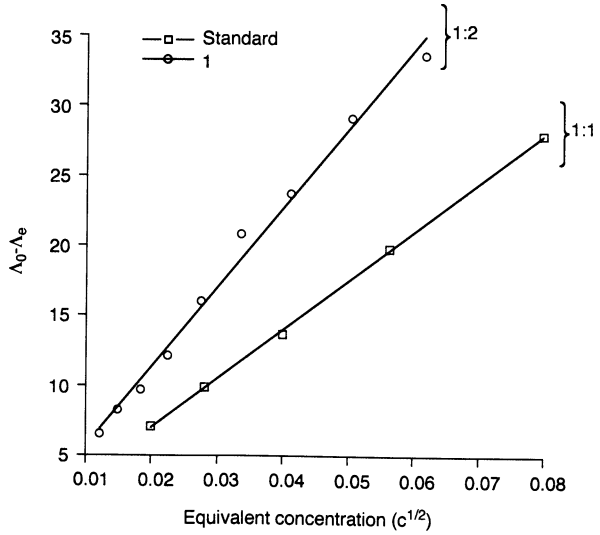


Figure 2. Onsager plot of conductance data for **1** and the 1:1 standard Me_4NClO_4 in CH_3CN solution.

X-ray Crystallography. A crystal of $\mathbf{2}_n$ was mounted on a glass fiber with traces of viscous oil and then transferred to a Nonius KappaCCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) for data collection at 200(1) K. An initial set of cell constants was obtained from 10 frames of data that were collected with an oscillation range of 1 deg/frame and an exposure time of 20 s/frame. Final cell constants were determined from a set of strong reflections from the actual data collection. These reflections were indexed, integrated, and corrected for Lorentz, polarization and absorption effects using DENZO−SMN and SCALEPAC.[12] The structure was solved by a combination of direct and heavy-atom methods using SIR 97. All of the non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were assigned isotropic displacement coefficients U(H) = 1.2U(C) or 1.5U(C$_{methyl}$), and their coordinates were allowed to ride on their respective carbons using SHELXL97.

Structure Solution and Refinement. Complex **2** crystallizes in the space group $P\bar{1}$. Four carbon atoms (C(1), C(2), C(20), and C(21)) and two thioether sulfur atoms (S(1) and S(3)) were found to exhibit disorder. The atoms of one thioether arm (S(1)/C(1)/C(2)) were split into two fragments, with the second being denoted by a prime, and were refined. This refinement led to a 0.88/0.12 occupancy ratio. The atoms of the other thioether arm (S(3)/C(20)/C(21)) were split into two fragments, with the second being denoted by a prime, and were refined. This refinement led to a 0.92:0.08 occupancy ratio.

Results

Properties of 1 in Acetonitrile Solution. Conductance. Variable concentration conductance measurements performed on acetonitrile solutions of **1** indicate 1:2 electrolyte behavior, consistent with the presence of a binuclear [(bmnpaZn)$_2$(μ-OH)$_2$]$^{2+}$ cation in CH_3CN (Figure 2). This conclusion is derived from the observed greater slope of the Onsager plot for **1** (Figure 2) versus that found for the 1:1 electrolyte standard Me_4NClO_4 and from the similar slope value of **1** compared to that found for [(bmnpaCd)$_2$(μ-OH)$_2$](ClO$_4$)$_2$ and [(bmnpa)Cd(ClO$_4$)]ClO$_4$, both of which exhibit 1:2 electrolyte behavior in CH_3CN solution.[33,35]

Table 1. ^{1}H NMR Data for bmnpa, **1**, and [(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4 in CD_3CN and CD_3OD

compound	solvent	^{1}H NMR chemical shift (ppm) $-SCH_3$	$-C(CH_3)_3$	$-CH_2-$[a]	$-CH_2-$[b]
bmnpa	CD_3CN	2.04	0.93	3.12	3.60
	CD_3OD	2.06	0.97	3.11	3.60
1[c]	CD_3CN	2.14	0.85	2.70	3.94
	CD_3OD	2.21	1.06	3.05	3.95
[(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4[c]	CD_3CN	2.03	0.93	3.00	3.89
	CD_3OD	2.15	1.02	3.06	3.96

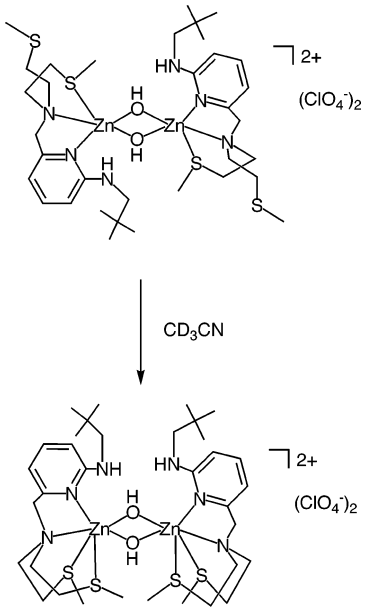
[a] Neopentyl $-CH_2-$ group. [b] Benzylic $-CH_2-$. [c] Thioether sulfur coordination in **1** and [(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4 in CD_3CN and CD_3OD is proposed on the basis of the identification of a complex multiplet pattern for the methylene protons of the thioether appendages. This pattern is consistent with these methylene protons being diastereotopic as a consequence of chelate ring formation.

NMR. Selected resonances in the ^{1}H NMR spectrum of $[(bmnpaZn)_2(\mu\text{-}OH)_2](ClO_4)_2$ (**1**) in CD_3CN are shifted significantly upfield relative to the position of the same resonances for the free ligand under identical conditions (Table 1). For example, an upfield shift (~0.4 ppm) is found for the neopentyl methylene resonance of **1** in CD_3CN. Similar upfield shifts have been noted in the ^{1}H NMR spectrum of a binuclear cadmium hydroxide complex, $[(bmnpaCd)_2(\mu\text{-}OH)_2](ClO_4)_2$.[33] In the solid-state structure of $[(bmnpaCd)_2(\mu\text{-}OH)_2](ClO_4)_2$, weak CH/$\pi$ interactions are found between the neopentyl alkyl protons on one chelate ligand and the pyridyl ring of the bmnpa ligand on the other cadmium center within the binuclear cation.[36] Retention of the binuclear cationic structure in CH_3CN solutions of $[(bmnpaCd)_2(\mu\text{-}OH)_2](ClO_4)_2$ has been confirmed by conductance measurements.[33] As a binuclear cation is also present for **1** in CH_3CN solution (vida supra), we propose that the upfield shifts of the neopentyl methylene and methyl resonances also result from CH/π interactions.[36] The formation of these interactions requires a structural rearrangement in the cationic portion of **1**, as compared to that found in the solid-state structure of the complex. As shown in Scheme 1, we propose that this rearrangement involves the formation of six-coordinate zinc centers and ligation of all of the available donors of the bmnpa chelate ligand. This proposed structure is similar to the cationic portion of the X-ray structure of $[(bmnpaCd)_2(\mu\text{-}OH)_2](ClO_4)_2$.[33] CH/$\pi$ interactions in this cadmium complex are present as indicated by short contacts involving the neopentyl group of one ligand and the pyridyl ring on the other cadmium center.[36]

Properties of 1 in Methanol Solution. The conductance properties of **1** in methanol solution were not evaluated because of the low solubility of the complex in the alcohol.

NMR. The ^{1}H NMR properties of **1** in CD_3OD are strikingly different from those of the same complex in CD_3CN. As shown in Table 1, the chemical shifts of the neopentyl methylene and methyl ^{1}H resonances of **1** in CD_3OD are within 0.1 ppm of the shifts observed for the free ligand resonances under identical conditions. On the basis of these data, it is reasonable to conclude that if CH/π interactions are present for **1** in acetonitrile, as proposed above, these interactions are not present in methanol solution.

Scheme 1



Electrospray Mass Spectrometry. Electrospray mass spectral analysis of a methanol solution of **1** revealed an intense cluster at *m*/*z* 436.2 (Figure 3). This cluster exhibits a relative intensity of 100%, whereas all other clusters had a relative intensities of <5% in the positive-ion mode. The isotope pattern of this cluster matches with that predicted for cationic $[(bmnpa)Zn-OCH_3]^+$ (Figure 3), confirming that a zinc methoxide species is present in CD_3OD solutions of **1**, even though the nuclearity of this species cannot be conclusively stated from the mass spectral experiment. However, we have previously demonstrated that use of the bmnpa ligand does enable the isolation of mononuclear N_2S_2-ligated zinc aryloxide complexes (e.g., [(bmnpa)Zn-*p*-OC_6H_4-

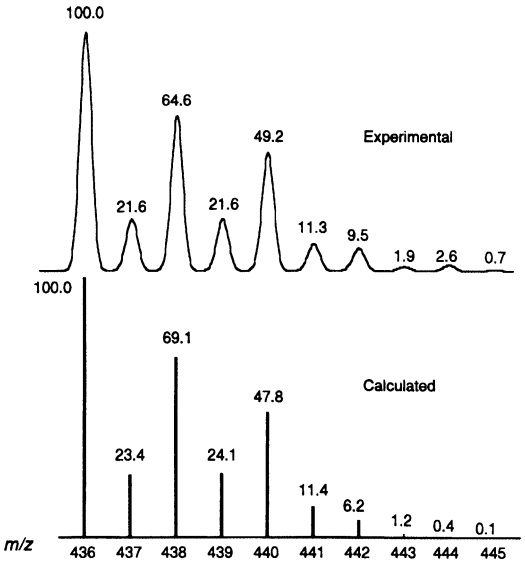


Figure 3. (top) Cluster found at *m*/*z* 436.2 in the electrospray mass spectrum of **1** in methanol solution. (bottom) Theoretical isotope pattern for cationic $[(bmnpa)Zn-OCH_3]^+$ ($C_{18}H_{34}N_3S_2OZn$). The relative intensity is listed above each peak in the experimental and theoretical patterns.

(35) Geary, W. J. *Coord. Chem. Rev.* **1971**, *7*, 81−122.
(36) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665−8701.

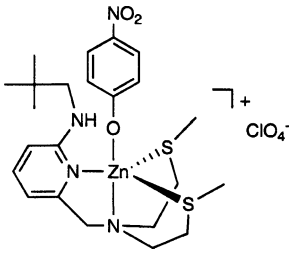


Figure 4. Structure of [(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4.[3]

NO_2]ClO_4, Figure 4).[14] As shown in Table 1, the ^{1}H NMR features of **1** in CD_3OD are generally similar to those found for the aryloxide derivative [(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4 in CD_3OD. On the basis of this spectral similarity, we favor a mononuclear formulation for the methoxide species formed from **1** in CD_3OD solution and use the designation [(bmnpa)-Zn−OCD_3]ClO_4 for this complex throughout the rest of this document.

Despite the presence of a spectroscopically distinct methoxide species in CD_3OD solutions of **1**, attempts to crystallize a methoxide complex from methanol-containing solvent mixtures has thus far yielded only crystals of the binuclear zinc hydroxide starting material. This suggests that a Zn−OH/Zn−OCH_3 equilibrium is present in methanol solutions of [(bmnpaZn)$_2$(μ-OH)$_2$](ClO_4)$_2$ (eq 1). Formation of a Zn−OH/Zn−OCH_3 equilibrium in methanol has been reported for zinc hydroxide complexes of hydrotris(pyrazolyl)borate ($Tp^{R,R'}$) ligands.[14−16] These equilibria lie far toward the hydroxide component, even though the methoxide complex, $Tp^{Ph,Me}$Zn−OCH_3, has been crystallized from a methanol-containing solution of $Tp^{Ph,Me}$Zn−OH.[37,38] Additionally, Walton and co-workers have recently reported that recrystallization of a zinc hydroxide complex of the hydrophobic *cis*,*cis*-1,3,5-tris[(*E*,*E*)-3-(2-furyl)acrylideneamino]cyclohexane ligand (L) from methanol/methylene chloride produces a solid state mixture of [(L)Zn−OH]BPh_4 and [(L)Zn−OCH_3]BPh_4.[39] As noted above, our laboratory has demonstrated that use of a N_3S-donor ligand containing two internal hydrogen-bond donors enables the characterization of a novel Zn−OH/Zn−OCH_3 equilibrium in which the equilibrium postion approaches unity (K_{eq} = 0.30(8) at 304(1) K).[4] Overall, these combined results indicate that zinc hydroxide complexes can undergo reaction with methanol to produce zinc methoxide species in an acid/base equilibrium fashion, with the position of the equilibrium depending on the nature of the supporting chelate ligand. In the case of the zinc hydroxide complex **1**, while a zinc methoxide species is generated in methanol solutions of **1**, the poor solubility of the hydroxide component in the equilibrium mixture (eq 1) is likely the reason that it is the only crystalline species isolated from methanol-containing solutions. Finally, we note that attempts to quantitatively examine the proposed equilibrium shown in eq 1 in CD_3CN solution, as has been done for the aforementioned N_3S-ligated Zn−OH complex,[4] did not yield interpretable data because of peak broadening and overlap.

$$[(\text{bmnpaZn})_2(\mu\text{-OH})_2](ClO_4)_2 + 2CD_3OD = \underset{(\mathbf{1})}{} 2[(\text{bmnpa})\text{Zn}-OCD_3]ClO_4 + 2H_2O \quad (1)$$

Scheme 2

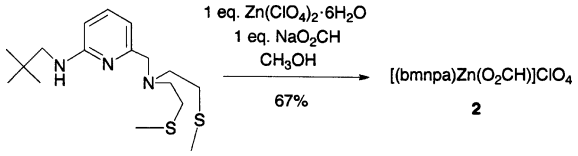


Table 2. Summary of X-ray Data Collection and Refinement for $\mathbf{2}_n$[a]

empirical formula	$C_{36}H_{64}Cl_2N_6O_{12}S_4Zn_2$
fw	1102.81
cryst syst	triclinic
space group	$P\bar{1}$
a (Å)	8.3253(2)
b (Å)	14.0611(5)
c (Å)	20.5801(7)
α (deg)	86.6090(10)
β (deg)	88.420(2)
γ (deg)	88.105(2)
V (Å^3)	2402.84(13)
Z	2
density (calcd, Mg m^{-3})	1.524
temp (K)	200(1)
cryst size (mm)	0.28 × 0.20 × 0.15
diffractometer	Nonius KappaCCD
abs coeff (mm^{-1})	1.346
2θ max (deg)	66.38
completeness to 2θ (%)	78.3
reflns collected	17 052
indep. reflns	14 397
variable params	590
R1/wR2[b]	0.0613/0.1515
GOF (F^2)	1.013
largest diff (e Å^{-3})	2.023/−0.984

[a] Mo Kα (λ = 0.71073 Å) radiation used. [b] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$; $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/[\sum(F_o^2)^2]]^{1/2}$, where $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$.

Formyl Ester Cleavage Reactivity of 1 in Acetonitrile. Characterization of a Zinc Formate Complex. Treatment of **1** with methyl formate (eq 2) in acetonitrile results in the stoichiometric hydrolysis of the formyl ester to produce a zinc formate complex, [(bmnpa)Zn(O_2CH)]ClO_4 (**2**), and methanol. Complex **2** was identified via independent synthesis (Scheme 2) and characterization. X-ray quality crystals of $\mathbf{2}_n$ were obtained via recrystallization of the independently prepared complex from CH_3CN/Et_2O. Details of the X-ray

$$[(\text{bmnpaZn})_2(\mu\text{-OH})_2](ClO_4)_2 + 2HC(O)OCH_3 \rightarrow \underset{(\mathbf{1})}{} 2[(\text{bmnpa})\text{Zn}(O_2CH)]ClO_4 + 2CH_3OH \quad (2)$$
$$\underset{(\mathbf{2})}{}$$

data collection and refinement for $\mathbf{2}_n$ are given in Table 2, and selected bond distances and angles for $\mathbf{2}_n$ are listed in Table 3. The structure of $\mathbf{2}_n$ has a stoichiometry of one formate anion per zinc center, and it exists in the solid-state as a formate-bridged coordination polymer (Figure 5). In this structure, each zinc center has a pseudo-octahedral geometry with monodentate formate coordination. The Zn(1)−O(3) and

(37) Ruf, M.; Burth, R.; Weis, K.; Vahrenkamp, H. *Chem. Ber.* **1996**, *129*, 1251−1257.
(38) Boerzel, H.; Koeckert, M.; Bu, W.; Spingler, B.; Lippard, S. J. *Inorg. Chem.* **2003**, *42*, 1604−1615.
(39) Cronin, L.; Walton, P. H. *Chem. Commun.* **2003**, 1572−1573.

Table 3. Selected Bond Distances (Å) and Angles (deg) for $\mathbf{2}_n$[a]

Zn(1)−N(1)	2.189(3)	N(1)−Zn(1)−N(2)	80.45(10)	O(3)−Zn(1)−S(1)	96.61(7)	O(2)−Zn(2)−O(4)	94.75(10)
Zn(1)−N(2)	2.124(3)	N(1)−Zn(1)−O(1)	89.86(10)	O(3)−Zn(1)−S(2)	92.41(8)	O(2)−Zn(2)−S(3)	96.37(7)
Zn(1)−S(1)	2.5695(11)	N(1)−Zn(1)−O(3)	174.84(11)	S(1)−Zn(1)−S(2)	88.82(4)	O(2)−Zn(2)−S(4)	92.22(8)
Zn(1)−S(2)	2.6578(11)	N(1)−Zn(1)−S(1)	80.86(8)	N(4)−Zn(2)−N(5)	80.50(10)	O(4)−Zn(2)−S(3)	93.36(7)
Zn(1)−O(1)	2.165(2)	N(1)−Zn(1)−S(2)	83.08(8)	N(4)−Zn(2)−O(2)	174.50(10)	O(4)−Zn(2)−S(4)	172.56(7)
Zn(1)−O(3)	2.035(2)	N(2)−Zn(1)−O(1)	87.65(10)	N(4)−Zn(2)−O(4)	90.13(10)	S(3)−Zn(2)−S(4)	88.44(4)
Zn(2)−N(4)	2.185(3)	N(2)−Zn(1)−O(3)	101.92(10)	N(4)−Zn(2)−S(3)	80.80(8)		
Zn(2)−N(5)	2.127(3)	N(2)−Zn(1)−S(1)	161.26(7)	N(4)−Zn(2)−S(4)	83.03(8)		
Zn(2)−S(3)	2.5792(10)	N(2)−Zn(1)−S(2)	87.66(8)	N(5)−Zn(2)−O(2)	102.17(10)		
Zn(2)−S(4)	2.6435(10)	O(1)−Zn(1)−O(3)	94.80(10)	N(5)−Zn(2)−O(4)	87.93(10)		
Zn(2)−O(2)	2.040(2)	O(1)−Zn(1)−S(1)	93.59(7)	N(5)−Zn(2)−S(3)	161.26(8)		
Zn(2)−O(4)	2.152(2)	O(1)−Zn(1)−S(2)	172.08(8)	N(5)−Zn(2)−S(4)	88.06(8)		

[a] Estimated standard deviations in the last significant figure are given in parentheses.

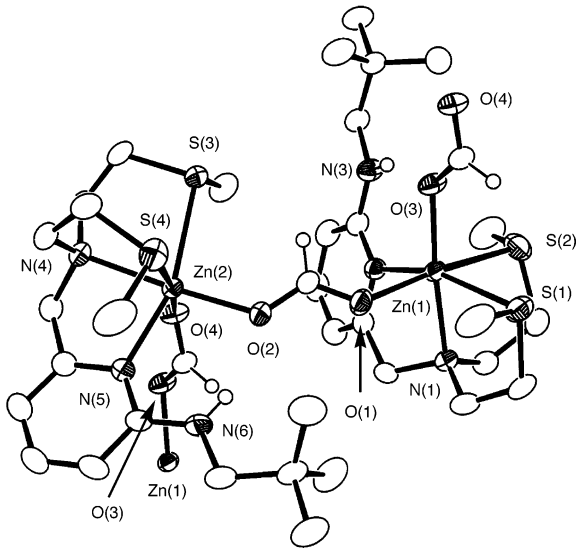


Figure 5. ORTEP drawing of the unique repeat portion of the coordination polymer found in the X-ray crystal structure of $\mathbf{2}_n$. All ellipsoids are drawn at the 50% probability level. Hydrogen atoms other than the secondary amine and formate hydrogen atoms are omitted for clarity.

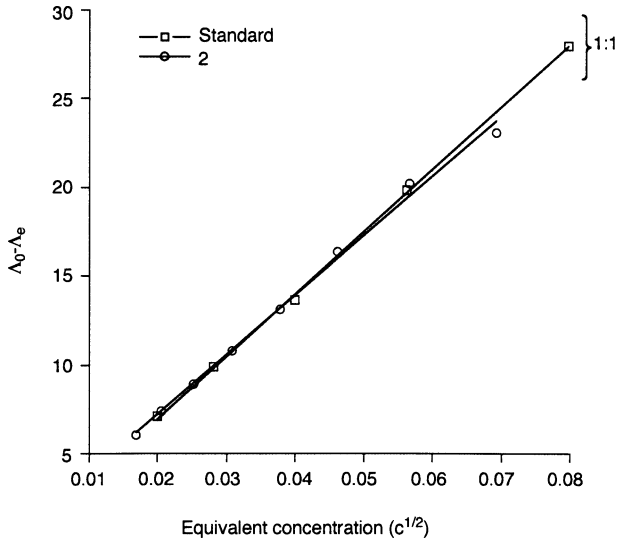


Figure 6. Onsager plot of conductance data for **2** and the 1:1 standard Me_4NClO_4 in CH_3CN solution.

Zn(2)−O(2) distances are identical within experimental error (2.04 Å). The Zn(1)−O(1) and Zn(2)−O(4) distances are longer (2.165(2) and 2.152(2) Å, respectively). The average Zn−S distance in $\mathbf{2}_n$ (2.61 Å) is longer than that found in mononuclear complexes of the bmnpa ligand, such as [(bmnpa)Zn-*p*-$OC_6H_4NO_2$]ClO_4 (av 2.46 Å; Figure 4).[3]

Nitrogen/sulfur-ligated zinc formate derivatives are of interest in regard to product-bound structures of the Zn(II)-containing form of peptide deformylase.[19,22] As noted previously, an X-ray structure of Zn(II)-containing *E. coli* PDF with a bound formate has been recently reported.[31] In this structure, the formate binds in a mondentate fashion with a Zn−O distance of 2.09(17) Å. The second oxygen atom of the formate is located 2.88 Å from the metal center. Monodentate formate coordination has also been reported for the Zn(II)-PDF from *Leptospira interrogans* (Zn−O = 2.31 Å; Zn···O = 2.58−2.85 Å).[40] Finally, while $\mathbf{2}_n$ is not structurally relevant to the formate adduct in Zn(II)-PDF, a synthetic N_2S(thiolate)-ligated mononuclear zinc formate complex of structural relevance to PDF has been reported wherein the formate anion is coordinated in an anisobidentate motif,[41,42] with the shortest Zn−O distance (Zn(1)−O(1) = 2.0050(19) Å) being ∼0.05 Å longer than that found in $\mathbf{2}_n$.

Each formate anion in the unique portion of $\mathbf{2}_n$ participates in one moderate hydrogen-bonding interaction involving the secondary amine donor of the bmnpa ligand.[13] This interaction involves the zinc-coordinated oxygen atom and is similar for both formate anions (N(3)···O(3) = 2.977(4) Å, N(3)−H(3)···O(3) = 160°; N(6)···O(2) = 2.982(4) Å, N(6)−H(6)···O(2) = 161°). In the X-ray structure of *E. coli* Zn(II)-PDF containing a bound formate anion, hydrogen bonding occurs between the bound formate and the backbone NH of Leu91, as well as with the side chains of Gln50 and Glu133.[31]

In CH_3CN solution, the polymeric chain structure of $\mathbf{2}_n$ is broken into monomeric species (**2**, 1:1 electrolyte) as indicated by conductance measurements (Figure 6). This breakdown into monomers likely involves cleavage of the weaker Zn−O(formate) interactions (Zn(1)−O(1) and Zn(2)−O(4)).

The ^{1}H NMR spectrum of **2** in CD_3CN contains a formyl proton resonance at 8.36 ppm and a secondary amine proton resonance at 7.67 ppm. The latter resonance is shifted significantly downfield from its position in the free bmnpa

(40) Zhou, Z.; Song, X.; Li, Y.; Gong, W. *J. Mol. Biol.* **2004**, *339*, 207−215.

(41) Chang, S.; Sommer, R. D.; Rheingold, A. L.; Goldberg, D. P. *Chem. Commun.* **2001**, 2396−2397.

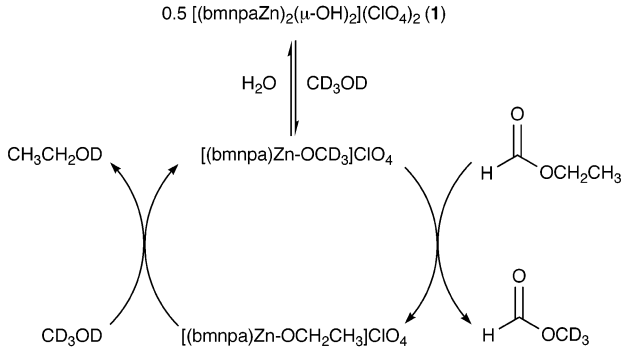
(42) Kleywegt, G. J.; Wiesmeijer, W. G. R.; Van Driel, G. J.; Driessen, W. L.; Reedijk, J.; Noordik, J. H. *J. Chem. Soc., Dalton Trans.* **1985**, 2177−2184.

ligand (5.01 ppm) under identical conditions.[2] This is consistent with retention of the intramolecular hydrogen-bonding interaction involving the secondary amine group and the formate anion in the mononuclear species produced in acetonitrile solution. The carbonyl carbon of the bound formate exhibits a ^{13}C resonance at 169.4 ppm. The formyl proton and carbonyl carbon resonances of **2** are upfield of those reported for [(Tp^{tBu})Zn(O_2CH)] (8.91 ppm, 166.7 ppm (in C_6D_6); Tp^{tBu} = tris(3-*tert*-butylpyrazolyl)hydroborato).[43] While the solid-state structure of [(Tp^{tBu})Zn(O_2CH)] has not been determined by X-ray crystallography, the coordination mode of the formate has been suggested to be monodentate on the basis of the stretching frequencies of the $\nu_{asym}(CO_2)$ (1655 cm^{-1}) and $\nu_{sym}(CO_2)$ (1290 cm^{-1}) vibrations.[44] The $\nu_{sym}(CO_2)$ vibrations have not been definitively assigned for **2** because of overlap with chelate ligand vibrations.

Formanilide Cleavage Reactivity of 1 in Acetonitrile. As a nitrogen/sulfur-ligated zinc hydroxide moiety is suggested to act as the nucleophile for formamide hydrolysis in Zn(II)-containing peptide deformylase,[45] we have examined the formanilide cleavage reactivity of **1** in CD_3CN solution. Heating of a CD_3CN solution of **1** with 2 equiv of formanilide at 45(1) °C for 48 h does not yield formanilide hydrolysis but instead results in the slow decomposition of **1** to free bmnpa ligand and an insoluble inorganic solid, presumably a zinc hydroxide or oxide species. The lack of formanilide cleavage reactivity for the binuclear zinc hydroxide complex **1** in CD_3CN is not surprising, as literature examples of zinc hydroxide complex-mediated amide hydrolysis reactions are currently limited to activated amides.[1,46]

Formyl Ester Reactivity of 1 in Methanol. Treatment of **1** with a slight stoichiometric excess of methyl formate ($HC(O)OCH_3$) per zinc center in CD_3OD at ambient temperature results in the rapid (<10 min) formation of 1 equiv each of methanol and d_3-methyl formate. A control reaction, using protio methyl formate in CD_3OD, indicated that this transesterification reaction is not observed on the same time scale in the absence of the metal complex. In the presence of excess ethyl formate (ethyl formate/**1** ratio ≈ 3430:1), ~1000 equiv of free ethanol and d_3-methyl formate are generated after ~60 min at 22(1) °C (29% conversion). While catalytic transesterification conditions were not optimized during the course of this work, it is clear that the zinc methoxide species formed from **1** in CD_3OD solution is a very active transesterification catalyst for formyl esters.[47] We propose that the catalytic transesterification reactivity of **1** involving ethyl formate in CD_3OD may occur as outlined in Scheme 3. The initial transesterification reaction would yield a bmnpa-ligated zinc ethoxide species that, in CD_3OD solution, would quickly undergo an acid/base reaction with the solvent (pK_a(methanol) = 15.2; pK_a(ethanol) = 16)[48] to

Scheme 3



regenerate the reactive zinc methoxide species and ethanol. We note that if a solution of **1** in CD_3OD containing ethyl formate is stored at ambient temperature for 1.5 h, the formyl proton resonance of **2** becomes identifiable, indicating that formyl ester hydrolysis can also occur in methanol solution. This result supports the notion that a zinc hydroxide/methoxide equilibrium in present in methanol solutions of **1**.

Formanilide Cleavage Reactivity of 1 in Methanol. NMR tube solutions of **1** (0.5 equiv), formanilide (1 equiv), and the internal standard cyclohexane (1 equiv) were prepared to further examine the formyl substrate cleavage reactivity of **1** in CD_3OD solution,. As expected, the initial ^1H NMR spectra (e.g., Figure 7a) of a reaction mixture of this type show two formyl proton resonances for formanilide, corresponding to the cis (8.25 ppm, 75%) and trans (8.69 ppm, 25%) isomers (Scheme 4).[49] Heating of the alcoholic reaction mixture for 1 h at 45(1) °C results in the appearance of ^1H NMR resonances (Figure 7b) consistent with the formation of aniline and d_3-methyl formate. After 12 h (Figure 7c), a new resonance at 8.40 ppm indicates the formation of the zinc formate complex, **2**, the identity of which was confirmed via crystallization of the complex from the reaction mixture. After a long period (120 h) of additional heating at 45(1) °C, one full equivalent of aniline is formed, along with an approximate 30−50% yield of d_3-methyl formate and a 50−70% yield of the zinc formate complex **2**. A control reaction at 45(1) °C indicated that no formanilide cleavage took place in the absence of **1** in CD_3OD solution.

The initial formation of d_3-methyl formate in this reaction suggests an amide methanolysis cleavage pathway (Scheme 5). This is consistent with the presence of a reactive zinc methoxide species (e.g., [(bmnpa)Zn−OCD_3]ClO_4) in methanol solutions of **1** and is reminiscent of the formyl ester cleavage reactivity of **1** in CD_3OD. Attack of the zinc-bound methoxide of [(bmnpa)Zn−OCD_3]ClO_4 on the formanilide carbonyl carbon atom could yield a tetrahedral intermediate. Loss of aniline (PhNHD) from this intermediate requires a proton (or deuteron). This protonation likely involves solvent and may occur directly or involve transient stabilization of the deprotonated anilido group (Scheme 5) by the zinc center.

(43) Looney, A.; Han, R.; Gorrell, I. B.; Cornebise, M.; Yoon, K.; Parkin, G. Rheingold, A. L. *Organometallics* **1995**, *14*, 274−288.
(44) Deacon, G. B.; Phillips, R. J. *Coord. Chem. Rev.* **1980**, *33*, 227−250.
(45) Rajagopalan, P. T. R.; Grimme, S.; Pei, D. *Biochemistry* **2000**, *39*, 779−790.
(46) Ruf, M.; Vahrenkamp, H. *Chem. Ber.* **1996**, *129*, 1025−1028.
(47) Otera, J. *Chem. Rev.* **1993**, *93*, 1449−1470.
(48) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985.
(49) Quintanilla-Licea, R.; Colunga-Valladares, J. F.; Caballero-Quintero, A.; Rodriguez-Padilla, C.; Tamez-Guerra, R.; Gomez-Flores, R.; Waksman, N. *Molecules* **2002**, *7*, 662−673.

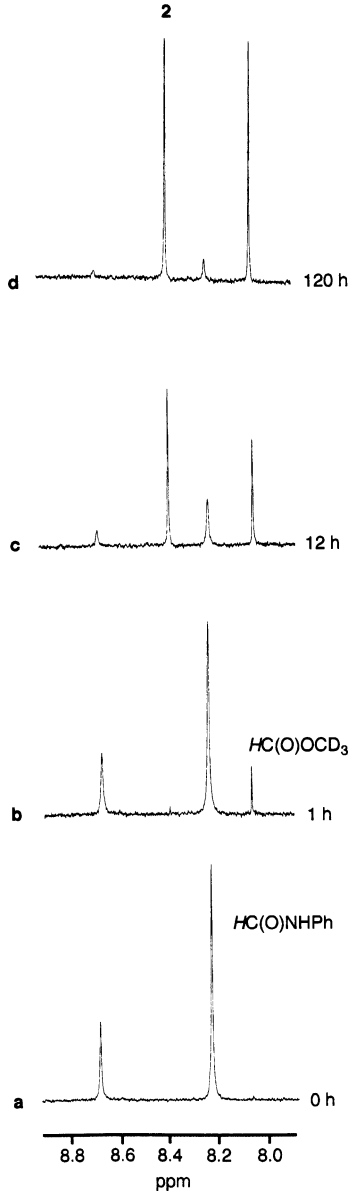
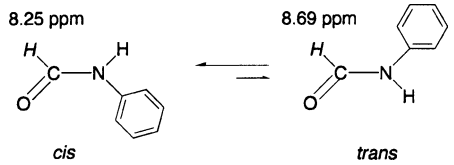


Figure 7. Region of the ^{1}H NMR spectra obtained at varying times for the reaction of **1** with formanilide in CD_3OD at 45(1) °C.

Scheme 4



In either case, the net result would be regeneration of the reactive [(bmnpa)Zn−OCD_3]ClO_4 complex in CD_3OD and catalytic formanilide cleavage reactivity. However, over the course of this slow formanilide cleavage reaction, which requires ∼120 h at 45(1) °C to reach completion, formation of zinc formate complex **2**, is also occurring. This formate derivative in all likelihood forms via the reaction of a zinc hydroxide component of the reaction mixture in CD_3OD (eq 2) with d_3-methyl formate. In other words, this hydrolysis reaction would be similar to that shown in eq 2 (vida supra) except in methanol solution. We favor formyl carboxylate ester hydrolysis, not formanilide hydrolysis, as the means for generating **2**, as this is consistent with the reactivity studies reported herein of the hydroxide derivative **1** and formyl carboxylate ester substrates in acetonitrile solution.

Scheme 5

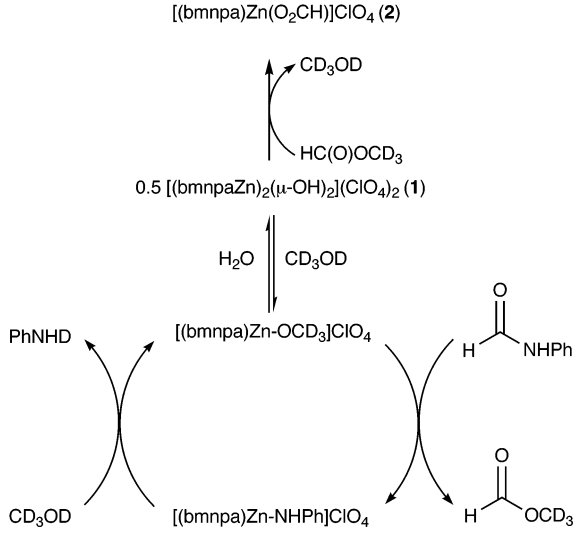


Table 4. Comparison of the ^{1}H NMR Chemical Shifts of **1**, **2**, and the bmnpa-ligated Species Present in a Typical Final Formanilide Cleavage Reaction Mixture in CD_3OD Solution Heated for 120 h at 45(1) °C

		^{1}H NMR chemical shift (ppm)			
compound	solvent	$-SCH_3$	$-C(CH_3)_3$	$-CH_2-^a$	$-CH_2-^b$
1	CD_3OD	2.21	1.06	3.05	3.95
2	CD_3OD	2.14	1.05	3.07	4.01
final formanilide cleavage reaction mixture	CD_3OD	2.19	1.05	3.05	3.95

[a] Neopentyl $-CH_2-$ group. [b] Benzylic $-CH_2-$.

In the series of ^{1}H NMR spectra shown in Figure 7 it can be seen that, after 120 h of heating at 45(1) °C, a mixture of **2** and d_3-methyl formate is present. The less than quantitative yield of **2** indicates that a second zinc complex must be present in solution after 120 h. However, only one set of bmnpa-related ^{1}H NMR resonances is apparent in the reaction mixture. As outlined in Table 4, this can be rationalized because the chemical shifts of the ^{1}H NMR resonances of the zinc methoxide species ([(bmnpa)Zn−OCD_3]ClO_4) and those of **2** in CD_3OD are very similar. Specifically, other than the formyl C−*H* proton resonance of **2**, the only subtle spectroscopic differences of note between [(bmnpa)Zn−OCD_3]ClO_4 and **2** involve the $-SCH_3$ and benzylic $-CH_2-$ resonances (Table 4). For a typical formanilide cleavage product reaction mixture, a single $-SCH_3$ resonance is found at 2.19 ppm, a chemical shift intermediate between that of [(bmnpa)Zn−OCD_3]ClO_4 (2.21 ppm) and **2** (2.14 ppm) in CD_3OD solution. The benzylic $-CH_2-$ resonance in the product reaction mixture is observed at 3.95 ppm, a chemical shift identical to that observed for [(bmnpa)Zn−OCD_3]ClO_4, which is only slightly upfield of the position of the same resonance in analytically pure **2** (4.01 ppm). On the basis of these spectral similarities, we propose that after 120 h, the formanilide cleavage reaction contains the Zn(II) complexes [(bmnpa)Zn−OCD_3]ClO_4 and **2**, with the formate derivative typically being the dominant component (50−70% yield).

To test this hypothesis, excess ethyl formate (5 equiv) was added to a ^{1}H NMR tube containing a final formanilide cleavage reaction mixture in CD_3OD (~50% **2**). Within the time necessary to obtain the ^{1}H NMR spectrum (<10 min) all of the ethyl formate had been converted to d_3-methyl formate and ethanol, indicating the presence of an active catalyst for formyl ester transesterification. This is consistent with the presence of [(bmnpa)Zn−OCD_3]ClO_4 in the final reaction mixture. In a control reaction, we have found that, while **2** also catalyzes the transesterification of ethyl formate in CD_3OD, the reaction is slower, requiring ~20 min for ~6 turnovers at ambient temperature.

Discussion

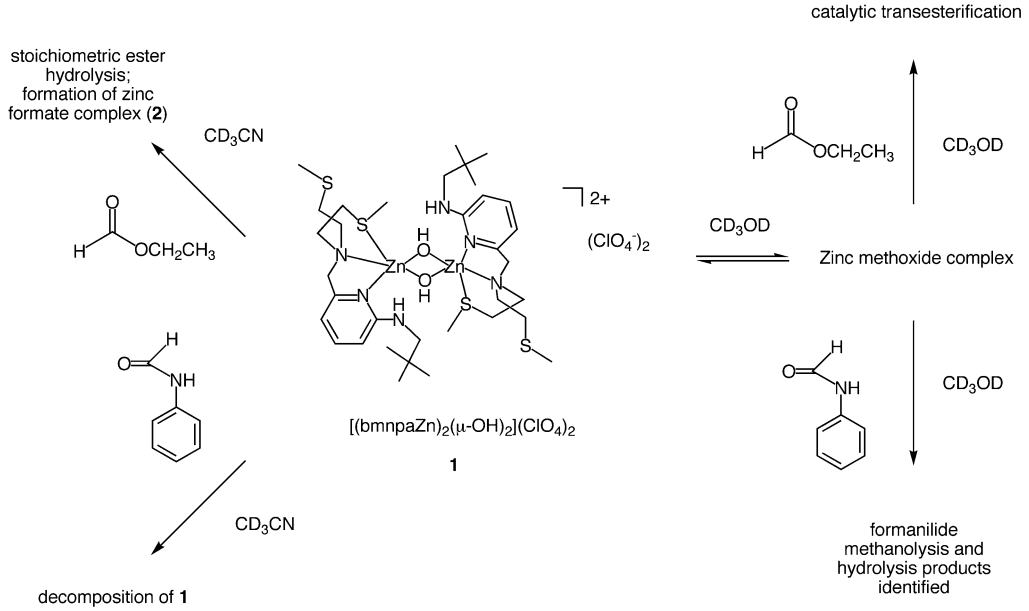
In this contribution, we have qualitatively examined the solution structural and formyl substrate reactivity properties of a binuclear nitrogen/sulfur-ligated zinc hydroxide complex (**1**). This complex is supported by a chelate ligand containing a single internal hydrogen-bond donor. Nitrogen/sulfur-ligated zinc hydroxide species, although they have biological relevance,[1] are still somewhat rare, with X-ray structures of only six such complexes having been reported to date.[2−4,50−53] Notably, an attempt to prepare a nitrogen/sulfur-ligated zinc hydroxide complex using a recently reported new N_2S-(thiolate) chelate ligand resulted in the formation of a binuclear complex with a noncoordinated disulfide moiety formed from the oxidative coupling of two ligand thiolate moieties.[54] Using another N_2S(thiolate) ligand containing an alkanethiolate appendage, Goldberg and co-workers have spectroscopically characterized a mononuclear N_2S-ligated zinc hydroxide complex and have shown that it will hydrolyze the activated ester 4-nitrophenyl acetate (4-NP) and the phosphate triester tris(4-nitrophenyl)phosphate (TNP).[55−57] Interestingly, kinetic studies of the 4-NP hydrolysis reaction support a mechanism in which the zinc hydroxide moiety acts as a nucleophile to attack the ester substrate in the rate-determining step.[56] Kinetic studies of the TNP hydrolysis reaction instead suggest a hybrid mechanism in which the zinc center functions to activate both the substrate and the nucleophile.[57] Overall, these results suggest that the mechanistic pathway of hydrolysis reactions mediated by a N_2S(thiolate)-ligated zinc center like that found in Zn(II)-containing peptide deformylases depends on the nature of the substrate. On this basis, it is obvious that, to fully understand the unique metal ion-dependent behavior of PDF enzymes, studies are needed that focus on cleavage reactions involving formyl substrates and, particularly, formamides.

In this work, we have outlined the first examples of formyl substrate cleavage reactivity mediated by a nitrogen/sulfur-ligated zinc hydroxide complex. While this complex does not have structural relevance to the active site zinc center in peptide deformylases, the experiments described herein provide information in terms of the conditions required for formyl substrate reactivity. For example, we have shown that **1**, a binuclear nitrogen/sulfur-ligated zinc hydroxide complex in acetonitrile solution, undergoes slow reaction with methyl formate to yield a zinc formate complex and methanol. In regard to this reaction, we note that few studies have been reported in which a zinc-hydroxide moiety is involved in the hydrolysis of an unactivated ester.[1] The most extensively explored reaction of this type is the catalytic hydrolysis of methyl acetate ($CH_3C(O)OCH_s$) in the presence of Zn(II)−[12]aneN_3 ([12]aneN_3 = 1,5,9-triazacyclododecane) in water at pH 8 and 25 °C.[58] The catalytic turnover time for this reaction is ca. 60 min.

In methanol solution, **1** undergoes reaction with solvent to produce a zinc methoxide species, [(bmnpa)Zn−OCH_3]-ClO_4, which has been characterized by ^{1}H NMR and electrospray mass spectrometry. On the basis of our previous work involving zinc hydroxide/alkoxide complexes of a supporting chelate ligand having two internal hydrogen bond donors,[4] we expect that the presence of the single internal hydrogen bond donor in the bmnpa chelate ligand will enhance the thermodynamic stability of [(bmnpa)Zn−OCH_3]-ClO_4 with respect to hydrolysis. This methoxide derivative promotes the stoichoimetric and catalytic transesterification of formyl carboxylate esters. The stoichiometric reaction is fast at room temperature, being complete within minutes. The catalytic transesterification reactivity of **1** in CD_3OD solution is interesting, with ~1000 turnovers/h at ambient temperature. The driving force for this catalytic reaction is likely derived from the relative thermodynamic stability of [(bmnpa)Zn−OCD_3]ClO_4 versus [(bmnpa)Zn−OCH_2CH_3]ClO_4 in CD_3OD solution. Literature precedent shows that in an acid/base type reaction, the zinc ethoxide complex formed following the initial turnover should be protonated by d_4-methanol to produce the less acidic ethanol and [(bmnpa)-Zn−OCD_3]ClO_4.[59] In regard to tranesterification reactivity, various zinc complexes have been shown to promote the stoichiometric or catalytic transesterification of carboxylate esters. In some of these cases, the presence of a zinc alkoxide species has been clearly demonstrated, whereas for others, the nature of the active metal complex remains unknown. For example, Vahrenkamp and Brombacher have demonstrated that pyrazolylborate-ligated zinc methoxide complexes will mediate the stiochiometric transesterification of activated esters containing the *p*-nitrophenolate leaving group (e.g., $CF_3C(O)O$-*p*-$C_6H_5NO_2$).[60] These reactions result in the

(50) Ma, C. Q.; Wang, X.-N.; Zhang, W.-X.; Yu, Z.-G.; Jiang, D.-H.; Dong, S.-L. *Acta Chim. Sin.* **1996**, *54*, 562−567.
(51) Baggio, S.; Pardo, M. I.; Baggio, R.; Garland, M. T. *Acta Crystallogr.* **1997**, *C53*, 551−554.
(52) Hammes, B. S.; Carrano, C. J. *Chem. Commun.* **2000**, 1635−1636.
(53) Hammes, B. S.; Carrano, C. J. *Inorg. Chem.* **2001**, *40*, 919−927.
(54) Karambelkar, V. V.; Krishnamurthy, D.; Stern, C. L.; Zakharov, L. N.; Rheingold, A. L.; Goldberg, D. P. *Chem. Commun.* **2002**, *23*, 2772−2773.
(55) Chang, S.; Karambelkar, V. V.; Sommer, R. D.; Rheingold, A. L.; Goldberg, D. P. *Inorg. Chem.* **2002**, *41*, 239−248.
(56) diTargiani, R. C.; Chang, S.; Salter, M. H., Jr.; Hancock, R. D.; Goldberg, D. P. *Inorg. Chem.* **2003**, *42*, 5825−5836.
(57) Goldberg, D. P.; diTargiani, R. C.; Namuswe, F.; Minnihan, E. C.; Chang, S.; Zakharov, L. N.; Rheingold, A. L. *Inorg. Chem.* **2005**, *44*, 7559−7569.
(58) Kimura, E.; Shiota, T.; Koike, T.; Shiro, M.; Kodama, M. *J. Am. Chem. Soc.* **1990**, *112*, 5805−5811.
(59) Brombacher, H.; Vahrenkamp, H. *Inorg. Chem.* **2004**, *43*, 6054−6060.
(60) Brombacher, H.; Vahrenkamp, H. *Inorg. Chem.* **2004**, *43*, 6050−6053.

Scheme 6



formation of TpZn−O-*p*-$C_6H_5NO_2$ (Tp = $Tp^{Ph,Me}$ or $Tp^{Cum,Me}$) complexes. Carrano and co-workers have reported that a binuclear zinc hydroxide complex of the tris(3-carboxyethyl-5-methyl)pyrazolylborate ligand, [{($Tp^{CO2Et,Me}$)Zn}$_2$(μ-OH)]ClO_4, catalyzes a self-transesterification reaction in methanol to produce [{($Tp^{CO2Me,Me}$)Zn}$_2$(μ-OH)]ClO_4.[61] The pseudo-first-order rate constant for this reaction in pure CD_3OD is 4.1(4) × 10^{-2} h^{-1} at 25 °C. Brown and co-workers have studied the Zn(II)−OCH_3-promoted transesterification of various aliphatic and aryl carboxylate esters in methanol in the presence of the 1,5,9-triazacyclododecane chelate ligand.[62] Under these conditions, the methanolysis of phenyl acetate was increased by 1.6 × 10^6-fold relative to the reaction involving only the methoxide anion. Finally, efforts toward the development of zinc catalysts for transesterification reactions of synthetic and technological utility are currently in progress. For example, it was recently reported that a zinc complex of 3-hydroxy-2-methyl-4-pyrone can catalyze the transesterification of soybean oil in a reaction that is relevant to the production of biodiesel.[63] A C_3-symmetric chiral trisoxazoline zinc complex has recently been demonstrated to catalyze the kinetic resolution of racemic chiral esters in methanol via tranesterification.[64]

The formanilide cleavage reaction mediated by **1** in CD_3OD is complex. The products of this reaction indicate both methanolysis- and hydrolysis-type reactivity. The formation of d_3-methyl formate and aniline as the first identifiable products in this reaction suggests that a methanolysis reaction is responsible for the formanilide cleavage. Coupled with the fact that no formanilide cleavage reactivity is found for **1** in CD_3CN solution, where the complex contains a binuclear $Zn_2(OH)_2$ cation, it appears that an alkoxide nucleophile is required for the formanilide cleavage reaction. This notion is supported by a literature precedent which indicates that zinc alkoxide species are better nucleophiles than the corresponding zinc hydroxide species.[64−67] In regard to amide methanolysis, Brown and co-workers have demonstrated that the Zn^{2+} ion will catalyze the methanolysis of activated amides such as acetylimidazole.[68,69] Over the time required for formanilide to completely undergo reaction, the hydrolysis product [(bmnpa)Zn(O_2CH)]ClO_4 (**2**) is observed to form. On the basis of our complementary studies in CD_3CN solution, we propose that **2** is formed upon reaction of a Zn−OH component of the reaction mixture (e.g., [(bmnpaZn)$_2$(μ-OH)$_2$](ClO_4)$_2$) with methyl formate. Overall, this leads to a final reaction mixture in which a portion of the zinc ion is present as **2** (50−70%) and the remaining portion remains in solution as a zinc hydroxide/methoxide equilibrium mixture.

Summary

These studies provide a qualitative description of the solution structural and formyl substrate reactivity properties of **1**. A general summary of this reactivity is shown in Scheme 6. Depending on the solvent, **1** promotes either formyl carboxylate ester hydrolysis or transesterification. We note that reactivity studies with formyl carboxylate ester substrates are warranted as peptide deformylases have also been shown to exhibit esterase behavior with the formyl

(61) Hammes, B. S.; Luo, X.; Carrano, M. W.; Carrano, C. J. *Inorg. Chim. Acta* **2002**, *341*, 33−38.
(62) Neverov, A. A.; Sunderland, N. E.; Brown, R. S. *Org. Biomol. Chem.* **2005**, *3*, 65−72.
(63) Abreu, F. R.; Lima, D. G.; Hamu, E. H.; Einloft, S.; Rubim, J. C.; Suarez, P. A. Z. *J. Am. Oil Chem. Soc*. **2003**, *80*, 601−604.
(64) Dro, C.; Bellemin-Laponnaz, S.; Welter, R.; Gade, L. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 4479−4482.
(65) Xia, J.; Shi, Y.-b.; Zhang, Y.; Miao, Q.; Tang, W.-x. *Inorg. Chem.* **2003**, *42*, 70−77 and references therein.
(66) Kimura, E.; Kikuta, E. *J. Biol. Inorg. Chem*. **2000**, *5*, 139−155.
(67) Bräuer, M.; Anders, E.; Sinnecker, S.; Koch, W.; Rombach, M.; Brombacher, H.; Vahrenkamp, H. *Chem. Commun.* **2000**, 647−648.
(68) Neverov, A. A.; Montoya-Pelaez, P. J.; Brown, R. S. *J. Am. Chem. Soc.* **2001**, *123*, 210−217.
(69) Brown, R. S.; Neverov, A. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1039−1049.

carboxylate ester substrate 2-formyloxycaproylleucyl-*p*-nitroanilide.[70] In methanol solution, **1** promotes formanilide cleavage, likely via an amide methanolysis pathway. To our knowledge, this is the first reported example of formamide cleavage mediated by a zinc complex. While these reactions are not directly relevant to the chemistry of peptide deformylases because of the nature of the zinc complex involved, this work does provide important initial insight into the chemical factors governing formyl substrate reactivity with zinc complexes.

(70) Hu, Y.-J.; Wei, Y.; Zhou, Y.; Rajagopalan, P. T. R.; Pei, D. *Biochemistry* **1999**, *38*, 643−650.

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Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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