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Pyrazolylborate–Zinc Alkoxide Complexes. 2. Solvolytic Chemistry

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The methoxides $Tp^{Ph,Me}$Zn–OMe and $Tp^{Cum,Me}$Zn–OMe were tested for their reactivity toward substrates that are hydrolytically cleaved with Tp*Zn–OH complexes. They do not induce the cleavage of nonactivated esters, phosphoesters, lactones, or lactams. They cleave the P–O–P linkage of tetraalkylpyrophosphates, but not the C–O–C linkage of dialkyl pyrocarbonates. Transesterification of esters and phosphoesters occurs when they are activated as *p*-nitrophenolates. The most facile cleavage occurs for thiolate functions present in dithioesters, thiolactones, and trithiocarbonates. These findings indicate that, while the leaving group properties of the methoxide unit are essential, it is the strength of the resulting zinc–substrate bonds that decides upon the occurrence or nonoccurrence of the cleavage reactions.

Introduction

An extensive amount of work has been performed on the modeling of hydrolytic zinc enzymes by means of functionalized coordination compounds of zinc.[3−6] As a result of this and the underlying biochemical studies, it has become a well-established paradigm that the essential species in the catalytic center is a Zn−OH function resulting from deprotonation of a zinc-bound water molecule at physiological pH. We have contributed to this with our work on pyrazolylborate−zinc hydroxide complexes, Tp*Zn−OH.[7]

Three properties qualify the zinc-bound hydroxide for its high catalytic efficiency: its high nucleophilicity, its superior leaving-group character, and the presence of a highly mobile proton, which together enable the fast group transfer processes during the catalytic cycles. Removing or blocking one of these properties should result in an extremely reduced or completely altered reactivity of the enzymes as well as the model complexes.

We ran into this when trying to reproduce the many reactions of the Tp*Zn−OH complexes with Tp*Zn−SH complexes,[8] which was a formidable failure because the high stability of the zinc−thiolate connection kills the leaving group properties of the hydrosulfide ligand. Yet the Zn−SH and Zn−SR complexes are powerful nucleophiles, and from our efforts to overcome the leaving-group problem resulted the modeling of a new class of zinc enzymes, the thiolate-alkylating ones, by using Tp*Zn−SR complexes.[9]

The replacement of the Zn−OH function by the Zn−OR function also blocks one of the three essential properties, this time the presence of a mobile proton. Yet, as we have already demonstrated, the nucleophilicity of the Tp*Zn−OR complexes surpasses that of the Tp*Zn−OH complexes and the high leaving tendency of the zinc-bound alkoxides is evident from the facile insertions of heterocumulenes into the Zn−OR bonds.[1] It was therefore attractive to find out how the Tp*Zn−alkoxides would behave toward substrates that undergo hydrolytic cleavage with Tp*Zn-hydroxides, being able to cleave the hydrolyzeable bond but not to release the cleavage products in their protonated forms.

This paper describes our studies toward this end. It is the second in our series on the reactivity of pyrazolylborate−zinc alkoxides.[1,2] Our entry into the field and the related literature are given in the first paper,[1] which also describes the synthesis of the two Tp*Zn−OR complexes **1a** and **1b** used for the present study.

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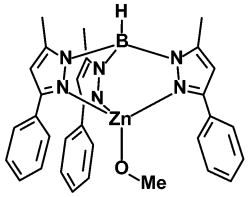
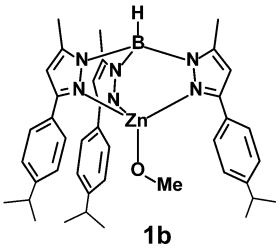


1a



1b

Results and Discussion

Nonactivated Substrates. Complexes **1** do not undergo reactions with simple esters, amides, or phosphoesters, nor do they cleave lactones or lactams. Lactams containing NH functions are deprotonated, however, as described in the following paper.[2]

Pyrophosphates, however, which are very prone to cleavage by Tp*Zn−OH complexes,[10] are also cleaved by the alkoxides. Reactions of tetraalkylpyrophosphates with **1a** and **1b** on the NMR scale in $CDCl_3$ allowed the identification of the cleavage products $(MeO)(RO)_2PO$ by their typical ^1H NMR data.[11,12] Preparative scale reactions according to eq 1 were run with tetraethyl and tetrabenzylpyrophosphate and the resulting zinc complexes **2** and **3** were isolated.

$$\mathbf{1a} + (RO)_2PO{-}O{-}PO(OR)_2 \rightarrow Tp^{Ph,Me}Zn{-}OPO(OR)_2 + (MeO)(RO)_2PO \quad (1)$$

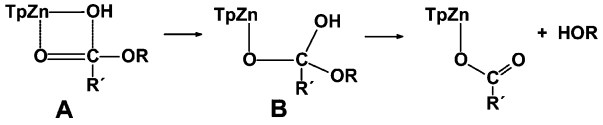
2: $R = C_2H_5$

3: $R = CH_2C_6H_5$

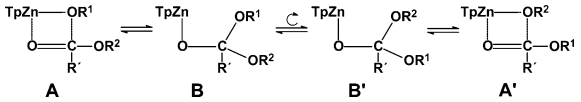
2 and **3** were identified by their spectra, which correspond to those of the various Tp*Zn−diorganophosphate complexes that we have prepared and structurally characterized.[10,13] The cleavage reactions can be described by the usual four-center mechanism, during which one P═O oxygen approaches the zinc ion while the Zn−OR oxygen approaches the other phosphorus atom. No proton transfer is needed to release the reaction product $(MeO)(RO)_2PO$, while the remaining anionic residue $(RO)_2PO_2^-$ stays attached to zinc. The biochemical implication of this process is its resemblance to the phosphorylation of nucleophilic amino acids (serine, threonine, tyrosine) during the zinc enzyme catalyzed phosphoryltransfer reactions.[14,15]

The ready cleavage of the pyrophosphates made us expect that pyrocarbonates, which are also prone to hydrolytic cleavage by Tp*Zn−OH complexes,[16] might also undergo cleavage by Tp*Zn−OR. Yet there was no reaction between **1a** or **b** and dimethyl or diethyl pyrocarbonate, even under forcing conditions.

Scheme 1. Mechanistic Pathway for Ester Hydrolysis by Tp*Zn−OH



Scheme 2. Mechanistic Pathway for Transesterification by Tp*Zn−OR



Activated Substrates. It is a common practice in bioinorganic model studies to resort to *p*-nitrophenolates (ONit) for the study of ester cleavages, due to the ease of reaction and the applicability of UV−vis spectroscopy for kinetic studies. We found that this is favorable here too. Both the related trifluoroacetate and diphenyl phosphate were cleaved by **1a** according to eqs 2 and 3. The products of both reactions, $Tp^{Ph,Me}Zn{-}ONit$,[17] CF_3COOMe,[18] and $PO(OPh)_2(OMe)$,[11] are all known compounds that could be identified by their spectra.

$$\mathbf{1a} + CF_3CO{-}ONit \rightarrow Tp^{Ph,Me}Zn{-}ONit + CF_3CO{-}OMe \quad (2)$$

$$\mathbf{1a} + PO(OPh)_2(ONit) \rightarrow Tp^{Ph,Me}Zn{-}ONit + PO(OPh)_2(OMe) \quad (3)$$

For the ester substrates the reactions correspond to a transesterification, for the zinc complexes they are the replacement of the electron-rich alkoxide by the more suitable anionic ligand *p*-nitrophenolate. This points to a mechanistic detail which has not received as much attention as the formation and cleavage of the four-center intermediate **A** in the course of Zn−OH effected ester or amide hydrolyses.[19−21] That is the fate of the intermediate **B** succeeding the formation of **A** and the release of the leaving group from the zinc ion. In case of the hydrolytic reactions (Scheme 1), the mobile proton in **B** finds its way to the OR constituent, which is released as ROH. This is impossible for the Tp*Zn−OR reactions (Scheme 2), and the reversibility of the **A**−**B** interconversion takes effect. This opens the possibility for OR^2 to be attached to zinc and consequentially for the transesterification. The question whether transesterification really takes place is answered by the relative stabilities of both the zinc complexes $Tp^*Zn{-}OR^1$ and $Tp^*Zn{-}OR^2$ and the esters $RCOOR^1$ and $RCOOR^2$. The outcome of reactions 2 and 3 confirms this, as does the nonoccurrence of

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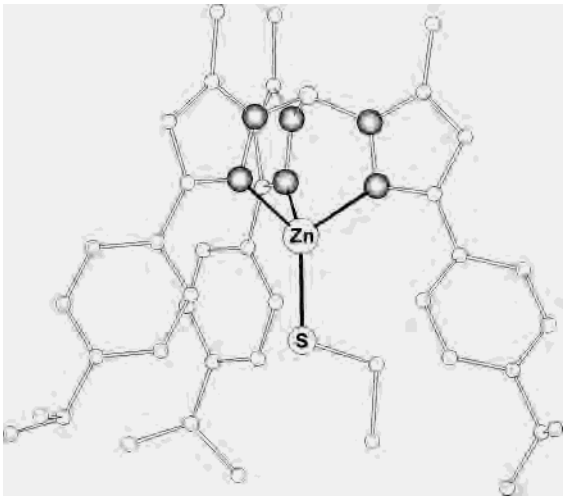

Figure 1. Molecular structure of $Tp^{Cum,Me}Zn-SEt$ (**4**).

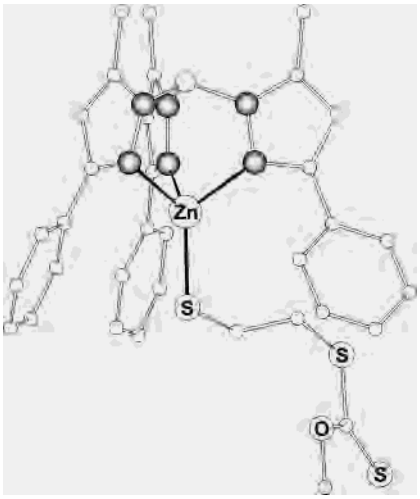

Figure 2. Molecular structure of $Tp^{Ph,Me}Zn-S(CH_2)_2SC(S)OMe$ (**7**).

transesterification for nonactivated substrates. Still a course of the reactions according to Scheme 2 should allow for the formation of equilibrium mixtures, e.g. producing some Tp*Zn−OEt and CH_3COOMe from Tp*Zn−OMe and CH_3COOEt. Yet this was not observed for the reaction temperatures and times applied here.

Sulfur-Containing Substrates. The logic behind Scheme 2 would dictate that any such reaction producing a thiolate Tp*Zn−SR should have a high driving force due to the superior stability and ease of formation of the pyrazolylborate−zinc thiolates.[9] This was borne out by the reactions of the three thioester substrates chosen. Complex **1b** and ethyldithioacetate yielded the thiolate **4** and methylthioacetate, **5**. γ-Thiobutyrolactone was opened by **1a** with formation of the thiolate **6**. Finally, the cyclic trithioester ethylenetrithiocarbonate was cleaved by **1a**, resulting in the thiolate **7**. All three reactions proceeded smoothly and with high isolated yields.

$$\underset{\mathbf{4}}{Tp^{Cum,Me}Zn-SEt} \quad \underset{\mathbf{5}}{CH_3C(S)OMe}$$

$$\underset{\mathbf{6}}{Tp^{Ph,Me}Zn-S(CH_2)_3COOMe}$$

$$\underset{\mathbf{7}}{Tp^{Ph,Me}Zn-S(CH_2)_2SC(S)OMe}$$

The known ester **5**[22] and the ester-substituted thiolate **6**, which has several structurally characterized analogues derived from cysteine esters,[23] were characterized by their spectra. The crystallographically determined structures of **4** and **7** are shown in Figures 1 and 2. They proved the course of the reactions and the identity of the products. The general molecular features of **4** and **7** and their Zn−S bond lengths (2.24 Å in **4**, 2.21 Å in **7**) correspond to those of the various other Tp*Zn−thiolate complexes.[9,17,23]

Conclusions

This work has shown that despite the lack of a mobile proton, the Tp*Zn−alkoxides can undergo reactions with hydrolyzable substrates that are mechanistically related to the corresponding reactions of the Tp*Zn−hydroxides. While the latter perform ester cleavage with release of the alcohol and attachment of the carboxylate to zinc, the former can effect transesterifications. The mechanistic interpretation of this asks for an intermediate **B** in the reaction sequence resulting from an opening of the well-accepted four-center intermediate **A** by release of the alkoxide group from zinc (see Scheme 2). This intermediate must be stable and long-lived enough to allow reorientation of the substrate followed by attachment of the substrate's alkoxide group to zinc. It is obvious that the originally zinc-bound alkoxide must be a good leaving group to allow this reaction sequence.

The outcome of the transesterification reactions shows, however, that their driving force comes from another factor, namely the stability of the resulting Tp*Zn−X complex. It has been established[1,24] that the simple alkoxide groups in Tp*Zn−OR are easily replaced by the more electronegative ones, specifically phenoxides, and that even the weakest acids release ROH from Tp*Zn−OR.[2] Accordingly, transesterification takes place with *p*-nitrophenolates but not with ethyl or benzyl esters, and the most facile reactions occur with thioesters because they produce the very stable Tp*Zn−SR complexes. This observation is in full accord with the intermediacy of **B**, which forms by the opening of the Zn−OR bond but which will not form again once the thiolate or *p*-nitrophenolate group has snapped in to form the secondary four-center intermediate **A′**, which is then broken up with release of the reaction products. Thus, the inability of the Tp*Zn−alkoxides to finish the sequence of steps for a full hydrolytic cleavage has allowed some new insight into the stability and interconversions of possible intermediates of the hydrolysis.

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Experimental Section

General Data. All experimental techniques and the standard IR and NMR equipments were as described previously.[25] The Tp*Zn−alkoxides were prepared as described.[1] Organic reagents were purchased from Merck and Aldrich. All manipulations involving the Tp*Zn−alkoxide complexes were performed in a Braun Labmaster 130 glovebox with degassed and dried solvents. The IR, ^{1}H NMR, and ^{13}C NMR spectral data for the $Tp^{Ph,Me}$ and $Tp^{Cum,Me}$ ligands in the new complexes vary only negligibly between themselves and the reference compounds.[1,9,17,23] Therefore, only the data for the coligands X in the Tp*Zn−X complexes are reported here. A frequent problem with the elemental analyses of this kind of complexes is that the carbon values found are too low. When this was the case here, at least one (but normally two) additional elemental analysis value (N, S, or Zn) was determined.

Pyrophosphate Cleavages. $P_2O_3(OEt)_4$. 1a (200 mg, 0.34 mmol) and 100 mg (0.34 mmol) of tetraethylpyrophosphate in 35 mL of toluene were stirred for 3 h. All volatiles were removed in vacuo. Recrystallization from hot acetonitrile yielded 179 mg (74%) of **2** as colorless crystals, mp 183 °C. IR (KBr): 2547m (BH), 1244s (PO). ^{1}H NMR ($CDCl_3$): 0.85 (t, J = 7.0 Hz, 6H, CH_3(Et)), 3.40 (dq, J = 7.0 and 7.2 Hz, 2H, CH_2(Et)). ^{13}C NMR ($CDCl_3$): 16.3 (CH_3(Et)), 60.9 (CH_2(Et)). ^{31}P NMR ($CDCl_3$): −4.4. Anal. Calcd for $C_{34}H_{38}BN_6O_4PZn$ (M_r = 701.89): C, 58.18; H, 5.46; N, 11.97. Found: C, 58.43; H, 5.56; N, 11.83.

$P_2O_3(OBn)_4$. 1a (150 mg, 0.26 mmol) and 139 mg (0.26 mmol) of tetrabenzylpyrophosphate in 20 mL of toluene were stirred at 60 °C for 20 h. All volatiles were removed in vacuo. Recrystallization from dichloromethane/di-*tert*-butyl ether (1:1) yielded 122 mg (57%) of **3** as colorless crystals, mp 163 °C. IR (KBr): 2548m (BH), 1281m (PO). ^{1}H NMR ($CDCl_3$): 4.58 (d, J = 6.2 Hz, 4H, OCH_2). ^{31}P NMR ($CDCl_3$): −1.8. Anal. Calcd for $C_{44}H_{42}BN_6O_4PZn$ (M_r = 826.03): C, 63.98; H, 5.12; N, 10.17. Found: C, 63.27; H, 5.25; N, 10.36.

Cleavages of *p*-Nitrophenolates. $CF_3COONit$. 1a (200 mg, 0.34 mmol) and 81 mg (0.34 mmol) of $CF_3COONit$ in 30 mL of dichloromethane were stirred for 3 h. Then the ^{1}H NMR spectrum showed the quantitative formation of CF_3COOMe.[18] All volatiles were removed in vacuo. Recrystallization from dichloromethane/acetonitrile yielded 218 mg (92%) of $Tp^{Ph,Me}Zn-OC_6H_4$-*p*-NO_2.[17]

$PO(OPh)_2$(ONit). This reaction was monitored by ^{1}H NMR. A solution of 23 mg (0.04 mmol) of **1a** and 15 mg (0.04 mmol) of $PO(OPh)_2ONit$ in 1 mL of $CDCl_3$ was kept in a sealed NMR tube. After 16 h, complete conversion of **1a** to $Tp^{Ph,Me}Zn-ONit$[17] was observed. From the ^{1}H NMR signal intensities, the yield of $PO(OPh)_2OMe$[11] was determined as 74%.

Cleavages of Sulfur-Containing Substrates. Ethyl Dithioacetate. 1b (200 mg, 0.28 mmol) and 34 mg (0.28 mmol) of ethyl dithioacetate in 20 mL of toluene were stirred at 50 °C for 1 d. Then the ^{1}H NMR spectrum showed the quantitative formation of **5**.[22] All volatiles were removed in vacuo. Recrystallization from benzene yielded 175 mg (84%) of **4** as yellow crystals, mp 264 °C. IR (KBr): 2551m (BH). ^{1}H NMR ($CDCl_3$): 0.37 (t, J = 7.4 Hz, 3H, CH_3(Et)), 1.00 (q, J = 7.4 Hz, 2H, CH_2(Et)). Anal. Calcd for $C_{41}H_{51}BN_6SZn$ (M_r = 736.16): C, 66.89; H, 6.98; N, 11.42; S, 4.36. Found: C, 66.63; H, 7.45; N, 11.42; S, 3.69.

Table 1. Crystallographic Data

	4	7
formula	$C_{41}H_{51}BN_6SZn$	$C_{34}H_{35}BN_6OS_3Zn$
MW	736.2	716.1
space group	$P2_1/n$	$P2_1/n$
Z	4	4
a (Å)	9.103(1)	12.150(2)
b (Å)	21.911(4)	19.721(4)
c (Å)	20.208(3)	14.685(3)
α (deg)	90	90
β (deg)	92.837(4)	96.548(4)
γ (deg)	90	90
V (Å^3)	4026(1)	3496(1)
d_{calc} (g cm^{-3})	1.21	1.36
μ(Mo Kα) (mm^{-1})	0.70	0.92
R1 (obs refl)[a]	0.064	0.089
wR2 (all refl)[a]	0.214	0.315

[a] The R values are defined as $R1 = \sum|F_o - F_c|/\sum F_o$, $wR_2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)]]^{1/2}$.

γ-Thiobutyrolactone. 1a (200 mg, 0.34 mmol) and 35 mg (0.34 mmol) of γ-thiobutyrolactone in 20 mL of toluene were stirred at 50 °C for 1 d. All volatiles were removed in vacuo. Recrystallization from hot acetonitrile yielded 219 mg (93%) of **6** as a colorless powder, mp 173 °C. IR (KBr): 2550m (BH), 1733s (CO). ^{1}H NMR ($CDCl_3$): 0.95 (m, 4H, C_2H_4), 1.67 (t, J = 7.6 Hz, 2H, SCH_2), 3.54 (s, 3H, OMe). Anal. Calcd for $C_{35}H_{37}BN_6O_2SZn$ (M_r = 681.98): C, 61.64; H, 5.47; N, 12.32; S, 4.70. Found: C, 60.77; H, 5.61; N, 12.24; S, 4.24.

Ethylenetrithiocarbonate. 1a (200 mg, 0.34 mmol) and 47 mg (0.34 mmol) of ethylenetrithiocarbonate in 20 mL of toluene were stirred at 40 °C for 7 h. All volatiles were removed in vacuo. Recrystallization from hot acetonitrile yielded 205 mg (83%) of **7** as yellow crystals, mp 229 °C. IR (KBr): 2541m (BH). ^{1}H NMR ($CDCl_3$): 1.21 (t, J = 8.4 Hz, 2H, CH_2CS), 2.14 (t, J = 8.4 Hz, 2H, SCH_2), 3.95 (s, 3H, OMe). Anal. Calcd for $C_{34}H_{35}BN_6OS_3Zn$ (M_r = 716.09): C, 57.03; H, 4.93; N, 11.74; S, 13.47. Found: C, 56.37; H, 5.14; N, 11.82; S, 13.00.

Structure Determinations. Crystals of **4** and **7** were obtained from the reaction solutions. Diffraction data were obtained at room temperature with a Bruker Smart CCD diffratometer and subjected to an empirical absorption correction. The structures were solved with SHELX.[26] Parameters were refined against F^2. Drawings were produced with SCHAKAL.[27] Table 1 lists the crystallographic data. For **7** the thermal ellipsoids for the atoms of the thioester chain grow very large with increasing distance from the zinc center, which is also reflected in the poor R value for the structure determination.

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Supporting Information Available: Fully labeled ORTEP plots and X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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