Biomimetic Thiolate Alkylation with Zinc Pyrazolylbis(thioimidazolyl)borate Complexes

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The NS_2ZnX coordination in thiolate-alkylating zinc enzymes is reproduced in (tripod)ZnX complexes with substituted pyrazolylbis(thioimidazolyl)borate tripod ligands. Intermediate (tripod)Zn nitrates and perchlorates are converted into (tripod)Zn thiolates, including the biologically relevant homocysteinate. Methylation with CH_3I converts these to (tripod)ZnI and the corresponding thioethers CH_3SR, including methionine. A kinetic investigation has shown the alkylations to be intramolecular S_N2 processes that take place at the zinc-bound thiolates. They are considerably faster for the $(NS_2)Zn$ thiolates than for the (N_2S)- and $(N_3)Zn$-thiolates with similar pyrazolylborate-derived tripod ligands, in agreement with Nature's choice of an NS_2 donor set for zinc.

Introduction

In two classes of zinc enzymes, a subgroup of the alcohol dehydrogenases and a subgroup of the thiolate alkylating enzymes, the zinc ion is in the unusual $(NS_2)ZnX$ coordination, with N representing histidine, S representing cysteinate, and X being the catalytic site.[1,2] Thus, as a complex the $(NS_2)ZnX$ unit is an uncharged molecular species, and the reacting substrates (alkoxides or thiolates) convert this into an anionic complex upon coordination to zinc. Obviously, this is of advantage for the reactions to be catalyzed (removal of a hydride from the α-carbon of the alkoxide or attack of the alkylating agent at the zinc-bound thiolate) due to the enhanced electron density at the substrates.

On the other hand, it is difficult to reproduce these bonding situations and chemical reactions in coordination compounds of zinc.[3] At present, alcohol dehydrogenase modeling has not gone beyond structural mimics, and thiolate alkylation has not yet been achieved for a thiolate bound to zinc in an anionic complex. Thiolate alkylation in other types of zinc complexes has, however, been performed in a number of cases. Thus, thiolates bound to ZnN_2O,[4,5] ZnN_2S,[5–7] $ZnNS_2$,[8] and ZnS_3 units[9] have been subjected to alkylations by our competitors in this field. The only anionic thiolate complex used for such reactions, $Zn(SPh)_4^{2-}$,[10] was found to dissociate prior to alkylation.

Our own contributions to this field have involved zinc thiolates with bidentate N_2[11] and tridentate N_2S ligands,[12] as well as the tris(pyrazolyl)borate as N_3 tripods.[13] During these studies it became obvious that the tripods of the pyrazolylborate type are the best substitutes for the biological ligand environment of zinc, as observed before,[14] due to their synthetic variability, which allows the encapsulation of the metal in a favorable way. It therefore seemed promising to us to use sulfur-containing pyrazolylborate ligands for studies of this kind, that is, to investigate the alkylation of **L**·Zn-SR complexes in which the ligands **L** are pyrazolylborate-derived tripods with N_2S, NS_2, and S_3 donor sets. A complete series of such ligands with substituted thioimidazolyl groups as sulfur donors is available now: after Reglinski's discovery of the tris(thioimidazolyl)borates,[15] Parkin[16] and ourselves[17] introduced the pyrazolylbis(thioimidazolyl)borates, and very recently we added the final member, the bis(pyrazolyl)(thioimidazolyl)borates.[18]

Following our introductory study on the alkylation of tris(pyrazolyl)boratozinc thiolates,[13] in the second part of the investigation we used the bis(pyrazolyl)(thioimidzolyl)-boratozinc thiolates.[19] The major, and unexpected, observation of this study was that the thiolate alkylations are slower than those of the tris(pyrazolyl)boratozinc thiolates, despite the increased electron density of the complexes. It remained to be demonstrated, however, that the trend continued for the (pyrazolyl)bis(thioimidazolyl)boratozinc thiolates. This is the subject of the present study, which is the third in the series. Work on part four, concerning the tris(thioimidazolyl)boratozinc thiolates, is in progress.

The zinc thiolate complexes of the present study, representing the $(NS_2)Zn$-SR ligand environment, are the closest structural models of the thiolate-alkylating zinc enzymes so far.[2,3] We chose $\mathbf{L^1}$ and $\mathbf{L^2}$ as the NS_2 ligands. The substitution pattern on their pyrazolyl and thioimidazolyl groups

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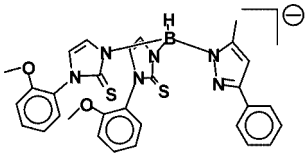
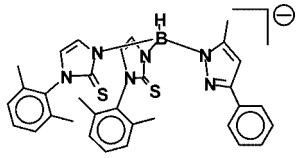
was meant to provide encapsulation of the zinc ion in a hydrophobic pocket. This was achieved for the pyrazolyl units in the usual way[14] by 3-phenyl-5-methyl substitution. The thioimidazolyl units bear *N*-phenyl groups with *ortho* substituents. This was found to be favorable for encapsulation as it induces the phenyl substituents that point away from the zinc centers to rotate such that their *ortho* positions get placed nearer to the metal.[20]



L¹



L²

Ligands L¹ and L²

L¹ has been described by us previously,[17] and **L²** was prepared by the same procedure from equimolar amounts of the thioimidazole and the pyrazole together with KBH_4 in boiling toluene. In order to purify **L²** it had to be subjected to column chromatography over silica gel. As a result of this the anionic ligand was protonated and isolated as the molecular species **HL²**. This is not unprecedented in the chemistry of the tris(pyrazolyl)borates.[21,22] We are, however, not aware of the existence of the protonated form of a pyrazolylborate-based heteroscorpionate like **HL²**. After isolating **HL²** it was straightforward to convert it into K**L²**, the standard form of all these tripod ligands, by treating it with KOH in methanol.

The identity of **HL²** was revealed by an X-ray structure determination (Figure 1). Compound **HL²** can be considered a zwitterion, with the positive charge on the protonated pyrazole nitrogen and the negative charge on boron. Although the pyrazole nitrogen is the only reasonable position for protonation, the NH hydrogen could not be located with certainty or refined freely. The geometry around the boron atom is close to ideally tetrahedral, and the B–N bond lengths are in the normal range for pyrazolylborates.[22] Unlike in the complexes of such ligands where the N and S donor atoms are locked in place by coordination to the metal, they seem to be locked in this free ligand by weak hydrogen bonds. One of these attaches one of the thioimidazole sulfur atoms to the oxygen atom of a co-crystallized methanol molecule, and the other links the pyrazole nitrogen atom with the other thioimidazole sulfur atom. This latter hydrogen bond serves as a reminder that the proton in question may actually be bound to sulfur rather than to nitrogen.

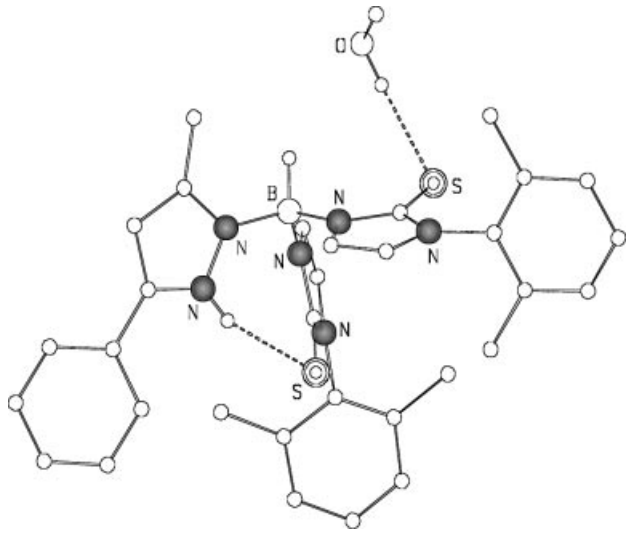


Figure 1. Molecular structure of **HL²**. Relevant distances [Å] and angles [°]: B–N 1.555, 1.534 and 1.550(4), C–S 1.677 and 1.695(3); N–B–N 108.1, 110.2, and 111.7(3); S···N 3.10; S···O 3.27.

Basic Complexes

While with the tris(pyrazolyl)borate ligands the starting point for all functional zinc complexes are the Zn–OH compounds,[14] these compounds have not been isolated yet with the pyrazolylbis(thioimidazolyl)borate ligands.[17] Instead, perchlorate and nitrate were found to be labile enough to be displaced from zinc by even weakly coordinating donors. Therefore, in addition to complexes **1a** and **1b** already described for ligand **L¹**,[17] the corresponding complexes **2a** and **2b** were prepared here for ligand **L²**. They resulted from the reaction of **HL²** with the zinc salts in methanol. It can be assumed that **2a** and **2b**, just like **1a** and **1b**,[17] contain the oxoanions attached to zinc through one of their oxygen atoms. As considerable amounts of complexes **1** and **2** are lost in the isolation process, further reactions with them were usually carried out by using them in situ.

When doing reactions with complexes **1** and **2**, or when trying to prepare further **L**Zn-X complexes by combining K**L** and ZnX_2, we observed many times, as before,[17] that these systems have a very high tendency to dismutate into ZnL_2 and ZnX_2. This is one of the reasons why the desired **L**Zn–OH complexes have evaded us so far and why the derivative chemistry with **L**Zn units is not nearly as rich as that of the tris(pyrazolyl)boratozinc units. For example, the attempted syntheses of **L²**Zn acetate from **HL²** and zinc acetate resulted in **3b**. The structure of **3b** (see Table 1 below and data deposited under CCDC-268609) complements those of other related ZnL_2 complexes.[16,17]

$L^1Zn\text{-}ONO_2$	$L^1Zn\text{-}OClO_3$	$L^2Zn\text{-}ONO_2$	$L^2Zn\text{-}OClO_3$
1a	**1b**	**2a**	**2b**

ZnL^1_2 ZnL^2_2

3a **3b**

On the other hand, halides coordinate readily to these **L**Zn units. Like other such **L**Zn halide complexes,[17] the iodides **4a** and **4b** were prepared here from the ligands and ZnI_2. They were fully characterized, including structure determinations for reference purposes, as they are one of the products of each of the alkylation reactions described below.

L^1Zn-I L^2Zn-I

4a **4b**

The structure of **4b** is shown in Figure 2, mainly for comparison with the structure of the free ligand in Figure 1. The tetrahedral coordination of zinc (bond angles 104–113°) and the Zn–N, Zn–S, and Zn–I bond lengths correspond to those reported for related **L**ZnI complexes.[17,23] One can say that in HL^2 the proton of the N–H···S hydrogen bond has the same role as the zinc ion in **4b** in fixing the orientation of the pyrazole and one thioimidazole of the ligand, but that in **4b** coordination to zinc overcomes the tendency of the second thioimidazole to point away from the center of the molecule. This comparison offers one explanation for the high tendency of formation of the ZnL_2 complexes, in which also only two donor units of the tripod are fixed, while the third is free and pointing away from the complex center.

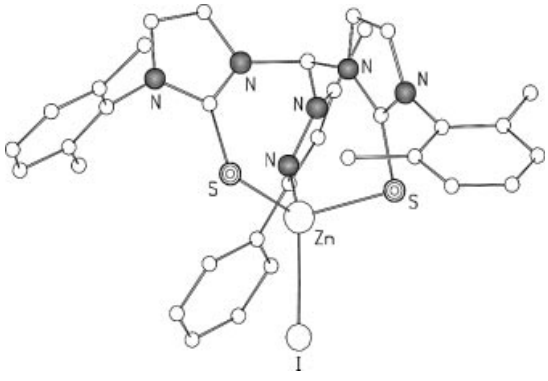


Figure 2. Molecular structure of L^2ZnI (**4b**). Relevant bond lengths [Å]: Zn–N 2.039(3), Zn–S 2.338 and 2.320(2), Zn–I 2.533(2).

Thiolates

While the preparation of (tripod)ZnSR complexes for the tris(pyrazolyl)borate[13] and bis(pyrazolyl)(thioimidazolyl)-borate tripods[18] is straightforward, in this case it required careful control of the reaction conditions. The high tendency of formation of the bis(ligand)complexes **3** and the oligomeric zinc bis(thiolates) prevented the isolation of most of the desired thiolate complexes with tripod L^2, and it allowed the isolation of the alkyl- and benzylthiolate complexes of tripod L^1 only when carefully controlling the reaction conditions. Only with the least electron-rich *p*-nitrothiophenolates was it easy to obtain the **L**ZnSR complexes.

Complexes **5a**–**c** and **6d** were prepared from the perchlorates **1b** and **2b** and the corresponding thiolates. Complex **5d** could be obtained in a one-pot synthesis from *p*-nitrothiophenol, $NaOCH_3$, $Zn(NO_3)_2{\cdot}6H_2O$, and KL^1. Likewise, the homocysteine derivative **5e**, which is the closest representation of the reactive intermediate in the synthesis of methionine from homocysteine by cobalamine-independent methionine synthase[2] reported so far, was prepared from *N*-acetylhomocysteine ethyl ester, NaOH, $Zn(NO_3)_2{\cdot}6H_2O$, and KL^1 in methanol. As mentioned above, **5a** and **5b** are very labile, dismutating in solution to $[Zn(SR)_2]_n$ and the ZnL_2 complex **3a**.

L^1Zn-SR L^2Zn-SR

5a-e **6d**

a: R = C_2H_5, **b**: R = $CH_2C_6H_5$, **c**: R = C_6H_5,

d: R = C_6H_4-p-NO_2, **e**: R = $CH_2CH_2CH(COOEt)NHAc$

The structures of the two most stable thiolate complexes (**5d** and **6d**) were determined. They are closely related, making it sufficient to display only the structure of **6d** in Figure 3. The coordination of zinc is severely distorted tetrahedral, with the largest angle (ca. 123°) being that between the pyrazole nitrogen and the thiolate sulfur and the smallest angle (ca. 101°) being that between the pyrazole nitrogen and one of the thioimidazolyl sulfurs. The Zn–N and Zn–S distances concerning the tripod ligand compare well with those in the other pyrazolylbis(thioimidazolyl)boratozinc complexes (this work and ref.[17]). The Zn–S (thiolate) bond lengths of 2.28 Å in both **5d** and **6d** are not much different

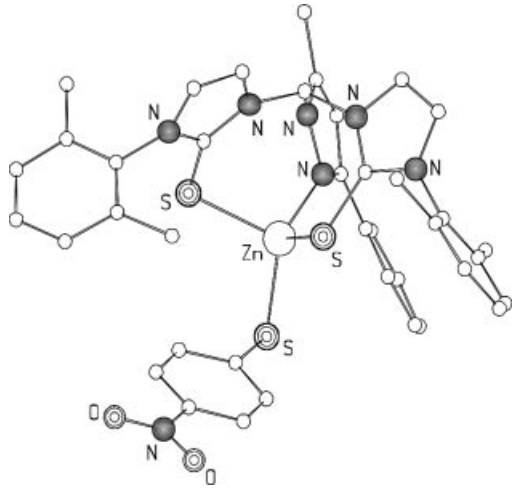


Figure 3. Molecular structure of the thiolate complex **6d**. Relevant bond lengths [Å]: Zn–S (tripod) 2.362(1) and 2.341(1), Zn–S (thiolate) 2.285(1), Zn–N 2.038(3).

from those in the related zinc *p*-nitrothiophenolate complexes of a tris(pyrazolyl)borate[13] and a bis(pyrazolyl)-(thioimidazolyl)borate ligand[19] [2.25 and 2.25 Å (av.) respectively]. A notable feature of the structure of **6d** is the orientation of one of the *o*-dimethylphenyl rings. As anticipated, it is rotated to such a degree that one of the methyl groups contributes to the encapsulation of the zinc ion in a similar way as the phenyl substituent on the pyrazole ring.

Methylation Reactions

As before for the N_3- and N_2S-ligated zinc thiolates,[13,19] all thiolate complexes **5** and **6** were subjected to methylation with methyl iodide in chloroform. In each case the reactions proceeded according to Equation (1) and, according, to ^{1}H NMR spectroscopy, they were quantitative. The solid reaction products **L**ZnI (**4a** and **4b**) were isolated, and the thioethers CH_3SR were identified by NMR spectroscopy; there were no other reaction products in the solutions.

$$\mathbf{L}ZnSR + CH_3I \rightarrow \mathbf{L}ZnI + CH_3SR \quad (1)$$

The ethyl and benzyl thiolates **5a** and **5b** reacted within minutes, whereas the phenyl and homocysteinyl thiolates **5c** and **5e** needed about an hour. Even the methylations of the *p*-nitrothiophenolates **5d** and **6d** came to completion within a few hours. This is in marked contrast to the reactions of the N_3- and N_2S-ligated zinc-*p*-nitrothiophenolates. Those of the tris(pyrazolyl)borates were found not to proceed at all at room temperature,[13] and those of the bis(pyrazolyl)-(thioimidazolyl)borates took weeks to come to completion. These observations lead to the rough estimate that the NS_2-ligated zinc thiolates react about two orders of magnitude faster than the N_3- and N_2S-ligated ones. Further work is needed to quantify this statement.

The popular alternative alkylating agent trimethylphosphate was also used here. We had found before that, under forcing conditions (i.e. in boiling DMSO), it does lead to methylation of neocuproinzinc bis(thiolates)[11] and of zinc thiolates bearing a tridentate N_2S ligand.[12] Yet, even under these forcing conditions, it reacted extremely slowly with the zinc thiolates bearing tripodal N_2S ligands.[19] This was now observed for complex **5d** too. In boiling DMSO it took three days to methylate about one third of the thiolate with $PO(OMe)_3$. While this is again about one to two orders of magnitude faster than the corresponding methylation of the complex ligated with a bis(pyrazolyl)(thioimidazolyl)borate,[19] it demonstrates again that zinc thiolate model complexes are not nearly as reactive as the thiolate-alkylating zinc enzymes, which employ such mild alkylating agents as methyl tetrahydrofolate.[2]

Kinetic data were obtained for the methylations of **5d** and **6d** with methyl iodide in $CDCl_3$ at 300 K. We found it convenient to record the intensity of the ^{1}H NMR signal of the SCH_3 group of the resulting *p*-nitrothioanisole during the kinetic runs. Complexes **5d** and **6d** were treated under pseudo-first-order conditions with a four- to tenfold excess of CH_3I. From the SCH_3 signal intensities, recorded for at least five $t_{½}$ intervals (see Figure 4), the pseudo-first-order rate constants were obtained according to $\ln(I_t - I_0) = \ln(I_\infty - I_0) - k_{obs} \times t$.

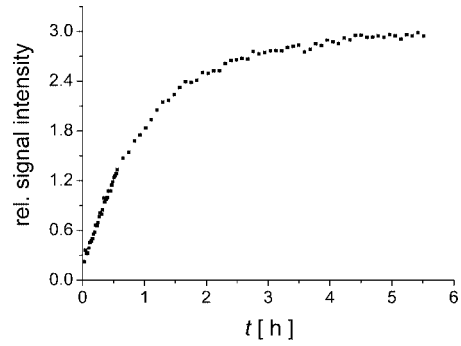


Figure 4. Intensities of the CH_3 ^{1}H NMR signals of $CH_3SC_6H_4$-*p*-NO_2 resulting from the reaction of **5d** with a sixfold excess of CH_3I.

The log plots for five different excess concentrations of CH_3I were linear with correlation coefficients greater than 0.995. The resulting k_{obs} values, plotted against the CH_3I concentrations (see Figure 5), define regression lines passing through the origin with correlation coefficients greater than 0.998. The second-order rate constants of the thiolate alkylations, taken from the slopes of these regression lines, are $8.5(1) \times 10^{-3}$ M^{-1} s^{-1} for **5d** and $1.5(1) \times 10^{-3}$ M^{-1} s^{-1} for **6d**.

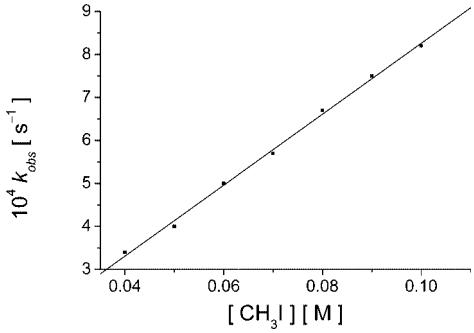


Figure 5. Plot of the pseudo-first-order rate constants against the CH_3I concentration for the methylation of **5d**.

Again, the clean second-order reactions support the statement that the alkylations occur at the zinc-bound thiolates, as proposed for the enzymes.[2,3] At present their rates can be compared only to one another, as comparable rates for other *p*-nitrothiophenolate complexes are not available. The fact that **5d** reacts faster than **6d** can be explained by electronic as well as steric effects: due to the *o*-methoxy substituents **5d** is slightly more electron-rich than **6d**, and the better encapsulation of the reactive center of **6d** (see discussion above) renders the latter less reactive. The fact that the thiolate complexes of this study are considerably more reactive than the previously studied ones with N_3[13] and N_2S tripods[19] certainly relates to the fact that sulfur donor ligands render the zinc ion, and hence the thiolate attached to it, more electron-rich.

Conclusions

The present study, the third in our series on thiolate alkylations of zinc complexes with pyrazolylborate-derived ligands, has yielded model complexes in which the (NS_2) ZnSR ligand environment of the zinc ion correctly reproduces that in the thiolate alkylating zinc enzymes like cobalamin-independent methionine synthase. The simple alkanethiolate complexes are labile, indicating that the electron-richness in these systems is reaching a borderline, comparable to the situation in the $Zn(SR)_4^{2-}$ species, among which the alkanethiolates have been inaccessible to date. Nevertheless, the homocysteinate complex could be prepared and methylated to yield methionine, which is the closest reproduction so far of the last step of enzymatic methionine synthesis.

The mechanistic investigation of the alkylation reactions has shown them to be second order and probably intramolecular again. They are significantly faster than the alkylations of the Zn-SR complexes with N_3 and N_2S tripod ligands, as expected due to their increased electron-richness. This relates well with Nature's choice of an NS_2 donor set for zinc in the thiolate-alkylating enzymes.

Nature, however, also uses a $Zn(SR)_4^{2-}$ system to dealkylate phosphate esters in the Ada repair protein.[24] Thus, model systems in the form of zinc complexes with an (S_3) Zn-SR composition are also a valuable subject of investigation. We are at present studying such a model system employing the tris(thioimidazolyl)boratozinc thiolates. The results of this study are to be published as the fourth part of our series on tripod-zinc thiolate complexes.

Experimental Section

General: For the general working and measuring procedures, see ref.[25] Ligand **L¹**,[17] 5-methyl-3-phenylpyrazole,[26] and *N*-(*o*-dimethylphenyl)thioimidazole[27] were prepared according to the published procedures. All other starting materials were commercially available. The methyl thioethers resulting from the methylations,[28–31] including *N*-acetylmethionine ethyl ester,[13] have been described and were identified by their ^{1}H NMR spectra, which are also reported in ref.[13]

A frequent problem with the elemental analyses of this kind of complexes is that the carbon values are outside the accepted range. When this was the case here, at least one additional analysis value (S or Zn) was determined.

Ligand HL²: a) HL²: A mixture of 5-methyl-3-phenylpyrazole (4.20 g, 26.5 mmol), *N*-(2,3-dimethylphenyl)-2-thioimidazole (5.42 g, 26.5 mmol), and KBH_4 (0.72 g, 13.3 mmol) was finely ground and heated to 100 °C in vacuo for 2 h. Then, 400 mL of freshly distilled toluene were added and the mixture refluxed at 160 °C in an oil bath for a week. The solvent was then removed in vacuo, the residue dissolved in dichloromethane, and filtered through celite. Chromatography through a 3 × 30 cm silica gel column with a gradient solvent system (dichloromethane/acetone, 200:0 → 200:4) yielded raw **HL²**. Repeating the chromatography yielded 5.32 g (69%) of **HL²** as a colorless powder, m.p. 194 °C. $C_{32}H_{33}BN_6S_2$ (576.60): calcd. C 66.78, H 5.60, N 14.60, S 11.14; found C 66.69, H 5.93, N 13.95, S 10.49. ^{1}H NMR ($CDCl_3$): δ = 2.25 [s, 6 H, Me(Ph)], 2.29 [s, 6 H, Me(Ph)], 2.92 [s, 3 H, Me(pz)], 6.78 [s, 1 H, H(pz)], 6.80 [d, J = 2.2 Hz, 2 H, H(im)], 7.20 [d, J = 2.2 Hz, 2 H, H(im)], 7.29 (m, 1 H, Ar), 7.33 (s, 3 H, Ar), 7.42 (m, 2 H, Ar), 7.64 (m, 3 H, Ar), 7.96 (m, 2 H, Ar) ppm.

b) KL²: 20 mL of a 0.1 M solution of KOH in methanol (2.00 mmol) was added dropwise to a solution of **HL²** (1.15 g, 2.00 mmol) in 20 mL of methanol. The solvent was removed in vacuo, the residue dissolved in dichloromethane, and the product precipitated by addition of petroleum ether (50–70 °C). Recrystallization from dichloromethane/heptane by slow evaporation yielded 0.71 g (58%) of **KL²** as a colorless powder, m.p. 240 °C (dec.). $C_{32}H_{32}BKN_6S_2$ (614.69): calcd. C 62.53, H 5.25, N 13.67, S 10.43; found C 62.75, H 5.42, N 13.28, S 10.14. ^{1}H NMR ($CDCl_3$): δ = 1.92 [s, 6 H, Me(Ph)], 1.96 [s, 6 H, Me(Ph)], 2.16 [s, 3 H, Me(pz)], 6.24 [s, 1 H, H(pz)], 6.43 [s, 2 H, H(im)], 6.47 [s, 2 H, H(im)], 6.98 (s, 1 H, Ar), 7.05 (m, 5 H, Ar), 7.30 (m, 2 H, Ar), 7.62 (m, 3 H, Ar) ppm.

Complex 2a: A solution of **HL²** (0.057 g, 0.10 mmol) in 20 mL of methanol was added with stirring to a solution of $Zn(NO_3)_2{\cdot}6H_2O$ (0.030 g, 0.10 mmol) in 20 mL of methanol. After stirring for 15 h the solvent was removed in vacuo and the residue dissolved in 20 mL of dichloromethane. After washing with water the dichloromethane solution was filtered through celite. The filtrate was then reduced to 5 mL in vacuo. Slow diffusion of *n*-pentane into the solution yielded 32 mg (46%) of **2a** as colorless crystals, m.p. 215 °C (dec.). $C_{32}H_{32}BN_7O_3S_2Zn$ (702.98): calcd. C 54.67, H 4.59, N 13.95, S 9.12; found C 54.98, H 4.49, N 13.36, S 8.73. ^{1}H NMR ($CDCl_3$): δ = 1.89 [s, 6 H, Me(Ph)], 1.93 [s, 6 H, Me(Ph)], 2.43 [s, 3 H, Me(pz)], 6.36 [s, 1 H, H(pz)], 6.77 [d, J = 2.1 Hz, 2 H, H(im)], 7.01 [d, J = 2.1 Hz, 2 H, H(im)], 7.04 (s, 2 H, Ar), 7.13–7.31 (m, 2 H, Ar), 7.45 (m, 6 H, Ar), 7.75 (s, 1 H, Ar) ppm.

Complex 2b: Prepared as **2a** from **HL²** (0.115 g, 0.20 mmol) in 50 mL of methanol and $Zn(ClO_4)_2{\cdot}6H_2O$ (0.074 g, 0.20 mmol) in 40 mL of methanol. Yield: 67 mg (45%) of **2a** as colorless crystals, m.p. 194 °C. $C_{32}H_{32}BClN_6O_4S_2Zn$ (740.43): calcd. C 51.91, H 4.36, N 11.35, S 8.66; found C 52.26, H 4.83, N 11.20, S 8.65. ^{1}H NMR ($CDCl_3$): δ = 1.70 [s, 3 H, Me(Ph)], 1.77 [s, 3 H, Me(Ph)], 1.83 [s, 3 H, Me(Ph)], 1.86 [s, 3 H, Me(Ph)], 2.45 [s, 3 H, Me(pz)], 6.59 [s, 1 H, H(pz)], 6.79 [s, br, 2 H, H(im)], 6.95 [s, br, 2 H, H(im)], 7.00 (s, 2 H, Ar), 7.10 (m, 4 H, Ar), 7.48 (m, 3 H, Ar), 7.87 (m, 2 H, Ar) ppm.

Complex 3b: This complex formed during an attempted synthesis of **L²Zn** acetate. It was prepared as **2a** from **HL²** (0.115 g, 0.20 mmol) and $Zn(OAc)_2{\cdot}6H_2O$ (0.044 g, 0.20 mmol). Workup yielded 144 mg (59%) of **3b** as colorless crystals, m.p. 210 °C (dec.). $C_{64}H_{64}B_2N_{12}S_4Zn$ (1216.6): calcd. C 63.19, H 5.30, N 13.82, S 10.54; found C 62.76, H 5.37, N 13.71, S 10.48. ^{1}H NMR ($CDCl_3$): δ = 1.60 [s, 3 H, Me(Ph)], 1.79 [s, 3 H, Me(Ph)], 1.83 [s, 3 H, Me(Ph)], 1.88 [s, 3 H, Me(Ph)], 2.66 [s, 3 H, Me(pz)], 6.28 [s, 1 H, H(pz)], 6.43 [d, J = 2.1 Hz, 2 H, H(im)], 6.49 [d, J = 2.1 Hz, 2 H, H(im)], 6.99 (s, 1 H, Ar), 7.02 (m, 2 H, Ar), 7.06 (s, 1 H, Ar), 7.17 (m, 3 H, Ar), 7.28 (m, 2 H, Ar), 7.84 (m, 2 H, Ar) ppm.

Complex 4a: A solution of **KL¹** (301 mg, 0.49 mmol) in 50 mL of methanol was slowly added dropwise, with stirring, to a solution of anhydrous ZnI_2 (155 mg, 0.49 mmol) in 30 mL of methanol. The resulting colorless precipitate was filtered off and the filtrate was reduced in vacuo to 20 mL to produce a precipitate of raw **4a**. Slow diffusion of toluene into a solution of raw **4a** in dichloromethane yielded 257 mg (69%) of **4a** as colorless crystals, m.p. 230 °C (dec.). $C_{30}H_{28}BIN_6O_2S_2Zn$ (771.83): calcd. C 46.69, H 3.66, N 10.89, S 8.31; found C 45.79, H 3.95, N 10.75, S 8.25. ^{1}H NMR ($CDCl_3$): δ = 2.49 [s, 3 H, Me(pz)], 3.85 (s, 6 H, OMe), 6.15 [s, 1 H, H(pz)], 6.91–7.95 [m, 17 H, H(im) + Ar] ppm.

Complex 4b: Prepared as **2a** from **HL²** (57 mg, 0.10 mmol) and anhydrous ZnI_2 (52 mg, 0.16 mmol). Yield: 37 mg (48%) of **4b** as colorless crystals, m.p. 240 °C (dec.). $C_{32}H_{32}BIN_6S_2Zn$ (767.88): calcd. C 50.05, H 4.20, N 10.94, S 8.35; found C 49.84, H 3.96, N 10.95, S 8.03. ^{1}H NMR ($CDCl_3$): δ = 1.93 [s, 6 H, Me(Ph)], 2.08 [s, 6 H, Me(Ph)], 2.40 [s, 3 H, Me(pz)], 6.32 [s, 1 H, H(pz)], 6.73 [d, J = 2.1 Hz, 2 H, H(im)], 7.01 [d, J = 2.1 Hz, 2 H, H(im)], 7.11 (m, 3 H, Ar), 7.19 (s, 2 H, Ar), 7.30 (m, 3 H, Ar), 7.40 (m, 3 H, Ar) ppm.

Complex 5a: A solution of 33 μL (28 mg, 0.45 mmol) of ethanethiol in 5 mL of methanol was deprotonated by addition of 1.8 mL (0.45 mmol) of a 0.25 M solution of $NaOCH_3$ in methanol. A solution of $Zn(ClO_4)_2{\cdot}6H_2O$ (112 mg, 0.30 mmol) in 15 mL of methanol and then a solution of **KL¹** (186 mg, 0.30 mmol) in 40 mL of methanol were added dropwise to this solution with stirring. After stirring for 4 d the volume of the solution was reduced to 15 mL in vacuo. Filtration yielded raw **5a**, which was dissolved in dichloromethane. Slow diffusion of *n*-hexane into this solution precipitated 126 mg (59%) of **5a** as a colorless powder, m.p. 215 °C (dec.). $C_{32}H_{33}BN_6O_2S_3Zn{\cdot}0.25CH_2Cl_2$ (706.05 + 21.23): calcd. C 53.26, H 4.64, N 11.56, S 13.23; found C 53.27, H 4.43, N 11.76, S 13.01. ^{1}H NMR ($CDCl_3$): δ = 1.32 [t, J = 7.4 Hz, 3 H, CH_3(SEt)], 2.48 [s, 3 H, Me(pz)], 2.54 [q, J = 7.4 Hz, 2 H, CH_2(SEt)], 3.71 (s, 6 H, OMe), 5.29 (s, 0.5 H, CH_2Cl_2), 6.31 [s, 1 H, H(pz)], 6.69–6.85 (m, 2 H, Ar), 6.91 [d, J = 2.0 Hz, 2 H, H(im)], 6.99 [d, J = 2.0 Hz, 2 H, H(im)], 7.02–7.05 (m, 4 H, Ar), 7.34 (m, 2 H, Ar), 7.36–7.58 (m, 3 H, Ar), 7.95 (d, J = 7.0 Hz, 2 H, Ar) ppm.

Complex 5b: Prepared as **5a** from 54 μL (56 mg, 0.45 mmol) of benzylmercaptan, $Zn(ClO_4)_2{\cdot}6H_2O$ (112 mg, 0.30 mmol), and **KL¹** (186 mg, 0.30 mmol). Yield: 128 mg (55%) of **5b** as a colorless powder, m.p. 190 °C (dec.). $C_{37}H_{35}BN_6O_2S_3Zn$ (768.12): calcd. C 57.86, H 4.59, N 10.94, S 12.52; found C 57.26, H 4.59, N 11.87, S 11.63. ^{1}H NMR ($CDCl_3$): δ = 2.36 [s, 3 H, Me(pz)], 3.62 (s, 6 H, OMe), 3.38 [s, 2 H, CH_2(Bz)], 6.31 [s, 1 H, H(pz)], 6.69–6.76 (m, 2 H, Ar), 6.90 [d, J = 2.2 Hz, 2 H, H(im)], 6.96 [d, J = 2.2 Hz, 2 H, H(im)], 7.01–7.05 (m, 4 H, Ar), 7.19 (m, 2 H, Ar), 7.30 (m, 2 H, Ar), 7.34 (m, 1 H, Ar), 7.39 (d, J = 1.8 Hz, 2 H, Ar), 7.52 (m, 3 H, Ar), 7.91 (d, J = 7.0 Hz, 2 H, Ar) ppm.

Complex 5c: A solution of thiophenol (45 mg, 0.41 mmol) in 15 mL of methanol was deprotonated by addition of a 0.25 M solution of $NaOCH_3$ in methanol (1.64 mL, 0.41 mmol). This solution was added dropwise with stirring to a solution of **1b** (306 mg, 0.41 mmol) in 40 mL of chloroform. After stirring for 12 h the solvent was removed in vacuo and the residue treated with 20 mL of dichloromethane. The dichloromethane extract was filtered and the filtrate evaporated to dryness. Recrystallization from dichloromethane/methanol (1:1) yielded 194 mg (63%) of **5c** as a colorless powder, m.p. 225 °C (dec.). $C_{36}H_{33}BN_6O_2S_3Zn$ (754.09): calcd. C 57.34, H 4.41, N 11.14, S 12.76; found C 56.87, H 4.36, N 10.85, S 12.63. ^{1}H NMR ($CDCl_3$): δ = 2.48 [s, 3 H, CH_3(pz)], 3.79 (s, 6 H, OMe), 6.34 [s, 1 H, H(pz)], 6.72 (m, 2 H, Ar), 6.82 [d, J = 2.0 Hz, 2 H, H(im)], 6.97 [d, J = 2.0 Hz, 2 H, H(im)], 7.22 (m, 2 H, Ar), 7.29 (m, 2 H, Ar), 7.36 (d, J = 1.8 Hz, 2 H, Ar), 7.39 (m, 1 H, Ar], 7.50–7.60 (m, 5 H, Ar), 7.92 (m, 2 H, Ar) ppm.

Complex 5d: A solution of *p*-nitrothiophenol (125 mg, 0.81 mmol) in 30 mL of methanol was treated with 5.0 mL of a 0.25 M solution of NaOH in methanol (1.25 mmol), thereby turning red. A solution of $Zn(ClO_4)_2{\cdot}6H_2O$ (240 mg, 0.81 mmol) in 15 mL of methanol was slowly added dropwise, with stirring, to the red solution, which turned yellow. Finally, a solution of **KL¹** (500 mg, 0.81 mmol) in 50 mL of methanol was slowly added with stirring, upon which a yellow precipitate formed. Filtration and drying in vacuo yielded 279 mg (43%) of **5d** as a yellow powder, m.p. 200 °C. $C_{36}H_{32}BN_7O_4S_3Zn$ (799.09): calcd. C 54.11, H 4.04, N 12.27, S 12.04; found C 54.68, H 4.24, N 12.60, S 10.75. ^{1}H NMR ($CDCl_3$): δ = 2.51 [s, 3 H, Me(pz)], 3.82 (s, 6 H, OMe), 6.31 [s, 1 H, H(pz)], 6.92 [d, J = 2.1 Hz, 2 H, H(im)], 7.01 [d, J = 2.1 Hz, 2 H, H(im)], 7.35 (m, 11 H, Ar), 7.55 (d, J = 8.8 Hz, 2 H, $C_6H_4NO_2$), 7.83 (m, 2 H, Ar), 8.11 (d, J = 8.8 Hz, 2 H, $C_6H_4NO_2$) ppm.

Complex 5e: Prepared as **5d** from *N*-acetylhomocysteine ethyl ester (168 mg, 0.82 mmol), NaOH (21.7 mg, 0.82 mmol), $Zn(NO_3)_2{\cdot}4H_2O$ (214 mg, 0.82 mmol), and **KL¹** (506 mg, 0.82 mmol). Yield: 390 mg (56%) of **5e** as a colorless powder, m.p. 200 °C (dec.). $C_{38}H_{42}BN_7O_5S_3Zn$ (849.19): calcd. C 53.75, H 4.98, N 11.55, S 11.33; found C 53.62, H 4.84, N 11.75, S 11.46. ^{1}H NMR ([D_6]DMSO): δ = 1.15 [t, J = 6.8 Hz, 3 H, CH_3(Et)], 1.69–1.93 (m, 2 H, CH_2), 1.85 [s, 3 H, CH_3(Ac)], 2.45 [s, 3 H, CH_3(pz)], 2.65–2.76 (m, 2 H, CH_2), 3.78 (s, 6 H, OMe), 4.07 [q, J = 6.8 Hz, 2 H, CH_2(Et)], 4.31 (m, 1 H, CH), 6.47 [s, 1 H, H(pz)], 6.75–7.66 [m, 15 H, H(im) + Ar], 7.91 (m, 2 H, Ar), 8.13 (m, 1 H, NH) ppm.

Complex 6d: A solution of *p*-nitrothiophenol (33 mg, 0.20 mmol) in 30 mL of methanol was deprotonated with 0.8 mL of a 0.25 M solution of NaOH in methanol (0.20 mmol). This solution was slowly added dropwise, with stirring, to a solution of **KL²** (123 mg, 0.20 mmol) in 50 mL of methanol. The resulting yellow precipitate was filtered off and dried in vacuo to yield 81 mg (51%) of **6d** as a yellow powder, m.p. 225 °C (dec.). $C_{38}H_{36}BN_7O_2S_3Zn$ (795.15): calcd. C 57.40, H 4.56, N 12.33, S 12.10; found C 57.41, H 4.68, N 12.37, S 11.98. ^{1}H NMR ($CDCl_3$): δ = 1.89 [s, 6 H, Me(Ph)], 2.07 [s, 6 H, Me(Ph)], 2.43 [s, 3 H, Me(pz)], 6.34 [s, 1 H, H(pz)], 6.75 [d, J = 2.1 Hz, 2 H, H(im)], 6.93 (d, J = 9.0 Hz, 2 H, $C_6H_4NO_2$), 7.02 [d, J = 2.1 Hz, 2 H, H(im)], 7.09 (s, 1 H, Ar), 7.13 (s, 1 H, Ar), 7.19 (m, 7 H, Ar), 7.36 (m, 2 H, Ar), 7.46 (d, J = 9.0 Hz, 2 H, $C_6H_4NO_2$) ppm.

Methylation Reactions: Methyl iodide was used as a 1 M solution in chloroform. Equimolar amounts (0.1–0.2 mmol) of methyl iodide and one of the complexes **5** or **6** were combined in 5 mL of chloroform (for **5e** DMSO was used as the solvent). Reactions were followed by ^{1}H NMR spectroscopy and were found to produce the resulting thioethers quantitatively. After 10 min (**5a**, **5b**), 2 h (**5c, 5e**), or 1 d (**5d**, **6d**) the solvent was removed in vacuo. The residue was washed with two 3-mL portions of diethyl ether and then dried in vacuo. The remaining solid was pure **4a** or **4b**, as seen from the ^{1}H NMR spectrum. Of the resulting thioethers, CH_3SEt was found in the condensate and the others in the diethyl ether extracts, which also contained part of the iodide complexes **4**.

Complex **5a** (44 mg, 0.062 mmol) gave 45 mg (94%) of **4a**.

Complex **5b** (48 mg, 0.062 mmol) gave 43 mg (89%) of **4a**.

Complex **5c** (87 mg, 0.12 mmol) gave 70 mg (79%) of **4a**.

Complex **5d** (88 mg, 0.11 mmol) gave 54 mg (64%) of **4a**.

Complex **5e** (5.1 mg, 006 mmol) gave 2.5 mg (55%) of **4a**.

Complex **6d** (72 mg, 0.09 mmol) gave 33 mg (48%) of **4b**.

Kinetic Measurements: The standard solutions of complexes **5d** and **6d** and of methyl iodide in $CDCl_3$ (99.8%) were kept in the dark. All reagents and the cavity of the NMR spectrometer were thermostatted to 300.0 K before the measurements. The reagents were combined immediately prior to the measurements. The intensities of the ^{1}H NMR resonance of the SCH_3 protons of the resulting *p*-nitrothioanisole were recorded automatically every 100 s and stored for digital data processing. Each kinetic run was repeated once, and the averaged data were used for the calculations.

Table 1. Crystallographic details.

	HL²	**3b**	**4a**	**4b**	**5d**	**6d**
Empirical formula	$C_{32}H_{33}BN_6S_2 \cdot CH_3OH$	$C_{64}H_{64}B_2N_{12}S_4Zn \cdot 2H_2O$	$C_{30}H_{28}BIN_6O_2S_2Zn$	$C_{32}H_{32}BIN_6S_2Zn \cdot CH_2Cl_2$	$C_{36}H_{32}BN_7O_4S_3Zn \cdot \frac{1}{2}CH_3OH$	$C_{38}H_{36}BN_7O_2S_3Zn$
Molecular mass	576.60 + 32.04	1216.57 + 36.03	771.78	767.88 + 84.93	799.09 + 13.96	795.15
Crystal size [mm]	0.2×0.2×0.2	0.4×0.2×0.2	0.2×0.1×0.1	0.2×0.2×0.2	0.2×0.1×0.1	0.4×0.2×0.2
Space group	$P2_12_12_1$	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Z	4	2	4	2	4	2
a [Å]	13.630(3)	13.522(2)	11.662(3)	10.112(9)	12.863(2)	10.163(3)
b [Å]	14.235(3)	14.939(2)	13.804(3)	11.852(10)	13.359(3)	11.762(4)
c [Å]	16.681(4)	16.844(3)	20.201(5)	17.166(14)	23.601(5)	17.824(6)
α [°]	90	80.214(3)	90	90.30(1)	95.950(4)	90.908(6)
β [°]	90	83.039(3)	95.976(4)	105.71(1)	100.031(4)	102.198(7)
γ [°]	90	74.849(3)	90	108.49(1)	100.469(4)	110.860(6)
V [Å^3]	3236(1)	3226(1)	3234(1)	1869(2)	3888(1)	1936(1)
d(calcd.) [g cm^{-3}]	1.24	1.29	1.59	1.49	1.39	1.38
μ(Mo-K_α) [mm^{-1}]	0.20	0.56	1.88	1.77	0.84	0.84
hkl range	h: –17 to 18	h: –17 to 17	h: –15 to 15	h: –13 to 13	h: –15 to 15	h: –13 to 11
	k: –19 to 19	k: –19 to 20	k: –18 to 18	k: –15 to 16	k: –15 to 15	k: –15 to 15
	l: –21 to 22	l: –22 to 21	l: –26 to 26	l: –22 to 22	l: –28 to 28	l: –22 to 23
Measured reflections	29296	29306	28220	16947	28935	11567
Independent reflections	7863	15099	7780	8763	13656	8225
Observed refl. [$I > 2\sigma(I)$]	4858	6692	3014	5308	5949	3719
Parameters	396	801	388	415	954	469
Refined reflections	7863	15099	7780	8763	13656	8225
R_1 (obsd. reflections)	0.061	0.063	0.063	0.042	0.075	0.054
wR_2 (all reflections)	0.175	0.198	0.242	0.121	0.246	0.125
Resid. e$^-$ density [e Å^{-3}]	+0.6/–0.4	+0.9/–0.6	+0.8/–1.4	+1.1/–1.0	+1.7/–0.6	+0.6/–0.6

The initial concentration of **5d** was adjusted to 0.010 M for all seven measurements, during which the concentrations of CH_3I were 0.040, 0.050, 0.060, 0.070, 0.080, 0.090, and 0.100 M. The resulting k_{obs} values for these concentrations were 3.4, 4.0, 5.0, 5.7, 6.7, 7.5, and 8.2×10^{-4} s^{-1}, respectively.

The initial concentration of **6d** was adjusted to 0.033 for all five measurements, during which the concentrations of CH_3I were 0.167, 0.209, 0.251, 0.293, and 0.335. The resulting k_{obs} values for these concentrations were 2.3, 2.9, 3.7, 4.2, and 4.9×10^{-4} s^{-1}, respectively.

Structure Determinations:[32] Crystals of **HL²**, **3b**, and **5d** were obtained by cooling saturated CH_2Cl_2/CH_3OH solutions, those of **4a** by diffusion of toluene into a CH_2Cl_2 solution, and those of **4b** and **6d** by cooling saturated CH_2Cl_2/*n*-pentane solutions. Diffraction data were recorded at room temp. with a Bruker Smart CCD diffractometer. Empirical absorption corrections (SADABS) were applied. The structures were solved by direct methods and refined anisotropically using the SHELX program suite.[33] Hydrogen atoms were included with fixed distances and isotropic temperature factors 1.2-times those of their attached atoms. Parameters were refined against F^2. Drawings were produced with SCHAKAL.[34] Table 1 lists the crystallographic details.

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