Functional Modeling of Cobalamine-Independent Methionine Synthase with Pyrazolylborate−Zinc−Thiolate Complexes

Udo Brand, Michael Rombach, Jan Seebacher, and Heinrich Vahrenkamp*

Institut für Anorganische und Analytische Chemie der Universität Freiburg, Albertstrasse 21, D-79104 Freiburg, Germany

Received May 15, 2001

A series of new pyrazolylborate−zinc−thiolate complexes $Tp^{Ph,Me}Zn-SR$ and $Tp^{Me,Me}Zn-SR$, including two homocysteine derivatives, were prepared and structurally characterized. Their reactions with methyl iodide in nonpolar media resulted in the formation of the thioethers MeSR, including two methionine derivatives, and $Tp^{R',Me}Zn-I$ in all cases. Methylation of the thiolates could also be achieved with dimethyl sulfate and trimethylsulfonium iodide but not with trimethyl phosphate or *N*-methylpyridinium salts. The accumulated evidence indicates that the methylation occurs intramolecularly, i.e., at the zinc-bound thiolates: (i) The reactions occur readily in nonpolar media. (ii) Thiolate exchange at $Tp^{Ph,Me}Zn-SR$ with [PPN]SR′ is slower than thiolate alkylation. (iii) The methylation of $Tp^{Ph,Me}Zn-SBn$ with MeI is a clean second-order reaction with $k'' = 1.75 \times 10^{-2}$ M^{-1} s^{-1} at 300 K.

Introduction

Several zinc enzymes are known which catalyze the alkylation of biological thiol functions, among them the methionine synthases,[1,2] farnesyl transferase,[3] the Ada repair protein,[4] methanol−CoM−methyltransferase,[5] and betaine−homocysteine *S*-methyltransferase.[6] Most information in terms of structure and catalytic function has been gathered for the methionine synthases, and it has been shown that the substrate homocysteine gets bound to the catalytic zinc in the course of the enzymatic reaction.[2]

In those cases where cobalamine does not act as an alkyl group transfer agent, typically in cobalamine-independent methionine synthase, the zinc ion must activate the thiol substrate to such an extent that it reacts directly with methyltetrahydrofolate, i.e., a methylammonium salt which is the source of the methyl groups. This is initially effected by binding of the homocysteine to zinc as the thiolate,[2,7] the driving force for which lies in the high affinity between zinc and sulfur which makes possible the deprotonation of the thiol at neutral pH. It is an open question whether alkylation takes place at the zinc-bound or at the free anionic thiolate.

Model studies by coordination chemists were first published for the Ada repair protein using thiolatozincates, and it was found that in these compounds the thiolate dissociates from zinc prior to alkylation.[8] Subsequent studies by Darensbourg,[9] Parkin,[10] Carrano,[11] and Riordan,[12] employing uncharged zinc thiolate complexes and nonpolar solvents, have rendered it more likely that the thiolate is alkylated in the zinc-bound state. Evidence for this comes from a detailed kinetic study of the alkylation of thiophenolate in a nickel complex[13] and the fact that in some cases the thioethers resulting from alkylation are found as ligands in place of their thiolate precursors.[9,11] Very recently a detailed paper by Carrano[14] has verified and complemented the proposals and observations related to the thiolate alkylation in the zinc-bound state.

Our own contributions to this field arose from the observation that mononuclear zinc thiolate complexes with encapsulating pyrazolylborate (Tp*) ligands, including complexes of cysteine and even of hydrosulfide, are easily formed and quite stable.[15−19] Specifically their spontaneous formation from Tp*Zn−OH (our enzyme model[20]) and any X−SH compound at neutral pH[15−19] relates directly to the biological activation of thiols. This combined with our knowledge about the high nucleophilicity of the related Tp*Zn−OH or Tp*Zn−OR species[20] made us assume that the thiolates Tp*Zn−SR would be potent nucleophiles for thiolytic cleavage reactions and for reactions with alkylating agents. While the former could not be verified so far (cf. ref 19), the latter worked well and has established the

(1) Matthews, R. G.; Goulding, C. W. *Curr. Opin. Chem. Biol.* **1997**, *1*, 332.
(2) For the most recent summary, see: Peariso, K.; Zhou, S.; Smith, A. E.; Matthews, R. G.; Penner-Hahn, J. E. *Biochemistry* **2001**, *40*, 987.
(3) Park, H. W.; Boduluri, S. R.; Moomaw, J. F.; Casey, P. J.; Beese, L. S. *Science* **1997**, *275*, 1800.
(4) Myers, L. C.; Terranova, M. P.; Ferentz, A. E.; Wagner, G.; Verdine, G. L. *Science* **1993**, *261*, 1164.
(5) Sauer, K.; Thauer, R. K. *Eur. J. Biochem.* **1997**, *249*, 280.
(6) Breksa, A. P.; Garrow, T. A. *Biochemistry* **1999**, *38*, 13991.
(7) Peariso, K.; Goulding, C. W.; Huang, S.; Matthews, R. G.; Penner-Hahn, J. E. *J. Am. Chem. Soc.* **1998**, *120*, 8410.
(8) Wilker, J. J.; Lippard, S. *Inorg. Chem.* **1997**, *36*, 969.
(9) Grapperhaus, C. A.; Tuntulani, T.; Reibenspies, J. H.; Darensbourg, M. Y. *Inorg. Chem.* **1998**, *37*, 4052.
(10) Bridgewater, B. M.; Fillebeen, T.; Friesner, R. A.; Parkin, G. *J. Chem. Soc., Dalton Trans.* **2000**, 4494.
(11) Hammes, B. S.; Carrano, C. J. *Inorg. Chem.* **2001**, *40*, 919 and references therein.
(12) Chiou, S. J.; Innocent, J.; Riordan, C. G.; Lam, K. C.; Liable-Sands, L.; Rheingold, A. L. *Inorg. Chem.* **2000**, *39*, 4347.
(13) Ram, M. S.; Riordan, C. G.; Ostrander, R.; Rheingold, A. L. *Inorg. Chem.* **1995**, *34*, 5884.
(14) Warthen, C. R.; Hammes, B. S.; Carrano, C. J.; Crans, D. C. *J. Biol. Inorg. Chem.* **2001**, *6*, 82.
(15) Alsfasser, R.; Powell, A. K.; Trofimenko, S.; Vahrenkamp, H. *Chem. Ber.* **1993**, *126*, 685.
(16) Ruf, M.; Vahrenkamp, H. *Inorg. Chem.* **1996**, *35*, 6571.
(17) Ruf, M.: Burth, R.; Weis, K.; Vahrenkamp, H. *Chem. Ber.* **1996**, *129*, 1251.
(18) Burth, R.; Vahrenkamp, H. *Z. Anorg. Allg. Chem.* **1998**, *624*, 381.
(19) Rombach, M.; Vahrenkamp, H. *Inorg. Chem.* **2001**, *40*, 6144.
(20) Vahrenkamp, H. *Acc. Chem. Res.* **1999**, *32*, 589.

10.1021/ic0105112 CCC: $20.00 © 2001 American Chemical Society
Published on Web 10/26/2001

Tp*Zn−OH → Tp*Zn−SR → MeSR sequence as a functional model for the action of cobalamine-independent methionine synthese.[21] This paper reports examples for both steps of this sequence and presents evidence for the intramolecular alkylation of the zinc-bound thiolates.

Results and Discussion

Starting Materials. Two substituted pyrazolylborate ligands, $Tp^{Ph,Me}$ and $Tp^{Me,Me}$, were chosen for the interconversion reactions of their Tp*Zn complexes. Of them, only $Tp^{Ph,Me}$ allows the formation of the "natural" starting material, the hydroxide complex **1**.[17] In case of $Tp^{Me,Me}$ the chloride complex **2** had to be used which resulted in very good yields from $ZnCl_2$ and $KTp^{Me,Me}$, in analogy to the known complex $Tp^{Me,Me}Zn-I$.[22]

$Tp^{Ph,Me}Zn\text{-}OH$ (**1**) $\qquad$ $Tp^{Me,Me}Zn\text{-}Cl$ (**2**)

Thiolate Complexes. We had already shown that all kinds of HSX compounds react with Tp*Zn−OH to form the corresponding Tp*Zn−SX species.[16−19] This was verified here for **1** by reaction with ethyl mercaptan, isobutyl mercaptan, benzyl mercaptan, and thiophenol, resulting in the thiolate complexes **3a**−**d**. The only other product of these reactions is water. They occur fast and quantitatively at neutral pH and, hence, are viable models for the activation of thiols by zinc enzymes under physiological conditions.

$Tp^{Ph,Me}Zn\text{-}SR$

3a: R = C_2H_5, **3b**: R = i-C_4H_9, **3c**: R = $CH_2C_6H_5$, **3d**: R = C_6H_5

That this is really the case was shown by applying the reactions to homocysteine itself, first in the *O*-ethyl and *N*-acetyl protected form H[HCys(OEt)(NAc)] and second in the unprotected form H_2[HCys]. In the first case the "simple" thiolate complex **4** resulted. In the second case both the carboxyl and the thiol function underwent reaction with the Zn−OH function, and the dinuclear complex **5** was formed.

$Tp^{Ph,Me}Zn\text{-}HCys(OEt)(NAc)$ (**4**) $\qquad$ $Tp^{Ph,Me}Zn\text{-}HCys\text{-}ZnTp^{Ph,Me}$ (**5**)

Complex **2** was converted to the thiolate complexes **6a,b** by treating it with sodium ethyl mercaptide and sodium benzyl mercaptide. The yields were good again. Unlike the elusive complex $Tp^{Me,Me}Zn-OH$ which is unstable with respect to Zn-$(OH)_2$ elimination and formation of $(Tp^{Me,Me})_2Zn$, **6a,b** are easy to handle and have no tendency to undergo degradation reactions with formation of thiolate bridged oligonuclear zinc complexes.

$Tp^{Me,Me}Zn\text{-}SR$

6a: R = C_2H_5, **6b**: R = $CH_2C_6H_5$

Structures. Of the simple thiolate complexes, **3b,d** were subjected to structure determinations. Figure 1, showing **3b**, is a representative drawing. The structure of **3d** is documented in the Supporting Information. As usual for this type of compounds,[15−19] the N_3ZnS unit is trigonally distorted tetrahedral, and the Zn−S bond lengths are in the very narrow range of 2.22−2.24 Å.

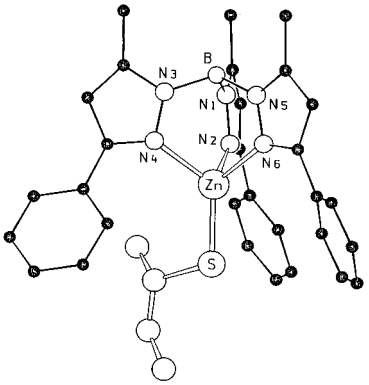


Figure 1. Molecular structure of **3b**. Bond lengths (Å): Zn−N1, 2.067-(2); Zn−N2, 2.077(2); Zn−N3, 2.085(3); Zn−S, 2.230(1). Bond angles (deg): N1−Zn−S, 125.6(1); N2−Zn−S, 123.2(1); N3−Zn−S, 123.9-(1).

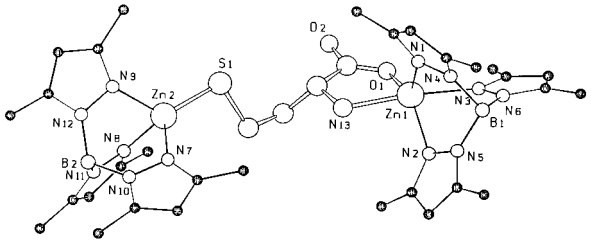


Figure 2. Molecular structure of the dinuclear homocysteine complex **5** (phenyl groups omitted for clarity). Bond lengths (Å): Zn1−N1, 2.052(3); Zn1−N2, 2.106(3); Zn1−N3, 2.127(3); Zn1−N13, 2.143-(3); Zn1−O1, 1.985(3); Zn2−N7, 2.059(3); Zn2−N8, 2.081(3); Zn2−N9, 2.037(3); Zn2−S, 2.183(1).

It can be assumed that the structure of the strictly S-functional homocysteinate complex **4** is analogous to those of **3b,d**, having the zinc ion in a N_3ZnS environment, as was also proved for the $Tp^{Cum,Me}Zn$ complex of O- and N-protected cysteine.[17] In contrast, unprotected, i.e., trifunctional, homocysteine offers various modes of attachment to Tp*Zn units. The structure determination of **5**, see Figure 2, showed that the most plausible ones of them are realized. The thiolate function acts as a monodentate ligand yielding the usual symmetrical N_3ZnS environment of the zinc ion in its $Tp^{Ph,Me}Zn$ unit. It does not combine with the amino function to become a N,S chelate ligand like in the $Tp^{Cum,Me}Zn$−cysteine complex[17] because this would involve a six-membered chelate ring. Instead the amino function combines with the carboxylate function as a N,O chelate ligand, forming a five-membered chelate ring with the zinc ion of the other $Tp^{Ph,Me}Zn$ unit. While this type of chelation is hithero unobserved in Tp*Zn chemistry, it is common in binary amino acid zinc complexes such as $Zn(Gly)_2$,[24] $Zn(Leu)_2$,[25] or Zn-$(Met)_2$.[26] The environment of the five-coordinate zinc ion in **5** is severely distorted trigonal-bipyramidal, with N3 and N13 in the axial positions, spanning a N−Zn−N angle of 173°.

Alkylation with Methyl Iodide. All eight thiolate complexes reacted with methyl iodide acording to eq 1. The reactions took

(21) A preliminary report of this work has been published: Brand, U.; Rombach, M.; Vahrenkamp, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2717.

(22) Rheingold, A. L.; Ostrander, R. L.; Haggerty, B. S.; Trofimenko, S. *Inorg. Chem.* **1994**, *33*, 3666.

(23) Rombach, M.; Maurer, C.; Weis, K.; Keller, E.; Vahrenkamp, H. *Chem. Eur. J.* **1999**, *5*, 1013.

(24) Newman, J. M.; Bear, C. A.; Hambley, T. W.; Freeman, H. C. *Acta Crstallogr., Sect. C* **1990**, *C46*, 44.

(25) Steren, C. A.; Calvo, R.; Piro, O. E.; Rivero, B. E. *Inorg. Chem.* **1989**, *28*, 1933.

(26) Wilson, R. B.; Meester, P.; Hodgson, D. J. *Inorg. Chem.* **1977**, *16*, 1498.

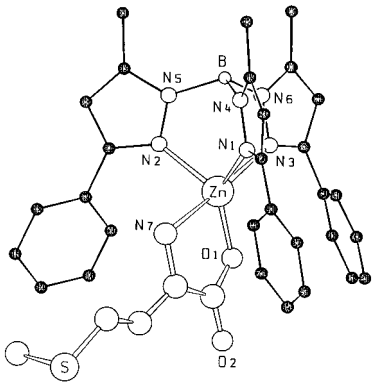


Figure 3. Molecular structure of complex **7**. Bond lengths (Å): Zn−N1, 2.032(4); Zn−N2, 2.060(4); Zn−N3, 2.250(4); Zn−N7, 2.214(4); Zn−O1, 1.933(3).

place in dichloromethane or chloroform at room temperature and were essentially quantitative according to ^{1}H NMR. Those of the alkanethiolates **3a,b** were the fastest. On a millimolar scale they went to completion within minutes. The benzyl and phenyl mercaptides **3c,d** were slower by a factor of 10−20. When the Tp^{Ph,Me}-derived thiolates **3a,c** are compared with the corresponding Tp^{Me,Me} derived thiolates **6a**,**b**, the latter were slower by a factor of about 10. The homocysteine-derived complexes **4** and **5** showed the slowest reactions, needing about 0.5 day on a millimolar scale to come to completion.

$$\text{Tp*Zn}-\text{SR} + \text{MeI} \rightarrow \text{Tp*Zn}-\text{I} + \text{MeSR} \qquad (1)$$

The resulting methyl thioethers were identified by their known ^{1}H NMR spectra. In case of **3a,c**, **5**, and **6a,b** the methyl iodide reactions were run on a preparative scale. The Tp*Zn−I complex was isolated in each case in good yields by crystallization. While the resulting methyl thioethers were normally removed with the volatiles, in case of the reaction of the dinuclear complex **5** the methyl thioether is methionine which is still bound to a Tp^{Ph,Me}Zn unit. This facilitated its isolation as complex **7**. The structure determination of **7** (see Figure 3) has confirmed this and leaves no doubt about the uncoordinated nature of the thioether function. The chelating coordination of the amino and carboxylate functions of methionine to zinc in complex **7** is completely analogous to the situation in complex **5**. This time N3 and N7 define the axial positions of the distorted trigonal bipyramid with a N−Zn−N angle of 177°.

Tp^{Ph,Me}Zn-HCys(SMe)
7

The sequence of thiolate reactivities at the Tp^{Ph,Me}Zn unit (alkyl > aryl > HCys) can be explained by steric and electronic effects. Alkanethiolates are stronger nucleophiles than arenethiolates, and the steric hindrance, i.e., the congestion around the sulfur atom in the complex, rises along the series. Specifically in the O- and N-protected homocysteine complex or in the dinuclear complex the accessibility of the zinc-bound thiolate functions should be severely reduced. The second Tp^{Ph,Me}Zn unit in complex **5** in addition to being a protective group for the amino and carboxylate groups is also an electron-withdrawing substituent which further reduces the nucleophilicity of the homocysteine thiolate function. In contrast, we do not see a convincing explanation for the fact that the Tp^{Me,Me}Zn−thiolates react slower than the Tp^{Ph,Me}Zn−thiolates. Possibly the higher hydrophobicity around zinc in the Tp^{Ph,Me} complexes due to encapsulation by the phenyl groups outweighs their lower accessibility due to steric hindrance by the same phenyl groups as a rate-determining factor. The alternative explanation, the release of the thiolate ligands as thiolate anions prior to alkylation (which should be more facile for the more crowded Tp^{Ph,Me}Zn−SR complexes), is not viable in our opinion, for the reasons outlined below in the discussion of the kinetic study.

It can be assumed that part of the driving force for the methylations by methyl iodide results from the affinity between Tp*Zn units and soft anionic ligands, in this case the iodide ion. However, the poor donor qualities of the resulting thioethers are at least equally important. Until now zinc complexes of nonchelating thioethers are unknown, and, more importantly, Tp*Zn units go along with uncharged coligands only when these are very good donors and only when the necessary anions are of the lowest donor strength.[17,27] On the other hand it has been an important mechanistic observation that methylation of chelating thiolates in zinc complexes can produce thioethers which are still zinc-bound.[9,11] This together with the evidence presented below is an argument in favor of the main conclusion of this paper, namely that the alkylation occurs at the zinc-bound thiolates.

Alkylations with Dimethyl Sulfate. Dimethyl sulfate is known to be a stronger alkylating agent than methyl iodide, and it is a closer relative than CH_3I to the alkyl phosphates which are actually used by zinc-containing enzymes for biological alkylations.[4] We therefore used it for methylation reactions of the simple thiolate complexes **3a**−**d** and **6a,b**. The reactions were slower than the methyl iodide reactions, and they were neither clean nor quantitative. ^{1}H NMR spectroscopy confirmed in all cases that the appropriate methyl thioethers were formed. But the fate of the remaining methyl sulfate anions was not clearly obvious. In case of the Tp^{Ph,Me}Zn−SR complexes **3a**−**d** the primary zinc complex seems to be the methyl sulfate complex **8**, as evidenced by appropriate ^{1}H NMR resonances for the Tp^{Ph,Me} ligand and a O−CH_3 resonance which is about 1 ppm upfield from that of dimethyl sulfate, thereby indicating in a typical fashion the embedding of the OSO_2OMe ligand between the phenyl groups of the Tp^{Ph,Me} ligand. However, we failed to isolate this complex in a pure form, in line with the elusive nature of Tp*Zn−sulfate or −organosulfate complexes.[28]

Tp^{Ph,Me}Zn-OSO$_2$OMe
8

(Tp^{Me,Me})$_2$Zn
9

The dimethyl sulfate reactions of the Tp^{Me,Me}Zn−thiolates **6a,b** did not yield good evidence for the formation of a Tp*Zn−methyl sulfate complex, mainly because the Tp^{Me,Me} ligands lack the high-field shift effect for the ^{1}H NMR resonances of the Zn−X coligands. Instead, in addition to the formation of the free thioethers that of the bis-ligand complex **9** was observed. **9** is known to be a dismutation product of unstable Tp^{Me,Me}Zn−X complexes.[31] It could be isolated from both reactions in about 50% yield.

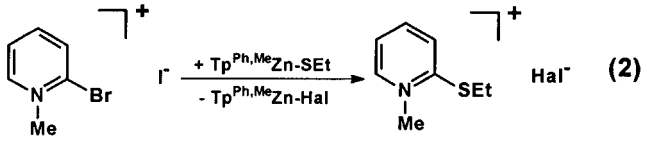
Both the slower speed and the less clean nature of the dimethyl sulfate reactions as compared to the methyl iodide reactions can be related to the improper nature of both the thioethers and the methyl sulfate ions as ligands for zinc. Methyl sulfate has only a slightly stronger tendency to be bound to

(27) Bergquist, C.; Parkin, G. *J. Am. Chem. Soc.* **1999**, *121*, 6322.
(28) Unpublished work by H. Vahrenkamp et al. Complexes of the type Tp*Zn−OSO_2R have, however, been described.[29]
(29) Brandsch, T.; Schell, F. A.; Weis, K.; Ruf, M.; Müller, B.; Vahrenkamp, H. *Chem. Ber.* **1997**, *130*, 283.
(30) Weis, K.; Vahrenkamp, H. *Eur. J. Inorg. Chem.* **1998**, 271.
(31) Looney, A.; Han, R.; Gorell, I. B.; Cornebise, M.; Yoon, K.; Parkin, G.; Rheingold, A. L. *Organometallics* **1995**, *14*, 274.

zinc than the thioethers, and hence, a reaction course analogous to eq 1 is not favored. Furthermore, if as proposed below the alkylation is an intramolecular process, the Zn−OSO_2OMe bond making is less efficient than the Zn−I bond making as a rate-determining factor, and hence, the dimethyl sulfate reactions should be less facile than the methyl iodide reactions.

Other Alkylating Reagents. To ensure even more "natural" reaction conditions we tried to react our Tp*Zn−SR complexes with other methylating agents. We used trimethyl phosphate (as a mimic of the organophosphates in the Ada repair process[4]), trimethylsulfonium iodide (as a mimic of *S*-adenosyl methionine in the *S*-methyltransferases[6]), and *N*-methylpyridinium salts (as mimics for tetrahydrofolate in the enzymatic methionine synthesis[1]). We found trimethyl phosphate to be nonreactive even with our most active thiolate complex **3a**. Neither did *N*-methylpyridinium iodide react with **3a**, not even upon proplonged refluxing in the more polar solvent acetonitrile.

Trimethylsulfonium iodide did, however, react with **3a** in boiling acetonitrile. The resulting thioether MeSEt was again identified by its ^{1}H NMR spectrum, and the resulting complex $Tp^{Ph,Me}$Zn−I was isolated in high yield. When 2-bromo-*N*-methylpyridinium iodide, which is a stronger electrophile than *N*-methylpyridinium iodide, was applied as an alkylating agent for **3a**, a reaction occurred which, however, took an unexpected course. Instead of transfer of the N-bound methyl group, the whole aromatic system was transferred by substitution of the bromide substituent according to eq 2, and the remaining zinc species was a mixture of $Tp^{Ph,Me}$Zn−Br and $Tp^{Ph,Me}$Zn−I.



(2)

While these reactions show that ionic alkylating agents are suitable for the Tp*Zn−SR complexes and that the latter can even attack aromatic halides, they did not fulfill our expectations. Complex **3a** was not reactive enough to attack the biorelevant substrates of the organophosphate or methylammonium types. It therefore remains a challenge to modify the Tp* ligands or to find better ligands for zinc to achieve this.

Kinetic Study. As observed above, the alkylations by methyl iodide are clean and quantitative and hence suitable for a kinetic analysis. The methylation of the benzyl mercaptide complex **3c** was chosen for this purpose because it occurs in a time frame which is convenient for NMR monitoring. **3c** was treated under pseudo-first-order conditions with a 5- to 10-fold excess of CH_3I in $CDCl_3$ at 300 K. The intensities of four sets of ^{1}H NMR signals were recorded for 5 $t_{1/2}$ intervals; see Figure 4. Thus four data sets were available to obtain the pseudo-first-order rate constants according to $\ln(I_t - I_o) = \ln(I_\infty - I_o) - k_{obs}t$.

The log plots for six different excess concentrations of CH_3I are linear with correlation coefficients > 0.995 (see Supporting Information). The resulting k_{obs} values, plotted against the CH_3I concentration (see Supporting Information), define a regression line which passes through the origin with a correlation coefficient of 0.987. The second-order rate constant, obtained according to $k_{obs} = k''[CH_3I]$, resulted as $k'' = 1.75 \times 10^{-2}$ M^{-1} s^{-1}.

The clean second-order reaction is an argument in favor of the intramolecular nature of the alkylation process. It does, however, not prove it, as a dissociation equilibrium involving free anionic thiolate may result in the same kinetic behavior. The rate constant observed here for benzyl mercaptide alkylation

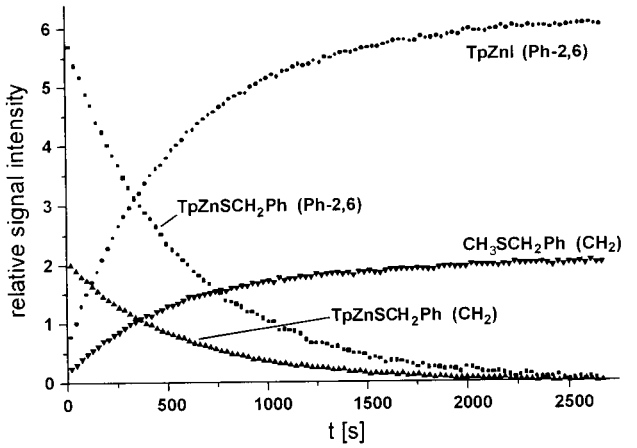


Figure 4. Intensities of selected ^{1}H NMR signals of $Tp^{Ph,Me}Zn-SCH_2C_6H_5$ (**3c**), $Tp^{Ph,Me}Zn-I$, and $CH_3SCH_2C_6H_5$ (MeSBn) in $CDCl_3$ at 300 K for starting concentrations of 0.02 M for **3c** and 0.10 M for CH_3I.

is about 20 times as high as that for the alkylation of the SH group in $Tp^{Ph,Me}Zn-SH$ under the same conditions.[19] This can be explained by the higher basicity of benzyl mercaptide, as reflected by the pK_a values of H_2S (7.2) and $C_6H_5CH_2SH$ (10.9). The only other comparable rate constant is that for the methylation of thiophenolate in $[Zn(SPh)_4]^{2-}$ by $PO(OMe)_3$ in DMSO at 24.5 °C, for which a dissociative mechanism was proposed and the k'' value was 1.6×10^{-2} M^{-1} s^{-1}.[8] Accidentally, this value is almost identical to the one observed here for a completely different set of reagents and reaction conditions.

We propose that the alkylation of Tp*Zn−SR by CH_3I is an intramolecular process. Hence it might be mechanistically equivalent to the formation of trialkylsulfonium salts from R_2S and R′I. This is borne out by the second-order rate constants for R_2S/MeI reactions at 25 °C in methanol which have the same order of magnitude as the one reported here.[32] In contrast, reactions of methyl iodide with anionic sulfur nucleophiles (thiolates, sulfite, thiosulfate) are several orders of magnitude faster.[32]

The standard process of nucleophilic substitution with methyl iodide liberates anionic iodide. This may not necessarily be the case for the methylations of the Tp*Zn−SR complexes. Here a fully concerted process may involve a Zn−S/C−I intermediate, e.g. a four-center transition state as proposed for the Zn−O/E−O situation in hydrolytic cleavages of RE(O)−X substrates by Tp*Zn−OH.[23] Such a fully concerted process would involve intramolecular transfer of iodide as well, avoiding the stepwise reaction sequence of releasing anionic iodide, solvating it in the nonpolar medium, and replacing the zinc-bound thioether ligand by it. In addition to the nonpolar reaction conditions, one other observation is in favor of this mechanistic proposal: the methylations of the more sterically hindered $Tp^{Ph,Me}Zn-SR$ complexes are faster than the ones of the $Tp^{Me,Me}Zn-SR$ complexes. This, as mentioned above, may involve a more favorable placement and interconversion of the CH_3I molecule inside the hydrophobic cavity created by the three phenyl groups around the Zn−SR center.

Thiolate Exchange. One further observation in favor of the intramolecular nature of the thiolate alkylation was made by studying thiolate exchange reactions. Assuming the release of free anionic thiolate prior to the alkylation, one should also

(32) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

assume that the Tp*Zn−SR complexes undergo thiolate exchange when exposed to anionic thiolates in solution, with rates comparable to those of the alkylations. This could be tested for the $Tp^{Ph,Me}Zn-SR$ complexes, because the high-field NMR shifts of their SCH_2 protons inside the aromatic cavity of the $Tp^{Ph,Me}$ ligands allow a facile distinction of free and zinc-bound thiolates by NMR methods.

With this in mind, the chloroform-soluble PPN thiolates of ethyl and benzyl mercaptan were prepared by cation metathesis.[33] Then solutions of **3a,c** of the same concentration as that for the kinetic measurements were treated with $PPN[SCH_2C_6H_5]$ (**3a**) and $PPN[SC_2H_5]$ (**3c**), respectively, using equimolar amounts or an up to 10-fold excess of the PPN thiolates. Whereas the methylations under these conditions needed between 1 min and 1 h to go to completion, the thiolate exchange reactions took between 10 h and 3 days. Thus, they are between 10 and 100 times slower than the alkylation with methyl iodide. The 1:1 combinations of Tp*Zn−SR and PPN[SR′] produced equilibrium mixtures in which the SC_2H_5 complexes are preferred. A 10-fold excess of the PPN thiolates resulted in complete thiolate exchange.

The low rates of thiolate exchange as compared to thiolate alkylation allow a straightforward interpretation: both the existence of relevant equilibrium concentrations of free thiolate and the release of free thiolate at relevant rates in solutions of the Tp*Zn-thiolate complexes are ruled out. This is another, and in our eyes the strongest, argument in favor of the intramolecular nature of the thiolate alkylations.

Conclusions

This paper has shown that essential steps and key intermediates of thiolate alkylations by zinc enzymes, specifically the action of cobalamine-independent methionine synthase can be modeled by (pyrazolylborato)zinc complexes. Thiol activation is represented by the attachment to zinc as thiolate, occurring at neutral pH by reaction between Tp*Zn−OH and HSR with release of water. Methylation of the zinc-bound thiolates occurs with various methylating agents. It produces the free methyl thioether, and the anionic constituent of the methylating agent gets bound to zinc. The reaction sequence could be applied to homocysteine, providing a chemical model for the methionine synthase process.

The driving force for the alkylation reactions lies both in the high nucleophilicity of the zinc-bound thiolates and in the low donor qualities of the resulting thioethers for zinc. The nonphysiological alkylating agents applied here provide another part of the driving force by the high affinity between zinc and their anionic constituents. The "dead end" in the form of the Tp*Zn−X products is also the reason the reaction sequence Tp*Zn−OH → Tp*Zn−SR → MeSR is stoichiometric and not catalytic in its present form.

Mechanistic evidence was collected supporting the intramolecular nature of the alkylation reaction, i.e., the noninvolvement of free anionic thiolate. The major pieces of evidence are (i) the occurrence of the alkylations in completely nonpolar media, i.e., lack of solvation of intermediate anionic species, (ii) the clean second-order kinetics for the methylation of $Tp^{Ph,Me}Zn-SCH_2C_6H_5$ by methyl iodide, and (iii) the fact that thiolate exchange between Tp*Zn−SR and PPN[SR′] is more than 1 order of magnitude slower than alkylation of Tp*Zn−SR.

With the given set of pyrazolylborate ligands and alkylating agents this study has reached its goals. But substantial challenges remain on the way to a more biorelevant model system which would have to be catalytic and have to use the milder alkylating agents applied by Nature. And it should also be worth the efforts of the experts to verify or falsify our suggestion of a four-center process for a nucleophilic substitution at methyl iodide.

Experimental Section

General Data. All experimental techniques and the standard IR and NMR equipment were as described previously.[34] Starting materials were obtained commercially. $Tp^{Ph,Me}Zn-OH$,[17] H[HCys(OEt)(NAc)],[35] 2-bromo-*N*-methylpyridinium iodide,[36] and the PPN salts of ethyl and benzyl mercaptan[33] were prepared as described.

Preparations. $Tp^{Me,Me}Zn-Cl$ (2). A solution of $KTp^{Me,Me}$ (340 mg, 1.01 mmol) in methanol (20 mL) was added to a solution of $ZnCl_2 \cdot 2H_2O$ (170 mg, 1.01 mmol) and NH_4Cl (108 mg, 2.02 mmol) in methanol/water (9:1, 20 mL) and stirred for 2 h. A 50 mL volume of dichloromethane was added, and the mixture was filtered over Celite and slowly evacuated to 10 mL. The resulting precipitate was filtered off, washed with methanol, and dried in vacuo, yielding 347 mg (86%) of **2** as a colorless microcrystalline material, mp 300 °C (dec): ν(BH) 2541 cm^{-1}; ^1H NMR ($CDCl_3$) 2.29 [s, 18H, Me], 5.68 ppm [s, 3H, H(pz)].

Anal. Calcd for $C_{15}H_{22}BClN_6Zn$ (M_r = 398.1): C, 45.26; H, 5.57; N, 21.11. Found: C, 45.80; H, 5.57; N, 21.32.

$Tp^{Ph,Me}Zn-SEt$ (3a). A solution of **1** (110 mg, 0.19 mmol) in dichloromethane (20 mL) was treated with 20 μL (0.27 mmol) ethanethiol and stirred for 2 h. After evaporation to 10 mL and layering with methanol, 84 mg (71%) of **3a**[18] was slowly separated as colorless crystals, mp 270 °C (dec).

$Tp^{Ph,Me}Zn-S\text{-}i\text{-}C_4H_9$ (3b). A solution of **1** (141 mg, 0.25 mmol) in dichloromethane was treated with a soltion of 2-butyl mercaptan (22.5 mg, 0.25 mmol) in dichloromethane (10 mL) and stirred for 24 h. After evacuation to dryness the residue was recrystallized from dichloromethane/acetonitrile (1:1), yielding 97 mg (61%) of **3b** as colorless crystals, mp 240 °C (dec): ν(BH) 2549 cm^{-1}; ^1H NMR ($CDCl_3$) 0.20 [m, 6H, CH_3(i-Bu)], 0.38 [m, 1H, CH(i-Bu)], 0.90 [m, 2H, CH_2(i-Bu)], 2.54 [s, 9H, Me(pz)], 6.18 [s, 3H, H(pz)], 7.37 [m, 9H, Ph], 7.69 ppm [m, 6H, Ph].

Anal. Calcd for $C_{34}H_{37}BN_6SZn$ (M_r = 638.0): C, 64.01; H, 5.85; N, 13.58; S, 5.03. Found: C, 63.80; H, 5.99; N, 13.12; S, 4.94.

$Tp^{Ph,Me}Zn-SCH_2C_6H_5$ (3c). This was made by a procedure similar to that for **3b** from **1** (110 mg, 0.19 mmol) and benzyl mercaptan (25 mg, 0.20 mmol): yield 97 mg (76%) of **3c**[18] as colorless crystals, mp 212 °C.

$Tp^{Ph,Me}Zn-SC_6H_5$ (3d). This was made by a procedure similar to that for **3b** from **1** (151 mg, 0.27 mmol) and thiophenol (29 mg, 0.27 mmol): yield 90 mg (51%) of **3d** as colorless crystals, mp 238 °C; ν(BH) 2550 cm^{-1}; ^1H NMR ($CDCl_3$) 2.56 [s, 9H, Me(pz)], 6.19 [s, 3H, H(pz)], 6.36 [m, 5H, SPh], 7.10 [m, 9H, Ph], 7.62 ppm [m, 6H, Ph].

Anal. Calcd for $C_{36}H_{33}BN_6SZn$ (M_r = 658.0): C, 65.72; H, 5.06; N, 12.77; S, 4.87. Found: C, 65.57; H, 5.07; N, 12.73; S, 4.68.

$Tp^{Ph,Me}Zn-HCys(OEt)(NAc)$ (4). A solution of *N*-acetylhomocysteine ethyl ester (60 mg, 0.29 mmol) in dichloromethane (10 mL) was added to a solution of **1** (165 mg, 0.29 mmol) in dichloromethane (10 mL). After the solution was stirring for 1 day, the volatiles were removed in vacuo and the residue recrystallized from dichloromethane/methanol (1:1), yielding 117 mg (53%) of **4** as a light yellow powder, mp 165 °C (dec): IR (KBr) ν = 3310 m (NH), 2534 w (BH), 1650 vs (amide I), 1546 s cm^{-1} (amide II); ^1H NMR ($CDCl_3$) 1.05 [m, 4H, CH_2], 1.08 [t, J = 7.1 Hz, 3H, CH_3(Et)], 1.85 [s, 3H, Ac], 2.54 [s, 9H,

(33) Law, W. F.; Kim, C.; Darensbourg, M. Y.; Rheingold, A. L. *J. Am. Chem. Soc.* **1989**, *111*, 3591.

(34) Förster, M.; Burth, R.; Powell, A. K.; Eiche, T.; Vahrenkamp, H. *Chem. Ber.* **1993**, *126*, 2643.

(35) Serafinowski, P.; Dorland, E.; Harrap, K. R.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 4576.

(36) Saigo, K.; Usui, M.; Kikuchi, K.; Shimada, E.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1863.

Me(pz)], 3.72 [m, 1H, NCH], 4.01 [q, $J = 7.1$ Hz, 2H, CH_2(Et)], 5.22 [m, 1H, NH], 6.19 [s, 3H, H(pz)], 7.40 [m, 9H, Ph], 7.69 ppm [m, 6H, Ph].

$Tp^{Ph,Me}Zn-HCys-ZnTp^{Ph,Me}$ (5). A solution of **1** (250 mg, 0.44 mmol) in dichloromethane/ethanol (1:2, 30 mL) was treated with a suspension of D,L-homocysteine (30 mg, 0.22 mmol) in dichloromethane (10 mL) and stirred for 16 h. After filtration and evacuation to dryness the residue was dissolved in *n*-heptane/dichloromethane (4:1, 10 mL). Slow evaporation in an open vessel yielded 230 mg (82%) of **5** as colorless crystals, mp 200 °C, which were filtered off and washed with methanol: IR (KBr) $\nu = 3364$ m (NH), 2546 m (BH), 1658 s (CO), 1605 s cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) −0.55 [m, 1H, CH], 0.18 [m, 3H, CH, NH_2], 0.45 [m, 1H, CH], 1.22 [m, 1H, CH], 1.65 [m, 1H, CH], 1.94 [s, 4H, H_2O], 2.53 [s, 9H, Me(pz)], 2.58 [s, 9H, Me(pz)], 6.16 [s, 3H, H(pz)], 6.21 [s, 3H, H(pz)], 6.89 [t, $J = 7.4$ Hz, 3H, Ph(para)], 7.20 [m, 15H, Ph], 7.50 [m, 6H, Ph], 7.61 ppm [m, 6H, Ph].

Anal. Calcd for $C_{64}H_{63}B_2N_{13}O_2SZn_2 \cdot 2H_2O$ ($M_r = 1230.8 + 36.0$): C, 60.68; H, 5.33; N, 14.37; S, 2.53. Found: C, 60.69; H, 5.40; N, 14.33; S, 2.43.

$Tp^{Me,Me}Zn-SC_2H_5$ (6a). A solution of **2** (687 mg, 1.70 mmol) in dichloromethane (130 mL) was treated with a solution of NaOH (73 mg, 1.8 mmol) and ethanethiol (110 mg, 1.8 mmol) in methanol (20 mL) and stirred for 14 h. After filtration over Celite the solution was evacuated to 10 mL, yielding a precipitate of 456 mg (63%) of **6a** as a colorless powder, mp 235 °C (dec): ν(BH) 2516 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.38 [t, $J = 7.2$ Hz, 3H, CH_3(Et)], 2.26 [s, 9H, Me(pz)], 2.29 [s, 9H, Me(pz)], 2.77 [q, $J = 7.2$ Hz, 2H, CH_2(Et)], 5.66 ppm [s, 3H, H(pz)].

Anal. Calcd for $C_{17}H_{27}BN_6SZn$ ($M_r = 423.7$): C, 48.19; H, 6.42; N, 19.83; Zn, 15.43. Found: C, 47.57; H, 6.26; N, 18.88; Zn, 15.04.

$Tp^{Me,Me}Zn-SCH_2C_6H_5$ (6b). This was made by a procedure similar to that for **6a** from **2** (345 mg, 0.87 mmol), NaOH (38 mg, 0.95 mmol), and benzyl mercaptan (111 mg, 0.89 mmol): yield 368 mg (87%) of **6b** as a colorless powder, mp 250 °C (dec); ν(BH) 2517 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.23 [s, 9H, Me(pz)], 2.29 [s, 9H, Me(pz)], 3.95 [s, 2H, SCH_2], 5.66 [s, 3H, H(pz)], 7.21 [m, 3h, Ph], 7.39 ppm [d, $J = 7.1$ Hz, 2H, Ph].

Anal. Calcd for $C_{22}H_{29}BN_6SZn$ ($M_r = 485.8$): C, 54.40; H, 6.02; N, 17.30; Zn, 13.46. Found: C, 53.92; H, 6.07; N, 16.33; Zn, 13.22.

Methyl Iodide Reactions. About 10 mg of each of the eight thiolate complexes was dissolved in about 1 mL of CD_2Cl_2 or $CDCl_3$. Methyl iodide was added in about 2-fold excess. The reactions were followed by ^{1}H NMR and were found to be quantitative in each case. The resulting Tp*Zn−I complexes were isolated from these reactions on a preparative scale (see below).

The ^{1}H NMR data for the resulting thioethers are as follows:

MeSEt (CD_2Cl_2), 1.26 [t, $J = 7.3$ Hz, 3H, CH_3(Et)], 2.11 [s, 3H, SMe], 2.45 ppm [q, $J = 7.3$ Hz, 2H, CH_2(Et)];

MeS-i-Bu ($CDCl_3$), 0.99 [t, $J = 7.2$ Hz, 3H, CH_3(i-Bu)], 1.27 [d, $J = 7.2$ Hz, 3H, CH_3(i-Bu)], 1.40−1.80 [m, 2H, CH_2(i-Bu)], 2.07 [s, 3H, SCH_3], 2.50−2.70 ppm [m, 1H, CH(i-Bu)];

$MeSCH_2Ph$ (CD_2Cl_2), 1.99 [s, 3H, SMe], 3.67 [s, 2H, SCH_2], 7.28 ppm [m, 5H, Ph];

MeSPh ($CDCl_3$), 2.52 [s, 3H, SCH_3], 7.25−7.55 ppm [m, 5H, Ph];

N-acetylmethionine ethyl ester ($CDCl_3$), 1.22 [t, $J = 8.0$ Hz, 3H, CH_3(Et)], 1.85−2.25 [m, 2H, $SCCH_2$], 2.02 [s, 3H, SCH_3], 2.09 [s, 3H, Ac], 2.50 [m, 2H, SCH_2], 4.21 [q, $J = 8.0$ Hz, 2H, CH_2(Et)], 4.58−4.71 [m, 1H, NCH], 6.06−6.15 ppm [m, 1H, NH].

Methylations of 3a,c. A 23 mg (0.037 mmol) amount of **3a** and 9 mg (4 μL, 0.06 mmol) of MeI in 10 mL of dichloromethane were stirred for 6 h. The volatiles were removed in vacuo, and the residue was dissolved in 1 mL of dichloromethane, which was layered with 3 mL of methanol. Within a few days 15 mg (60%) of $Tp^{Ph,Me}Zn-I$[21] had separated as colorless crystals: ^{1}H NMR ($CDCl_3$) 2.54 [s, 9H, Me(pz)], 6.17 [s, 3H, CH(pz)], 6.33 [m, 9H, Ph], 7.59 ppm [m, 6H, Ph].

Likewise 120 mg (0.18 mmol) of **3c** and 27 mg (0.19 mmol) of MeI yielded 82 mg (67%) of $Tp^{Ph,Me}Zn-I$.

Methylations of 6a,b. A 193 mg (0.46 mmol) amount of **6a** and 0.67 g (0.3 mL, 4.75 mmol) of MeI in 6 mL of dichloromethane were stirred for 24 h. Evaporation in vacuo to 2 mL and filtration yielded 174 mg (78%) of $Tp^{Me,Me}Zn-I$ as colorless crystals, mp 320 °C (dec): ν(BH) 2534 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.35 [s, 9H, Me(pz)], 2.42 [s, 9H, Me(pz)], 5.73 ppm [s, 3H, H(pz)].

Anal. Calcd for $C_{15}H_{22}BIN_6Zn$ ($M_r = 489.5$): C, 36.81; H, 4.53; N, 17.17. Found: C, 36.98; H, 4.58; N, 17.05.

Likewise 46 mg (0.095 mmol) of **6b** and 23 mg (0.16 mmol) of MeI yielded 27 mg (42%) of $Tp^{Me,Me}Zn-I$.

Methylation of 5. A solution of MeI (56 mg, 0.40 mmol) in chloroform (10 mL) was added to a solution of **5** (500 mg, 0.40 mmol) in chloroform (10 mL). After the solution was stirring for 16 h, all volatiles were removed in vacuo. The residue was suspended in 10 mL of acetonitrile by exposing it to ultrasound for 15 min. Then the mixture was filtered and the filtrate evaporated to dryness again. Recrystallization from benzene yielded 137 mg (52%) of **7** as colorless crystals, mp 172 °C, which lost solvated benzene when dried in vacuo: IR (KBr) $\nu = 3374/3364$ m (NH), 2548 m (BH), 1652 s cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) 0.43 [m, 1H, CH], 0.91 [s, 2H, NH_2], 1.81 [s, 3H, SCH_3], 1.91 [m, 4H, CH, SCH_2], 2.55 [s, 9H, Me(pz)], 6.18 [s, 3H, H(pz)], 7.40 [m, 9H, Ph], 7.56 ppm [m, 6H, Ph].

Anal. Calcd for $C_{35}H_{38}BN_7O_2SZn$ ($M_r = 697.0$): C, 60.31; H, 5.50; N, 14.07; S, 4.60. Found: C, 60.62; H, 5.37; N, 13.86; S, 4.36.

Dimethyl Sulfate Reactions. About 10 mg of the complexes **3a−d** and **6a,b** were dissolved in about 1 mL of $CDCl_3$ or CD_2Cl_2. Dimethyl sulfate was added in about 2-fold excess. The reactions were followed by ^{1}H NMR. The formation of the methyl thioethers could be ascertained in all cases by their ^{1}H NMR resonances (see above). In case of **3a−d** the NMR spectra of $Tp^{Ph,Me}$ ligands showed that initially only one new $Tp^{Ph,Me}Zn$ complex was formed which seems to be $Tp^{Ph,Me}Zn-OSO_2OMe$ (**8**; see below). However, further NMR resonances due to $Tp^{Ph,Me}$ ligands showed up subsequently, and attempts to isolate $Tp^{Ph,Me}Zn-OSO_2OMe$ were unsuccessful. In case of **6a,b** the reaction solutions showed the appearance of several new $Tp^{Me,Me}$ species, of which $(Tp^{Me,Me})_2Zn$ (**9**) could be isolated (see below).

Methylation of 3a. A solution of **3a** (5 mg, 0.008 mmol) in $CDCl_3$ (0.6 mL) was treated with 3 mg (2 μL, 0.02 mmol) of Me_2SO_4. After 1 h all **3a** had disappeared, and the ^{1}H NMR spectrum showed (beside Me_2SO_4, $\delta = 3.95$ ppm, and MeSEt) the presence of only one compound, which due to its ^{1}H NMR data can be assigned as **8**: $\delta =$ 2.54 [s, 9H, Me(pz)], 3.14 [s, 3H, OMe], 6.24 [s, 3H, H(pz)], 7.42 [m, 9H, Ph], 7.60 [d, $J = 7.0$ Hz, 6H, Ph].

Methylations of 6a,b. A solution of **6a** (76 mg, 0.18 mmol) in dichloromethane (10 mL) was treated with 28 mg (20 μL, 0.22 mmol) of Me_2SO_4. After the solution was stirring for 1 day, all volatiles were removed in vacuo. The residue was dissolved in 2 mL of dichloromethane, filtered, and layered with 5 mL of methanol. Within a few days 30 mg (50%) of **9**[30] had separated as colorless crystals.

Likewise 46 mg (0.95 mmol) of **6b** and 23 mg (0.16 mmol) of Me_2SO_4 yielded 27 mg (42%) of **9**.

Reaction of 3a with $[Me_3S]I$. A solution of **3a** (66 mg, 0.11 mmol) and trimethylsulfonium iodide (40 mg, 0.19 mmol) in acetonitrile (20 mL) was refluxed for 8 h. All volatiles were removed in vacuo. The residue was dissolved in 5 mL of dichloromethane and filtered. The filtrate was evaporated to 2 mL and layered with 5 mL of methanol. Within a few days 58 mg (78%) of $Tp^{Ph,Me}Zn-I$[21] had separated.

Reaction of 3a with 2-Bromo-*N*-methylpyridinium Iodide. A solution of **3a** (46 mg, 0.075 mmol) and 2-bromo-*N*-methylpyridinium iodide (23 mg, 0.077 mmol) in acetonitrile (15 mL) was refluxed for 18 h. Then the solvent was removed in vacuo, the residue suspended in 20 mL of dichloromethane, and the mixture extracted with five 5 mL portions of water. The remaining organic phase was filtered, evacuated to 1 mL, and layered with methanol. Within a few days 28 mg of a crystalline material had separated which according to ^{1}H NMR consisted of a mixture of $Tp^{Ph,Me}Zn-Br$ and $Tp^{Ph,Me}Zn-I$. The combined aqueous phases were freeze-dried, yielding 12 mg (52%) of 2-(thioethyl)-*N*-methylpyridinium iodide[36] as a brown oil:

^{1}H NMR ($CDCl_3$) 1.55 [t, $J = 7.4$ Hz, 3H, CH_3(Et)], 3.40 [q, $J =$ 7.4 Hz, 3H, CH_2(Et)], 4.38 [s, 3H, NMe], 7.75 [t, $J = 7.0$ Hz, 1H, Py-H_β], 7.92 [d, $J = 7.0$ Hz, 1H, Py-H_δ], 8.37 [t, $J = 7.0$ Hz, 1H, Py-H_γ], 9.32 ppm [d, $J = 7.0$ Hz, 1H, Py-H_α].

Kinetic Measurements. The standard solutions of complex **3c** and methyl iodide in $CDCl_3$ (99.99%) were kept in the dark. All reagents

Table 1. Crystallographic Data

	3b	**3d**	**5**	**7**
formula	$C_{34}H_{37}BN_6SZn$	$C_{36}H_{33}BN_6SZn$	$C_{64}H_{63}B_2N_{13}O_2SZn_2 \cdot 2H_2O$	$C_{35}H_{38}BN_7O_2SZn_2 \cdot 5C_6H_6$
MW	637.94	657.92	1266.78	892.23
space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/n$
Z	4	8	4	4
a (Å)	10.178(2)	19.461(3)	32.013(6)	9.878(1)
b (Å)	11.126(2)	11.186(2)	16.694(3)	18.404(2)
c (Å)	28.835(5)	29.978(4)	11.680(2)	25.762(2)
α (deg)	90	90	90	90
β (deg)	99.35(3)	96.426(3)	90.66(3)	90.00(2)
γ (deg)	90	90	90	90
V (Å^3)	3222.1(9)	6485(1)	6242(2)	4683.2(7)
d(calcd) (g cm^{-3})	1.32	1.35	1.34	1.27
m (Mo Kα) (mm^{-1})	0.86	0.86	0.86	0.62
R1 (obsd reflcns)	0.048	0.094	0.053	0.064
wR2 (all reflcns)	0.141	0.355	0.131	0.167

and the cavity of the NMR spectrometer were thermostated to 300.0 K before the measurements. The reagents were combined immediately prior to the measurements. The concentrations of the reagents were adjusted to 0.02 M for **3c** for all six measurements and to 0.10, 0.12, 0.14, 0.16, 0.18, and 0.20 M for CH_3I, respectively. The intensities of the ^{1}H NMR resonances of the phenyl (2,6) protons of **3a** and $Tp^{Ph,Me}Zn-I$ and the benzyl-CH_2 protons of **3a** and $MeSCH_2Ph$ were recorded automatically every 30 s and stored for digital data processing. Each kinetic run was repeated two times, and the data were reproducible within 10%. The averaged data were used for the calculations. The resulting K_{obs} values for 0.10, 0.12, 0.14, 0.16, 0.18, and 0.20 M CH_3I were 1.78×10^{-3}, 1.96×10^{-3}, 2.62×10^{-3}, 2.84×10^{-3}, 3.08×10^{-3}, and 3.52×10^{-3} s^{-1}, respectively.

Thiolate Exchange. Standard solutions of 0.1 M **3a,c** in $CDCl_3$ were combined with standard solutions of 0.1 M PPN[SEt] or PPN[SCH_2-Ph] in $CDCl_3$, respectively, and then brought to 0.01 M **3a** or **3c** by dilution with $CDCl_3$. The course of the thiolate exchange reactions was monitored by observing the most characteristic ^{1}H NMR resonances, i.e., the ethyl resonances of **3a** [0.24 (t) and 1.00 (q)] and PPN[SEt] [1.26 (t) and 2.59 (q)] or the methylene resonances of **3c** [2.20 (s)] and PPN[SCH_2Ph] [3.38 (s)].

The 1:1 mixture of **3a** and PPN[SCH_2Ph] needed 2 days to reach an equilibrium mixture containing about 10% **3c**. With a 10-fold excess of PPN[SCH_2Ph] complete conversion to **3c** was achieved after 3 days. The 1:5 mixture of **3c** and PPN[SEt] needed 1 day to reach an equilibrium mixture containing about 20% **3a**.

Structure Determinations. The crystals of **3b,d** were taken as obtained from the reactions, those of **5** were obtained by recrystallization from *n*-heptane/dichloromethane, and those of **7** were from benzene. The data sets were obtained at 200 K with a Bruker AXS Smart CCD diffractometer and subjected to an empirical absorption correction (SADABS). The structures were solved with direct methods and refined anisotropically using the SHELX program suite.[38] 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.[39] Table 1 lists the crystallographic data.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft. We thank Drs. W. Deck and M. Tesmer for their assistance.

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

IC0105112

(37) Fry, D. J.; Kendall, J. D. *J. Chem. Soc.* **1951**, 1716.
(38) Sheldrick, G. M. *SHELXS-86*; Universität Göttingen: Göttingen, Germany, 1986. Sheldrick, G. M. *SHELXL-93*; Universität Göttingen: Göttingen, Germany, 1993.
(39) Keller, E. *SCHAKAL for Windows*; Universität Freiburg: Freiburg, Germany, 1999.