(Neocuproin)zinc Thiolates: Attempts at Modeling Cobalamin-Independent Methionine Synthase

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Several new complexes [(neo)Zn(SR)$_2$] [neo = neocuproin (2,9-dimethylphenanthroline)] have been synthesized and structurally characterised. They react in a stepwise fashion with the alkylating agents CH_3I and $(CH_3)_2SO_4$ to afford the thioethers CH_3SR and first the mixed complexes [(neo)Zn(SR)X] (X = I, CH_3SO_4) and then [(neo)ZnX$_2$]. Similar alkylations occur with benzyl iodide, but not with trimethyl phosphate in nonpolar media. Under these conditions, thiolate exchange with [PPN]SR does not occur which indicates that the alkylations take place at the zinc-bound thiolates. In polar solvents (methanol, DMSO), thiolate exchange occurs readily, and at higher temperatures $(CH_3)_3PO_4$ also acts as an alkylating agent which indicates that under these conditions free thiolate is available in solution. Qualitative kinetic data support the associative alkylation mechanism in nonpolar media and the change of mechanism in polar media.

Introduction

In recent years the well-investigated classes of zinc enzymes, i.e. those for hydrolytic reactions and those of the alcoholdehydrogenase family, have been accompanied by a new class responsible for thiolate alkylations. Their most prominent function is the synthesis of methionine from homocysteine.[1,2] Other thiolate-alkylating enzymes include betain:homocysteine *S*-methyltransferase,[3] protein prenyltransferases[4−6] like farnesyl transferase,[7] methanol:CoM methyltransferase,[8] and the Ada repair protein.[9,10] It is believed that all these enzymes activate the thiol by attaching it to zinc as a thiolate.[5,11] We were able to show that this correlates with the ability of low-coordinate zinc to lower the pK_a of zinc-bound water to 7 or below, thereby generating Zn−OH species under physiological conditions which react with thiols to produce Zn−SR species and water.[12]

In cobalamin-independent methionine synthase[13] and several of the related enzymes,[14] zinc is attached to the protein by one histidine and two cysteinate residues and bears a labile ligand, typically water. Thereby its coordination in the resting state is $ZnNS_2O$, and after substrate attachment it is $ZnNS_3$. Several compounds modeling methionine synthase with zinc complexes have approximated this coordination. Darensbourg[15] alkylated ZnN_2S_2 species, Carrano[16−18] various ZnN_2SX and ZnN_2S_2 species, Parkin[19] a ZnS_4 complex, Riordan prepared $ZnNS_3$ and ZnS_4 complexes[20] and studied the alkylation of an NiN_4S complex,[21] and very recently Darbre[22] found that the ZnN_2S_2 complex [Zn(MEPA)$_2$] previously reported by us[23] can be methylated with trimethyl phosphate. So far the alkylation of a close model complex, i.e. one with $ZnNS_3$ coordination, has not been studied. In the cases where mechanistic investigations were undertaken, they indicated that the thiolates are alkylated in the zinc-bound state and the resultant thioethers are subsequently released. Only in the alkylation of anionic $[Zn(SR)_4]^{2-}$, which was studied as a model for the Ada repair protein, was it observed that the thiolate dissociates from zinc prior to being attacked by the alkylating agent.[24]

Our own contributions to this field have so far consisted of the investigation of (pyrazolylborato)zinc thiolate (Tp* Zn−SR) complexes, i.e. ZnN_3S systems. During the synthetic studies[25−28] it was found that such complexes are easily formed in neutral solutions from TpZn−OH and the corresponding thiol, i.e. their formation does not require a base. Detailed mechanistic studies[29,30] then revealed that the alkylation of their thiolates occurs intramolecularly and that the zinc−sulfur bond is broken after the formation of the thioether. The drawback of the model chemistry using TpZn−SR complexes is that their zinc coordination is different from that in the enzyme ($ZnNS_3$) and that they are not reactive toward the biological alkylating agents *N*-methyltetrahydrofolate or organic phosphates nor analogues thereof in the form of alkylammonium salts or trimethyl phosphate.

With the hope of increasing the reactivity of the zinc thiolates and to approximate the natural binding situation of zinc we therefore set out to investigate zinc thiolates with

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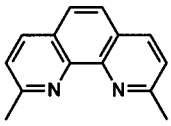
a more sulfur-rich ligand environment. This paper describes the chemistry of ZnN_2S_2 systems and work on $ZnNS_3$ and ZnS_4 systems is in progress. Ideally one would have taken a pyrazolylborate-derived tripodal N_2S ligand to study $(N_2S)Zn-SR$ complexes for this purpose. Since such a ligand is not available as yet, however, we resorted to an appropriate chelating N_2 ligand and the corresponding $(N_2)Zn(SR)_2$ complexes. Based on previous favourable experience with such complexes[31–34] we opted for neocuproin (neo, 2,9-dimethylphenanthroline). This paper reports the syntheses and structures of some new $[(neo)Zn(SR)_2]$ complexes and reactivity studies related to the stepwise removal of their thiolate ligands as thioethers by means of alkylation with various alkylating agents under a variety of conditions.



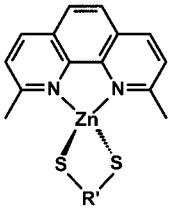
neocuproin (neo)

Results and Discussion

(Neocuproin)zinc Bis(thiolate) Complexes

The neocuproin ligand is favourable for stable and tetrahedral zinc complexes. It has already been observed that this is also true for bis(thiolate) complexes.[31–34] For the simple bis(thiolates), the benzenethiolate,[34] and the phenylethanethiolate[31] have also been structurally characterized and we now contribute the bis(thiolates) **1a**–**h**. Their preparation can be achieved with comparable yields by two alternative methods. The first of these consists of the successive treatment of sodium methoxide with the thiol, hydrated zinc perchlorate and then neocuproin. The other uses zinc bis[bis(trimethylsilyl)]amide as the base and the zinc precursor, which is added to a mixture of the thiol and neocuproin.

R	C_2H_5	$CH_2C_6H_5$	*p*-$CH_3C_6H_4$	*p*-$NO_2C_6H_4$	2,6-$(C_6H_5)_2C_6H_3$
	1a	**1b**	**1c**	**1d**	**1e**



R'	C_2H_4	*o*-$CH_2C_6H_4CH_2$	*o*-$CH_2C_6H_4$
	1f	**1g**	**1h**

In complexes **1a**–**e**, the monodentate thiolates were varied so as to have aliphatic, benzylic, and aromatic substituents, and among the aromatic substituents the electron density and the steric bulk were varied. The same aliphatic/benzylic/aromatic variation was the reason for the choice of the three bidentate thiolate ligands in **1f**–**h**. Specifically in **1h** the thiolate ligand is benzylic at one sulfur atom and aromatic at the other, and it was hoped that this would be reflected in the reactivity of the two thiolate functions.

All complexes **1** are yellow crystalline solids. Their IR spectra are not diagnostic since there are hardly any band shifts for the ligands upon coordination to zinc. Similarly the ^1H NMR spectra are characteristic only for the thiolate ligands (see Exp. Sect.), while the neocuproin resonances [typical values in $CDCl_3$: δ = 3.1 (s, CH_3), 7.5 (d, J = 8.4 Hz, 4-H), 7.9 (s, 5-H), 8.3 (d, J = 8.4 Hz, 3-H) ppm] show only very small shifts upon coordination.

Four of the eight bis(thiolate) complexes were subjected to structural determinations. One typical example of each of the monodentate (**1c**) and bidentate thiolates (**1h**) are presented as Figures 1 and 2. A summary of selected bond

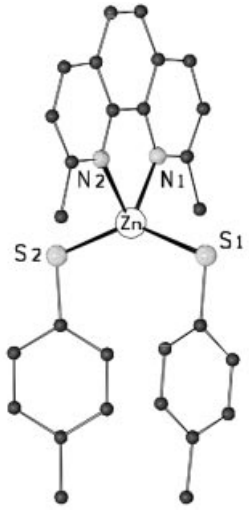


Figure 1. Molecular structure of complex **1c**

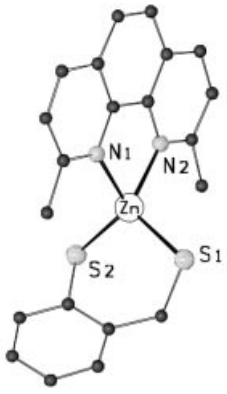


Figure 2. Molecular structure of complex **1h**

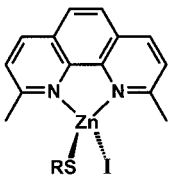
lengths and angles for all four structures is given in Table 1. The table shows {as does the comparison with previously reported [(neo)Zn(SR)] complexes[31,33,34]} that the Zn−N and Zn−S bond lengths are rather constant, irrespective of the electronic nature of the thiolate ligands. Likewise the N−Zn−N angle is fixed to its low value due to the steric constraints of the neocuproin ligand. The only variable quantities are the S−Zn−S and N−Zn−S angles. While the chelating bis(thiolate) in **1h** fixes the S−Zn−S angle near the tetrahedral value, it can extend to almost 140° in the absence of any restraints, as in **1c**. The average size of the N−Zn−N angle which is large for **1h** and small for **1c** is a mere consequence of the size of the S−Zn−S angles.

Table 1. Bond lengths [Å] and angles [°] for complexes **1**

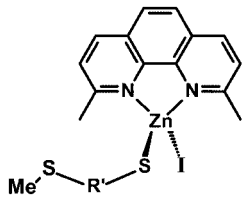
	1c	**1d**	**1g**	**1h**
Zn−S1	2.266(2)	2.287(1)	2.249(1)	2.271(3)
Zn−S2	2.267(2)	2.289(2)	2.260(1)	2.275(3)
Zn−N1	2.121(4)	2.104(2)	2.115(3)	2.081(8)
Zn−N2	2.121(4)	2.103(2)	2.122(3)	2.062(8)
S−Zn−S	137.62(5)	120.76(2)	123.58(5)	108.4(1)
N−Zn−N	78.85(1)	80.34(7)	79.1(1)	81.3(3)
S−Zn−N	103.0−109.7	106.6−118.4	109.6−113.6	114.8−119.2

Alkylation Reactions

As before,[30] the most convenient reagent for alkylation of the zinc-bound thiolates was methyl iodide. With the exception of **1e** all thiolates **1** were treated with 1 mol-equiv. of CH_3I in chloroform. Clean reactions occurred with the bis(thiolates) **1a−c** resulting in the liberation of the thioether CH_3SR and isolation of the iodide thiolate complexes **2a−c**. Complex **1d** reacted too slowly at room temperature, but yielded decomposition products at elevated temperatures which prevented the isolation of pure **2d**. Of the chelating bis(thiolates), **1f** and **1g** underwent clean release of one thiolate function, producing **2f** and **2g** with thioether thiolate ligands. The asymmetric chelating bis(thiolate) **1h** was found by NMR observation to be, as expected, more reactive at the benzylthiolate than at the phenylthiolate function, yet the methylation of the benzylthiolate unit did not go to completion before methylation of the phenylthiolate began. As a result the thioether thiolate complex **2h**, like **2d**, could only be identified by its NMR spectroscopic data.

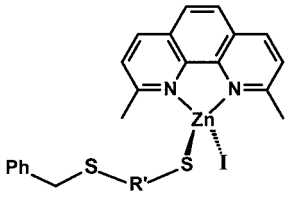


R	C_2H_5	$CH_2C_6H_5$	*p*-$CH_3C_6H_4$	*p*-$NO_2C_6H_4$
	2a	**2b**	**2c**	**2d**



R'	C_2H_4	*o*-$CH_2C_6H_4CH_2$	*o*-$CH_2C_6H_4$
	2f	**2g**	**2h**

Alkylations with benzyl iodide were performed with the chelate complexes **1f** and **1g**. They were slightly faster than the methyl iodide reactions and yielded the thioether thiolate complexes **3f** and **3g**.



R'	C_2H_4	*o*-$CH_2C_6H_4CH_2$
	3f	**3g**

Crystals of **3g** suitable for an X-ray analysis were obtained. Figure 3 shows the molecular shape which is an indication of the intramolecular nature of the alkylation reactions. The coordination of zinc in **3g** largely resembles that in the bis(thiolate) complexes **1**. Notably the N−Zn−S angles are spread over a range of 14°, and the S−Zn−I angle is close to the tetrahedral value.

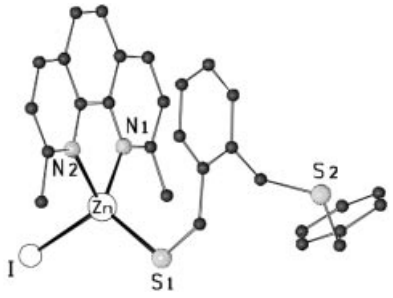
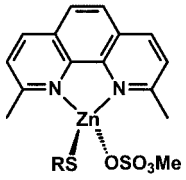


Figure 3. Molecular structure of **3g**; selected bond lengths [Å] and angles [°]: Zn−I 2.580(1), Zn−S 2.244(2), Zn−N1 2.082(5), Zn−N2 2.074(5); S−Zn−I 111.87(6), N1−Zn−N2 80.8(2), N1−Zn−S 118.2(2), N2−Zn−S 122.6(2), N1−Zn−I 110.6(1), N2−Zn−I 109.0(1)

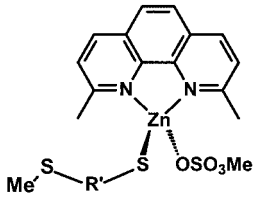
When 2 equiv. of methyl iodide were allowed to react with **1a−c**, **1f**, and **1g**, complete removal of the thiolate ligands occurred and the resultant methyl thioethers could be identified by their ^1H NMR spectra. The remaining zinc complex (neo)ZnI_2 was isolated from the reactions of **1c** and **1f** and characterised and its crystal structure deter-

mined (see Exp. Sect.). It was observed that the second step of the alkylations is not significantly slower than the first step. This also means that even with 1 equiv. of methyl iodide part of the starting materials **1** are converted into (neo)ZnI_2 and 2 equiv. of the thioether, which in some cases hampered the isolation of the mixed complexes **2**.

We have previously observed[30] that dimethyl sulfate is as good as methyl iodide for the alkylation of zinc-bound thiolates, but that the low stability of the resultant zinc−(methyl sulfate) complexes creates preparative problems. This was not so pronounced in the present study. Complexes **1a**, **b**, **f**, and **g** were chosen for the dimethyl sulfate reactions, representing two cases each of monodentate and chelating bidentate thiolates. Treatment with 1 equiv. of dimethyl sulfate produced the corresponding methyl thioethers, as evidenced by ^1H NMR spectroscopy. The resultant zinc complexes **4**, of which **4f** and **g** still contain the thioether as a ligand, were isolated in good yields. They are methyl sulfate complexes which are stable at room temperature. Yet both their NMR spectra and their elemental analyses showed that they were not pure, and attempts at purifying them by recrystallisation only increased their impurity content.



R	Et	Bn
	4a	**4b**



R'	C_2H_4	*o*-$CH_2C_6H_4CH_2$
	4f	**4g**

Treatment of **4a**, **b**, **f**, or **g** with an excess of dimethyl sulfate resulted in complete release of the corresponding methyl thioethers just as in the methyl iodide reactions, but the fate of the remaining zinc species is unclear. No evidence for the formation of [(neo)$Zn(OSO_3CH_3)_2$] was obtained. Only in one case could a small amount of a crystalline product be isolated from the reaction of **1f**. A structural determination, the result of which is shown in Figure 4, identified this product as complex **5**.

5: [$(neo)_2Zn-OSO_3Me$](OSO_3Me)

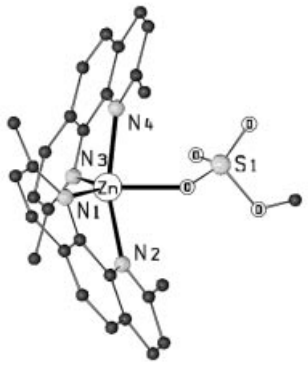


Figure 4. Molecular structure of **5**; selected distances [Å] and angles [°] in the complex cation: Zn−O 2.138(2), Zn−N1 2.093(2), Zn−N2 2.130(2), Zn−N3 2.059(2), Zn−N4 2.135(2), (Zn)O−S 1.465(2), S=O 1.435(2) and 1.437(2), S−O(C) 1.592(2); N2−Zn−N4 161.9(1), O1−Zn−N1 119.5(1), O1−Zn−N3 119.8(1), N1−Zn−N3 120.7(1); in the methyl sulfate anion: S=O 1.394(3), 1.430(5) and 1.420(7), S−O(C) 1.589(10)

The major piece of information from the structure of **5** is the demonstration of the existence of zinc−(alkyl sulfate) binding. The coordination of the zinc ion in **5** is somewhere between square-pyramidal and trigonal-bipyramidal. The suggested square-pyramidal coordination is impossible because the four methyl groups of the neocuproin ligands prevent a symmetric basal arrangement. The alternative trigonal-bipyramidal coordination is impossible because of the small intra-chelate-ligand N−Zn−N angles. The molecular shape of **5** and its bonding parameters closely resemble those in the corresponding nitrate complex.[35] The S=O bond lengths in the ligated and the free methyl sulfate groups do not differ significantly. This holds specifically for the S−O(Zn) bond which is much closer in length to the S=O bonds than to the real single bonds S−O(C). This situation resembles that in the zinc−(organyl phosphate) complexes[36,37] and, just as for the latter, indicates that there is a considerable amount of ionic character in the Zn−O bond.

A more "biological" alkylating agent is trimethyl phosphate, since the Ada repair protein dealkylates alkyl phosphates by transferring the alkyl groups from phosphate to thiolate.[9,10] As before,[30] we also found here that trimethyl phosphate does not alkylate the thiolate ligands of complexes **1** in nonpolar media. It has, however, been reported in the literature[22,24] that in strongly polar solvents and at elevated temperatures the alkylation does take place. This could be reproduced by us using complex **1c**. Heating equimolar amounts of **1c** and $PO(OMe)_3$ in DMSO to 80 °C for 2 weeks produced an almost quantitative formation (by NMR) of $MeSC_6H_4$-*p*-CH_3 and a good isolated yield of the phosphate complex **6**. Likewise with a fivefold amount of $PO(OMe)_3$ nearly quantitative formation of the bis(phosphate) complex **7** took place. The harsh reaction conditions required due to the low alkylating strength of trimethyl phosphate most probably involve a change in the mechanism of the alkylation. As suggested before,[22,24] we con-

clude (see below) that in these cases free thiolate is liberated and alkylated without the involvement of zinc.

6: [(neo)Zn(S−*p*-Tol)OPO(OMe)$_2$]

7: [(neo)Zn{OPO(OMe)$_2$}$_2$]

The biological alkylating agent in cobalamin-independent methionine synthase is N^5-methyltetrahydrofolic acid, a methylammonium salt. Two synthetic analogues, *N*,*N*,*N*-trimethylanilinium iodide and *N*-methyltetrahydroquinoxalinium iodide, were found to be good mimics,[38] yet they showed no methylating tendency even towards **1b**, the most reactive of the thiolates investigated here even at elevated temperatures.

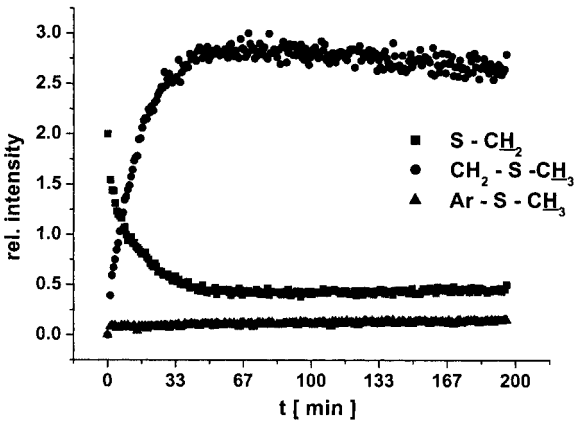


Figure 5. Kinetic traces (by ^{1}H NMR) for the reaction of **1h** (0.005 M) with a four-fold excess of CH_3I in chloroform at 300 K

Mechanistic Considerations

The question of whether the alkylation occurs at the zinc-bound or at the free anionic thiolates was addressed with the same procedures as used in our preceding work.[30] Both thiolate exchange experiments and kinetic investigations led to the conclusion that the [(neo)Zn(SR)$_2$] complexes just like the Tp*Zn−SR complexes undergo intramolecular alkylation, i.e. they do not dissociate in nonpolar media.

The thiolate exchange experiments were monitored by ^{1}H NMR spectroscopy. In no case could a replacement of SR in [(neo)Zn(SR)$_2$] by SR′ from [PPN]SR be observed in chloroform. In methanol, however, fast exchange between [(neo)Zn(SBn)$_2$] (**1b**) and NaSEt took place. Starting with a 1:1 mixture of the reagents, an equilibrium was reached in which [(neo)Zn(SBn)$_2$] and [(neo)Zn(SEt)$_2$] exist in a 10:1 ratio. When treating [(neo)Zn(SBn)$_2$] with the chelating thiolate $Na_2(SCH_2-C_6H_4-CH_2S)$, a quantitative conversion into the chelating dithiolate complex **1g** and NaSBn occurred within minutes. The driving force for this reaction is the precipitation of **1g** from the methanolic solution.

Kinetic data were accumulated for several of the alkylation reactions under pseudo-first-order conditions. Yet in no case could they be fitted cleanly by assuming first-order behaviour. The reasons for this are mainly due to the early onset of the second alkylation step and precipitation of some of the mixed iodide thiolate complexes **2**. A characteristic plot is displayed in Figure 5 which shows in the trace at the bottom the formation of the doubly alkylated bis(thiolate) and in the trace at the top the appearance and subsequent disappearance of the monoalkylated species **2h**.

A qualitative estimate of the second-order rate constant could be obtained for the reaction of **1g** with an excess of methyl iodide. By comparing initial rates at identical concentrations with those of the previously reported Tp*Zn−SR/MeI reaction[30] a value of k'' of the order of 10^{-4} $M^{-1}s^{-1}$ was obtained. This is considerably slower than for [Tp*Zn−SR] complexes, but compares favourably with the k'' value obtained by Carrano[18] for the MeI methylation of an [(N_2O)Zn−SPh] complex. There still exist too few second-order rate constants for such alkylations to allow a meaningful discussion, however.

Finally, another argument in favour of a dissociative alkylation process in polar media (i.e. a nondissociative process in chloroform) was found in the comparison of reaction speeds: in methanol the reaction between **1b** and methyl iodide is roughly one order of magnitude faster than in chloroform. As for the thiolate exchange reactions and for the alkylations with trimethyl phosphate (see above) the simplest explanation for this is the existence of free anionic thiolate in the polar medium.

Conclusions

The present work represents the second step in our investigations on modeling biological thiolate alkylations with tetrahedral zinc complexes. After the ZnN_3S situation in (pyrazolylborato)zinc thiolates the ZnN_2S_2 situation in (neocuproin)zinc thiolates was addressed. Again, the accumulated evidence indicates that the thiolates are alkylated in the zinc-bound state. Furthermore, while the coordination environment of zinc in the enzymes could be approximated, the alkylating agents had to be much stronger than the naturally occuring *N*-methyltetrahydrofolate.

It was found that both thiolate ligands in the [(neo)Zn(SR)$_2$] complexes are alkylated in a stepwise fashion. When, as in complex **1h**, both an aromatic and a benzylic thiolate are offered, the benzylic one as expected reacts first, although not significantly faster than the aromatic one. Compared with the [Tp*Zn−SR] complexes the [(neo)Zn(SR)$_2$] complexes are more reactive due to their more electron-rich ZnN_2S_2 situation.

Unlike the pyrazolylborate ligands the neocuproin ligand cannot encapsulate the zinc ion, thereby approximating its enzymatic environment. This would call for tripodal N_2S ligands, possibly derived from the pyrazolylborates. The synthesis of such ligands is still a challenge. Similar tripodal ligands of the NS_2 and S_3 type exist, however,[39,40] and we are investigating thiolate alkylations of [L·Zn−SR] complexes derived from them.

Experimental Section

General: For general working and measuring procedures, see ref.[41] Starting materials were obtained commercially, except for $Zn[N(SiMe_3)_2]_2$,[42] *o*-(mercaptomethyl)thiophenol,[43] and *o*-bis-(mercaptomethyl)benzene.[44] The methyl thioethers resulting from the methylations have been described[45−48] and were identified by their ^1H NMR spectra. The PPN salts of the thiols were prepared by cation exchange as described.[49]

Elemental Analyses: All new compounds were characterized by elemental analyses which were satisfactory in most cases. Yet, as mentioned in the text, several of the alkylation reactions yielded product mixtures, from which the expected products could not be isolated in a fully pure form. For these products four elements were analyzed, giving an overall satisfactory picture for **1b**, **1e**, **1g**, **4a**, **4b**, and **4g**. Only for **2f**, **3f**, and **4f** was the purity obviously insufficient.

Complex 1a: A solution of $Zn[N(SiMe_3)_2]_2$ (1.71 g, 4.42 mmol) in toluene (50 mL) was added slowly with stirring to a solution of neo·H_2O (1.00 g, 4.42 mmol) and ethanethiol (0.66 mL, 550 mg, 8.8 mmol) in toluene (100 mL) over a period of 2 h. A light yellow precipitate resulted which was filtered and washed two times each with toluene (3 mL) and diethyl ether (3 mL). **1a** (1.50 g, 86%) remained as a light yellow powder, m.p. 250 °C (dec.). $C_{18}H_{22}N_2S_2Zn$ (395.91): calcd. C 54.61, H 5.60, N 7.08, Zn 16.52; found C 53.02, H 5.64, N 6.75, Zn 15.89. ^1H NMR ($CDCl_3$): δ = 1.16 [t, *J* = 7.4 Hz, 6 H, CH_3(Et)], 2.46 [q, *J* = 7.4 Hz, 4 H, CH_2(Et)] ppm.

Complex 1b: Similar procedure to that for **1a** from $Zn[N(SiMe_3)_2]_2$ (1.71 g, 4.42 mmol), neo·H_2O (1.00 g, 4.42 mmol), and benzylmercaptan (1.10 g, 8.84 mmol). Yield 2.10 g (91%) of **1b** as light yellow powder, m.p. 148 °C. $C_{28}H_{26}N_2S_2Zn$ (520.05): calcd. C 64.67, H 5.04, N 5.39, Zn 12.57; found C 65.98, H 5.27, N 4.87, Zn 11.49. ^1H NMR ($CDCl_3$): δ = 3.54 [s, 4 H, CH_2(Bn)], 6.65−6.71 (m, 6 H, Bn), 6.86−6.91 (m, 4 H, Bn) ppm.

Complex 1c: A solution of $Zn(ClO_4)_2·6H_2O$ (0.372 g, 1.00 mmol) in methanol (80 mL) was added very slowly with stirring to a solution of *p*-thiocresol (0.248 g, 2.00 mmol) and NaOMe (0.108 g, 2.00 mmol) in methanol (100 mL) over a period of 3 h; neo·H_2O (0.208 g, 1.00 mmol) in methanol (15 mL) was then added and the mixture stirred overnight. The volume was reduced to 30 mL in vacuo, the precipitate filtered, dried in vacuo, and recrystallized from hot methanol; **1c** (0.41 g, 79%) resulted as yellow crystals, m.p. 207 °C. $C_{28}H_{26}N_2S_2Zn$ (520.05): calcd. C 64.67, H 5.04, N 5.39, S 12.33; found C 64.54, H 5.53, N 5.59, S 12.25. ^1H NMR ([D_6]DMSO): δ = 1.89 [s, 6 H, CH_3(Tol)], 6.28 (d, *J* = 8.0 Hz, 4 H, Tol), 6.64 (d, *J* = 8.0 Hz, 4 H, Tol) ppm.

Complex 1d: Similar to **1a** from $Zn[N(SiMe_3)_2]_2$ (1.46 g, 3.77 mmol), neo·H_2O (0.785 g, 3.77 mmol), and *p*-nitrothiophenol (1.17 g, 7.54 mmol). Recrystallization from toluene yielded **1d** as dark yellow crystals (1.05 g, 48%), m.p. 213 °C. $C_{26}H_{20}N_4O_4S_2Zn$ (581.99): calcd. C 53.66, H 3.46, N 9.63, S 11.02; found C 53.45, H 3.53, N 9.78, S 10.76. ^1H NMR ($CDCl_3$): δ = 7.20 (d, *J* = 8.0 Hz, 4 H, Ar), 7.54 (d, *J* = 8.0 Hz, 4 H, Ar) ppm.

Complex 1e: Like **1c** from $Zn(ClO_4)_2·6H_2O$ (0.093 g, 0.25 mmol), 2,6-diphenylthiophenol (0.131 g, 0.50 mmol), NaOMe (0.027 g, 0.50 mmol), and neo·H_2O (0.052 g, 0.25 mmol). Yield 0.114 g (57%) of **1e** as yellow crystals, m.p. 260 °C (dec.). $C_{50}H_{38}N_2S_2Zn$ (796.39): calcd. C 75.41, H 4.81, N 3.52, S 8.05; found C 74.35, H 4.95, N 3.45, S 7.97. ^1H NMR ($CDCl_3$): δ = 6.74−6.92 (m, 18 H, Ar), 7.11−7.16 (m, 8 H, Ar) ppm.

Complex 1f: Like **1a** from $Zn[N(SiMe_3)_2]_2$ (1.71 g, 4.42 mmol), neo·H_2O (1.00 g, 4.42 mmol) and ethanedithiol (0.41 g, 4.4 mmol). Yield 1.12 g (69%) of **1f** as a yellow solid, m.p. 270 °C (dec.). $C_{16}H_{16}N_2S_2Zn$ (365.84): calcd. C 52.53, H 4.41, N 7.66, S 17.87; found C 52.59, H 4.44, N 7.59, S 17.10. ^1H NMR ($CDCl_3$): δ = 3.03 (s, 4 H, CH_2) ppm.

Complex 1g: Like **1c** from $Zn(ClO_4)_2·6H_2O$ (0.447 g, 1.20 mmol), *o*-bis(mercaptomethyl)benzene (0.204 g, 1.20 mmol), NaOMe (2.45 mmol of a 0.25 M solution), and neo·H_2O (0.272 g, 1.20 mmol). Yield 0.240 g of **1g** as a light yellow powder and, after reducing the volume of the filtrate and cooling, 0.030 g of **1g** as yellow crystals. Total yield 0.270 g (51%) of **1g**, m.p. 270 °C (dec.). $C_{22}H_{20}N_2S_2Zn$ (441.94): calcd. C 59.79, H 4.56, N 6.34, Zn 14.80; found C 58.14, H 4.45, N 6.01, Zn 13.70. ^1H NMR ($CDCl_3$): δ = 4.03 (s, 4 H, CH_2), 7.12−7.18 (m, 2 H, Ph), 7.35−7.39 (m, 2 H, Ph) ppm.

Complex 1h: Like **1c** from $Zn(ClO_4)_2·6H_2O$ (2.62 g, 7.04 mmol), *o*-(mercaptomethyl)thiophenol (1.10 g, 7.04 mmol), NaOMe (0.807 g, 14.9 mmol), and neo·H_2O (1.59 g, 7.04 mmol). Yield 1.56 g of **1h** as a yellow powder and, after reducing the volume of the filtrate and cooling, 0.16 g of **1h** as yellow crystals. Total yield 1.72 g (58%) of **1h**, m.p. 265 °C (dec.). $C_{21}H_{18}N_2S_2Zn$ (427.91): calcd. C 58.95, H 4.24, N 6.55, S 14.99; found C 58.49, H 3.78, N 6.02, S 14.34. ^1H NMR (CD_3OD): δ = 3.97 (s, 2 H, CH_2), 6.95−7.07 (m, 2 H, Ar), 7.27−7.32 (m, 1 H, Ar), 7.46−7.55 (m, 1 H, Ar) ppm.

Alkylations with Methyl Iodide

2a: Complex **1a** (500 mg, 1.26 mmol) and MeI (79 μL, 180 mg, 1.26 mmol) in chloroform (40 mL) were stirred for 2 d. Reduction of the volume in vacuo to 20 mL and layering with diethyl ether (10 mL) yielded **2a** (17 mg, 3%) as a colourless powder, m.p. 300 °C (dec.). $C_{16}H_{17}IN_2SZn$ (461.68): calcd. C 41.63, H 3.71, N 6.07, Zn 14.16; found C 41.00, H 3.58, N 5.86, Zn 14.63. ^1H NMR ($CDCl_3$): δ = 1.33 [t, *J* = 7.3 Hz, 3 H, CH_3(Et)], 2.73 [q, *J* = 7.3 Hz, 2 H, CH_2(Et)] ppm.

2b: Complex **1b** (100 mg, 0.19 mmol) and MeI (12 μL, 27.3 mg, 0.19 mmol) in chloroform (25 mL) were stirred for 2 d. The volume was reduced to 1 mL in vacuo. The precipitate was filtered and washed three times with cold chloroform (1 mL) leaving behind **2b** (90 mg, 89%) as a colourless solid, m.p. 270 °C (dec.) which was not analytically pure. $C_{21}H_{19}IN_2SZn$ (523.75): EI MS: *m/z* (%) = 399.2 (100) [$M^+ - C_6H_5CH_2S$], 314.2 (30) [$C_6H_5CH_2SZnI$]. ^1H NMR ($CDCl_3$): δ = 3.54 (s, 2 H, CH_2), 7.02−7.12 (m, 5 H, Ph) ppm.

2c: Like **1b** with **1c** (133 mg, 0.26 mmol) and MeI (36 mg, 0.26 mmol) for one week. Yield 56 mg (40%) of **2c** as a light yellow solid, m.p. 200 °C. $C_{21}H_{19}IN_2SZn$ (523.75): calcd. C 48.16, H 3.66, N 5.35, S 6.12; found C 48.00, H 3.99, N 5.42, S. 5.75. ^1H NMR ([D_6]DMSO): δ = 1.89 [s, 3 H, Me(Tol)], 6.29 (d, *J* = 7.8 Hz, 2 H, Tol), 6.64 (d, *J* = 7.8 Hz, 2 H, Tol) ppm.

2f: Like **1a** with **1f** (250 mg, 0.68 mmol) and MeI (97 mg, 0.68 mmol). Yield 167 mg (48%) of **2f** as light yellow crystals, m.p. 210 °C (dec.). $C_{17}H_{19}IN_2S_2Zn$ (507.78): calcd. C 40.21, H 3.77, N 5.52, Zn 12.88; found C 36.29, H 3.08, N 5.10, Zn 12.40. ^1H NMR ($CDCl_3$): δ = 2.16 (s, 3 H, SCH_3), 2.77−2.89 (m, 2 H, CH_2), 2.91−3.02 (m, 2 H, CH_2) ppm.

2g: Complex **1g** (500 mg, 1.13 mmol) and MeI (161 mg, 1.13 mmol) in chloroform (40 mL) were stirred for 1 d. The resultant precipitate was filtered, washed with diethyl ether, and dried in vacuo, leaving behind **2g** (302 mg, 47%) as a colourless powder, m.p. 220

°C (dec.). $C_{23}H_{23}IN_2S_2Zn$ (583.87): calcd. C 47.31, H 3.97, N 4.80, Zn 11.20; found C 47.16, H 3.89, N 4.67, Zn 12.50. ^{1}H NMR ($CDCl_3$): δ = 2.02 (s, 3 H, SMe), 3.90 [s, 2 H, CH_2(Ar)], 3.96 [s, 2 H, CH_2(Ar)], 6.57−6.70 (m, 1 H, Ar), 6.72−6.84 (m, 1 H, Ar), 6.87−6.95 (m, 1 H, Ar), 6.97−7.05 (m, 1 H, Ar) ppm.

Alkylations with Benzyl Iodide

3f: Complex **1f** (250 mg, 0.68 mmol) and benzyl iodide (149 mg, 0.68 mmol) in chloroform (50 mL) were stirred for 1 d. Layering with hexane yielded **3f** (323 mg, 81%) as a colourless powder, m.p. 330 °C (dec.) which was filtered and dried in vacuo. $C_{23}H_{23}IN_2S_2Zn$ (583.87): calcd. C 47.31, H 3.97, N 4.80, S 10.98; found C 48.61, H 4.33, N 4.52, S 10.14. ^{1}H NMR ($CDCl_3$): δ = 2.79−2.85 (m, 2 H, CH_2), 2.91−2.99 (m, 2 H, CH_2), 3.79 [s, 2 H, CH_2(Bn)], 7.23−7.40 (m, 5 H, Ph) ppm.

3g: Like **1f** with **1g** (567 mg, 1.28 mmol) and benzyl iodide (279 mg, 1.28 mmol). Yield 228 mg (27%) of **3g** as colourless crystals, m.p. 220 °C (dec.). $C_{29}H_{27}IN_2S_2Zn{\cdot}0.5CHCl_3$ (659.97 + 119.38): calcd. C 49.23, H 3.85, N 3.98; found C 49.68, H 3.79, N 4.18. ^{1}H NMR ($CDCl_3$): δ = 3.64 [s, 2 H, CH_2(Ph)], 3.81 [s, 2 H, CH_2(Ph)], 3.91 [s, 2 H, CH_2(Ph)], 6.54−6.62 (m, 1 H, Ar), 6.68−6.75 (m, 1 H, Ar), 6.84 (d, *J* = 7.6 Hz, 1 H, Ar), 7.00 (d, *J* = 7.6 Hz, 1 H, Ar), 7.05−7.30 (m, 5 H, Ar) ppm.

Twofold Methylations

With 1c: Complex **1c** (103 mg, 0.20 mmol) and CH_3I (450 mg, 3.2 mmol) in chloroform (25 mL) were stirred for 2 d. All volatiles were then removed in vacuo and the residue washed with diethyl ether (2 mL) and dichloromethane (2 mL), leaving behind (neo)ZnI_2 (48 mg, 46%) as a colourless powder, m.p. 320 °C (dec.). Crystals for the structure determination were obtained by recrystallization from chloroform. $C_{14}H_{12}I_2N_2Zn$ (527.46): calcd. C 31.88, H 2.29, N 5.31; found C 31.67, H 2.41, N 5.04. ^{1}H NMR ($CDCl_3$): δ = 3.25 (s, 6 H, CH_3), 7.78 (d, *J* = 8.4 Hz, 2 H, H_B), 7.95 (s, 2 H, H_C), 8.47 (d, *J* = 8.4 Hz, 2 H, H_A).

With 1f: Complex **1f** (50 mg, 0.14 mmol) and CH_3I (2.27 g, 16.0 mmol) in chloroform (25 mL) were stirred for 1 week. Workup as above yielded (neo)ZnI_2 (12 mg, 17%).

Methylations with Dimethyl Sulfate

4a: Complex **1a** (281 mg, 0.71 mmol) and $(MeO)_2SO_2$ (67 μL, 89 mg, 0.71 mmol) in chloroform (40 mL) were stirred for 2 d. Reduction of the volume to 20 mL in vacuo and layering with diethyl ether yielded a precipitate which was filtered and washed twice with diethyl ether (5 mL), leaving behind **4a** (285 mg, 90%) as a colourless powder, m.p. 300 °C (dec.). $C_{17}H_{20}N_2O_4S_2Zn$ (445.88): calcd. C 45.79, H 4.52, N 6.28, Zn 14.67; found C 43.48, H 4.15, N 6.07, Zn 14.26. ^{1}H NMR ($CDCl_3$): δ = 1.34 [t, *J* = 7.3 Hz, 3 H, CH_3(Et)], 2.58 [q, *J* = 7.3 Hz, 2 H, CH_2(Et)], 3.68 (s, 3 H, OMe) ppm.

4b: Like **1a** with **1b** (150 mg, 0.29 mmol) and $(MeO)_2SO_2$ (27 μL, 36 mg, 0.29 mmol), yielded **4b** (146 mg, 99%) as a colourless powder, m.p. 150 °C. $C_{22}H_{22}N_2O_4S_2Zn$ (507.95): calcd. C 52.02, H 4.37, N 5.52, Zn 12.87; found C 48.70, H 4.42, N 5.25, Zn 11.57. ^{1}H NMR ($CDCl_3$): δ = 3.66 (s, 3 H, OMe), 3.72 (s, 2 H, CH_2), 6.36−6.51 (m, 3 H, Ph), 6.76−6.85 (m, 2 H, Ph) ppm.

4f: Complex **1f** (160 mg, 0.44 mmol) and $(MeO)_2SO_2$ (45 μL, 60 mg, 0.48 mmol) in chloroform (20 mL) were stirred for 2 d. Layering with hexane (30 mL) yielded, within one week, a mixture of a colourless powder and colourless crystals, which was filtered, washed with diethyl ether, and dried in vacuo. Manual removal of the crystals left behind **4f** (25 mg, 12%), m.p. 270 °C (dec.). $C_{18}H_{22}N_2O_4S_3Zn$ (491.97): calcd. C 43.95, H 4.51, N 5.69, Zn 13.29; found C 42.15, H 3.84, N 6.22, Zn 13.62. ^{1}H NMR ($CDCl_3$, ppm): δ = 2.06 (s, 3 H, SMe), 2.72−2.85 (m, 2 H, CH_2), 2.91−3.01 (m, 2 H, CH_2), 3.69 (s, 3 H, OMe) ppm. The crystals amounted to 5 mg (2%) of **5**, m.p. 254 °C, which was identified by the structural determination.

4g: Like **1f** with **1g** (500 mg, 1.13 mmol) and $(MeO)_2SO_2$ (107 μL, 143 mg, 1.13 mmol), yield **4g** (520 mg, 81%) as a colourless powder, m.p. 160 °C. $C_{24}H_{26}N_2O_4S_3Zn$ (568.07): calcd. C 50.74, H 4.61, N 4.93, Zn 11.50; found C 48.82, H 4.34, N 4.96, Zn 11.47. ^{1}H NMR ($CDCl_3$): δ = 1.89 (s, 3 H, SMe), 3.70 (s, 3 H, OMe), 3.76 (s, 2 H, CH_2), 3.83 (s, 2 H, CH_2), 6.02−6.17 (m, 1 H, C_6H_4), 6.30−6.45 (m, 1 H, C_6H_4), 6.47−6.63 (m, 2 H, C_6H_4).

Methylations of 1c with Trimethyl Phosphate

With 1 Equiv.: Complex **1c** (200 mg, 0.38 mmol) and $PO(OMe)_3$ (54 mg, 0.38 mmol) in DMSO (10 mL) were stirred at 80 °C for 2 weeks. All volatiles were then removed in vacuo at 80 °C. The residue was washed with diethyl ether and dried in vacuo, leaving behind **6** (135 mg, 67%) as a light yellow powder, m.p. 148 °C. $C_{23}H_{25}N_2O_4PSZn$ (521.89): calcd. C 52.93, H 4.83, N 5.37, S 6.14; found C 53.56, H 4.92, N 6.32, S 7.08. ^{1}H NMR ([D$_6$]DMSO): δ = 1.91 [s, 3 H, CH_3(Tol)], 3.30 (d, *J* = 5.2 Hz, 6 H, OMe), 6.34 (d, *J* = 7.0 Hz, 2 H, Tol), 6.70 (d, *J* = 7.2 Hz, 2 H, Tol) ppm.

With 2 Equiv.: As above with **1c** (100 mg, 0.19 mmol) and $PO(OMe)_3$ (133 mg, 0.95 mmol), yielded **7** (85 mg, 85%) as a light yellow powder, m.p. 142 °C. $C_{18}H_{24}N_2O_8P_2Zn{\cdot}H_2O$ (523.73 + 18.02): calcd. C 39.91, H 4.84, N 5.17; found C 39.89, H 5.02, N 4.69. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 2 H, H_2O), 3.59 (d, *J* = 10.9 Hz, 12 H, OMe) ppm.

NMR Experiments: For all alkylation reactions described above, from which zinc complexes were isolated, the resultant alkyl thioethers which are known compounds[45−48] were identified by ^{1}H NMR spectroscopy, specifically by their characteristic *S*-methyl resonances. The NMR spectroscopic data showed that none of the reactions were clean, i.e. decomposition reactions and subsequent alkylations set in before the first alkylation step was complete. In those cases where the resultant zinc complexes could not be isolated, i.e. in the CH_3I methylations of **1d** and **1h** and the double methylations with CH_3I and $(CH_3O)_2SO_2$, the information on the reaction course rests on the NMR spectroscopic data alone. Likewise the qualitative determinations of reaction rates were done by ^{1}H NMR spectroscopy. This concerns the rates for methylations versus benzylations, for single versus double methylations and for methylations in chloroform versus methanol.

Thiolate Exchange: 1. A mixture of **1b** (9.9 mg, 19.0 μmol) and NaSEt (1.6 mg, 19.0 μmol) in CD_3OD (0.5 mL) reached equilibrium within 1 h. The intensity ratio of the benzyl CH_2 singlets for **1b** vs. NaSBn was 10:1. 2. **1b** (12.3 mg, 23.8 μmol) and $Na_2[SCH_2-C_6H_4-CH_2S]$ (5.1 mg, 23.8 μmol) in CD_3OD (0.25 mL) immediately produced a light yellow precipitate of **1g**. ^{1}H NMR of the solution showed that no more **1b** remaind and the major organic component was NaSBn.

Kinetic Measurements: The measurements were performed on 0.005−0.02 M $CDCl_3$ solutions of the zinc complex. Kinetic traces were recorded at 10-min intervals for reaction mixtures containing 4−10 mol-equiv. of CH_3I. The intensities of isolated ^{1}H NMR resonances were recorded. In all cases it was observed that the second alkylation sets in before the first half-life of the first alkylation is

Table 2. Crystallographic details

	1c	**1d**	**1g**	**1h**	**3g**	(neo)ZnI_2	**5**
Empirical formula	$C_{28}H_{26}N_2S_2Zn$	$C_{26}H_{20}N_4O_4S_2Zn$	$C_{22}H_{20}N_2S_2Zn{\cdot}CH_2Cl_2$	$C_{21}H_{18}N_2S_2Zn$	$C_{29}H_{27}IN_2S_2Zn$	$C_{14}H_{12}I_2N_2Zn$	$C_{30}H_{30}N_4O_8S_2Zn$
Formula mass	520.00	581.95	526.82	427.86	659.97	703.23	704.10
Crystal size [mm]	0.3 × 0.2 × 0.1	0.3 × 0.3 × 0.2	0.3 × 0.2 × 0.2	0.3 × 0.2 × 0.2	0.4 × 0.2 × 0.2	0.4 × 0.2 × 0.2	0.5 × 0.5 × 0.4
Space group	*Pbca*	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_1/c$
Z	8	4	4	4	4	4	4
a [Å]	15.929(1)	12.369(5)	12.794(3)	9.722(4)	8.011(2)	8.287(1)	17.739(4)
b [Å]	11.056(1)	18.502(7)	14.928(3)	16.288(6)	37.246(7)	14.221(2)	13.653(3)
c [Å]	28.218(1)	12.005(5)	13.356(3)	11.688(5)	10.485(4)	13.765(2)	12.885(3)
α [°]	90	90	90	90	90	90	90
β [°]	90	116.651(6)	115.38(3)	92.116(7)	117.09(2)	103.376(3)	105.85(3)
γ [°]	90	90	90	90	90	90	90
V [Å^3]	4969.5(5)	2455.4(16)	2304.6(8)	1849.6(13)	2785.2(13)	1578.2(3)	3002(1)
$d_{calcd.}$ [g cm^{-3}]	1.39	1.57	1.52	1.54	1.57	2.22	1.56
μ(Mo-$K_α$) [mm^{-1}]	1.18	1.21	1.49	1.56	2.16	5.46	1.02
hkl range	*h*: −21 to 21	*h*: −16 to 11	*h*: −14 to 15	*h*: −12 to 11	h:-9 to 0	*h*: −9 to 9	*h*: −20 to 19
	k: −14 to 14	*k*: −23 to 24	*k*: 0 to 18	*k*: −19 to 9	*k*: 0 to 45	*k*: −15 to 15	*k*: −16 to 15
	l: −37 to 37	*l*: −15 to 16	*l*: −16 to 0	*l*: −11 to 15	*l*: −11 to 12	*l*: −15 to 15	*l*: 0 to 14
Reflections measured	43154	15529	4725	5544	5842	10802	10671
Independent reflections	6163	5941	4521	3991	5450	2269	5507
Obsd. reflections [$I > 2σ(I)$]	3094	4627	3339	1357	3603	1735	4495
Parameters	298	334	271	235	316	172	438
Reflections refined	6163	5941	4521	3991	5450	2269	5507
*R*1 (obsd. reflections)	0.056	0.031	0.049	0.076	0.051	0.023	0.036
*wR*2 (all reflections)	0.156	0.091	0.161	0.272	0.161	0.051	0.125
Residual density [e/Å^{-3}]	+0.6/−0.6	+0.5/−0.4	+0.6/−0.8	+0.8/−1.1	+0.8/−1.0	+0.5/−0.5	+1.6/−0.5

reached. This virtually prevented the determination of rate constants. Detailed investigations were made for the CH_3I methylation of **1g** and **1h**. Taking the data for the first hour of the methylation of **1g** (ca. 40% conversion), pseudo-first-order rate constants could be obtained which were roughly 100 times smaller than those for the methylation of $Tp^{Ph,Me}Zn-SBn$ under similar conditions.[30] The methylation of **1h**, for which the kinetic traces are displayed in Figure 5, is about one order of magnitude faster.

Structural Determiantions:[50] Crystals were obtained as described in the Exp. Sect. Diffraction data were recorded at room temp. [**1g**, **1h**, **3g**, (neo)ZnI_2, **5**] and at −90 °C (**1c**, **1d**) with a Nonius CAD4 (**5**) or a Bruker Smart CCD diffractometer [**1c**, **1d**, **1g**, **1h**, **3g**, (neo)ZnI_2]. Empirical absorption corrections were applied for **1c**, **1d**, **1g**, **1h**, **3g**, and (neo)ZnI_2. The structures were solved with direct methods and refined anisotropically using the SHELX[51] program suite. Hydrogen atoms were included at fixed distances and isotropic temperature factors 1.2 times those of the atoms to which they are attached. Parameters were refined against F^2. Drawings were produced with SCHAKAL.[52] Table 2 lists the crystallographic data.

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