Arabian Journal of Chemistry (2014) 7, 672–679

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Structural zinc(II) thiolate complexes relevant to the modeling of *Ada* repair protein: Application toward alkylation reactions

Mohamed M. Ibrahim [a,b,*], **A. Mosa** [c]

[a] *Chemistry Department, Faculty of Science, Kafr El-Sheikh University, Kafr El-Sheikh 33516, Egypt*
[b] *Chemistry Department, Faculty of Science, Taif University, Alhawiya 888, Saudi Arabia*
[c] *Chemistry Department, Faculty of Science for Girls, King Abd Al Aziz University, Jeddah, Saudi Arabia*

Received 14 October 2010; accepted 3 December 2010
Available online 13 December 2010

KEYWORDS

Biomimetic;
Zinc(II)-bound thiolate complexes;
Hydrogen bonding;
A*da* repair protein;
Alkylation

Abstract The **Tt**Zn(II)-bound perchlorate complex [TtZn–$OClO_3$] **1** (Ttxyly = hydrotris[*N*-xylyl-thioimidazolyl]borate) was used for the synthesis of zinc(II)-bound ethanthiothiol complex [**Tt**Zn–SCH_2CH_3] **2** and its hydrogen-bond containing analog **Tt**–ZnSCH_2CH_2–NH(C═O)$OC(CH_3)_3$ **3**. These thiolate complexes were examined as structural models for the active sites of *Ada* repair protein toward methylation reactions. The Zn[S_3O] coordination sphere in complex **1** includes three thione donors from the ligand Tti^{xyl} and one oxygen donor from the perchlorate coligand in ideally tetrahedral arrangement around the zinc center. The average Zn(1)–S(thione) bond length is 2.344 Å, and the Zn(1)–O(1) bond length is 1.917 Å.

1. Introduction

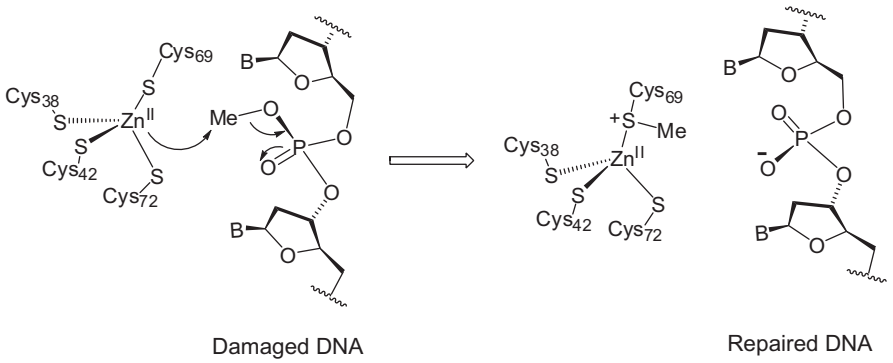
The coordination of zinc in a sulfur-ligated environment is a prominent feature of structural and functional sites of many important metalloproteins. Examples of such enzymes include the liver alcohol dehydrogenase (Jeremias and Vallee, 1960), *Ada* repair protein (Lindahl, 1993), the cobalamine-dependent and -independent methionine synthases, and farnasyltransferase (Matthews and Goulding, 1997). N-*Ada* protein contains a zinc ion tightly bound to four cysteine residues, one of which is Cys_{69}, the methyl acceptor. Alkylation occurs on Cys_{69}, showing that this particular cysteine ligand is electronically activated relative to the other three cysteines (Scheme 1). The thiolate sulfur atoms of Cys_{38}, Cys_{42}, and Cys_{72} are hydrogen-bonded to amide protons of the protein main chain, which not only suppresses their reactivity but also stabilizes the protein structure. On the other hand, the Cys_{69}–S^- is devoid of hydrogen-bonding interactions (Habazettl et al., 1996).

One of the approaches, adapted to resolve the nature of the active site in thiolate-alkylating zinc enzyme, has been to design various types of zinc complexes to account for or to

* Corresponding author at: Chemistry Department, Faculty of Science, Kafr El-Sheikh University, Kafr El-Sheikh 33516, Egypt. Tel.: +20 402253285; fax: +20 473223415.
E-mail address: ibrahim652001@yahoo.com (M.M. Ibrahim).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2010.12.001



Scheme 1 Repair of damaged DNA by sacrificial methylation of one of the zinc cysteine thiolate ligands of the N-Ada protein.

mimic the functions of the central zinc ion (Wilker and Lippard, 1995; Chiou et al., 2000; Melnick et al., 2006; Warthen et al., 2001; Brand et al., 2001; Ji et al., 2005). As a part of our studies in biomimetic zinc(II) chemistry, we have started a research program to understand how the nature of the bound thiolate coligand could affect the rate of methylation reactions (Ibrahim et al., 2005a,b,c, 2006a,b,c, 2009; Ibrahim and Vahrenkamp, 2006; Rombach et al., 2006; Shaban et al., 2007; Ibrahim, 2009, 2010; Ibrahim and Shaban, 2009). Here we report the reactivity studies of the thiolate complex [**Tt**ZnSCH_2CH_3] (**2**) and its H-bonding containing analog [**Tt**ZnSCH_2CH_2–NH(C═O)$OC(CH_3)_3$] (**3**) (Scheme 2) toward methylation reactions using both methyl iodide and trimethyl phosphate as methylating agents. The ^{1}H NMR measurements provided an important basis for the methylation reactions of these mentioned thiolate complexes. The aim of the present study is to understand how the structure of zinc thiolates is affected by the presence of intramolecular hydrogen-bonding interactions. The crystal structure of **Tt**Zn−$OClO_3$·$2CH_3OH$ (**1**) is also reported.

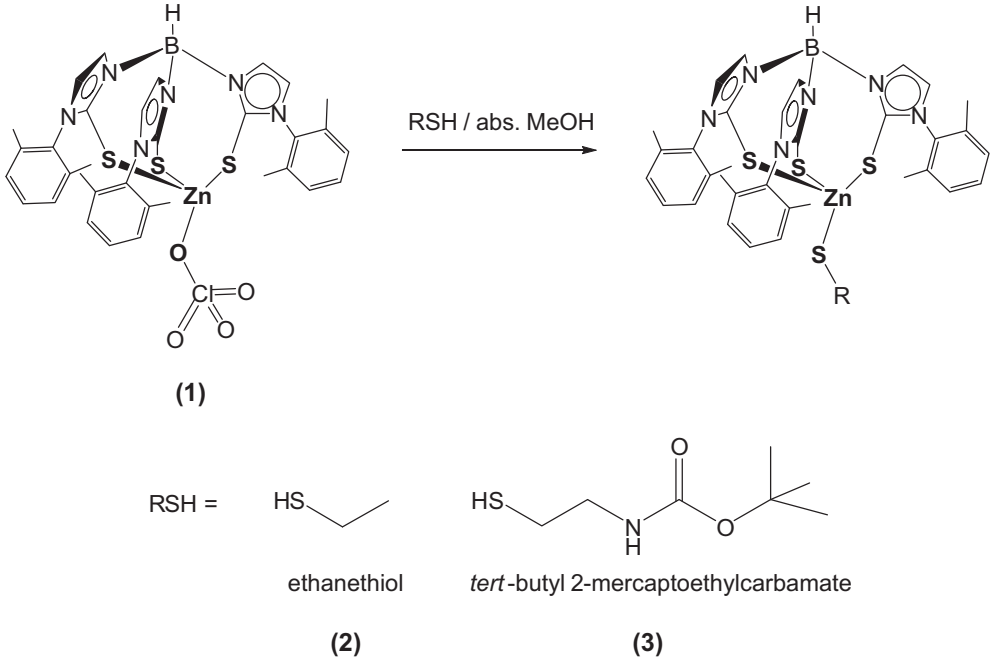
2. Experimental section

2.1. General

The synthesis of the zinc model complexes **Tt**ZnSCH_2CH_3 (**2**) and **Tt**ZnSCH_2CH_2–NH(C═O)$OC(CH_3)_3$ (**3**) (**Tt** = tris(2-mercapto-1-xylyl-imidazolyl)-hydroborate) by the reaction of equimolar amounts of the perchlorate complex **Tt**Zn–$OClO_3$ (**1**) Ibrahim et al., 2005a and the deprotonated forms of both ethanethiol and its protected form *tert*-Butyl *N*-(2-mercaptoethyl)carbamate, respectively, in absolute methanol was described previously (Ibrahim et al., 2005c). All other organic reagents were bought from Merck.

2.2. X-ray single crystal determination of complex (*1*)

Crystals of (**1**) were obtained by recrystallisation from methanol: dichloromethane (3:1) mixture, all others were taken as obtained from the workup procedures. Data sets (Table 1)



Scheme 2 Representation of the zinc(II)-bound perchlorate complex (**1**) and the thiolate complexes (**2**) and (**3**).

Table 1 Crystal data and structure refinement for complex **1**.

	1·2CH_3OH
Empirical formula	C_{35} $H_{41}BClN_6O_6S_3Zn$
Formula weight	849.55
Crystal size [mm]	$0.13 \times 0.17 \times 0.23$
Crystal color	colorless
Space group	P2(1)/c
Z	4
a [Å]	11.2526(18)
b [Å]	17.794(3)
c [Å]	23.128(4)
α [°]	90
β [°]	98.067(3)
γ [°]	90
Volume [$Å^3$]	4585.1(13)
d (calc.) [g/cm^3]	1.231
μ (MoKα) [mm^{-1}]	0.775
Temperature [K]	293(2)
Θ-range [°]	1.45–28.83
Index ranges	$-15 \leqslant h \leqslant 15$
	$-23 \leqslant k \leqslant 23$
	$-30 \leqslant l \leqslant 30$
Absorption correction	SADABS
Reflections collected	40,428
Independent reflections	11,104[R(int) = 0.0923]
Refelctions observed [$I > 2\sigma$ (I)]	4687
Data	11,104
Parameters	458
Goodness-of-fit	1.701
Final R indices [$I > 2\sigma$ (I)]	R1 = 0.1061, wR2 = 0.2925
R indices (all data)	R1 = 0.2408, wR2 = 0.3478
Largest diff. peak [e $Å^{-3}$]	3.111
And hole	−1.700

were obtained at 293 and 203 K for complex **1** with a Bruker AXS Smart CCD diffractometer and subjected to empirical absorption corrections (SADABS) SAINT 1999; Sheldrick, 1996. The structures were solved with direct methods and refined anisotropically using the SHELX program suite (Sheldrick, 1997). The relatively high value of R factor that we observe of 10.6% may be due to the disorder of the perchlorate oxygen atoms and the methanol molecules. Hydrogen atoms were included with fixed distances and isotropic temperature factors 1.2 times those of their attached atoms. Parameters were refined against F2. Table 1 lists the crystallographic details.

2.3. Reaction of *1* and *2* with methyl iodide, CH_3I

According to Table 2, the zinc-bound thiolate complexes (**2**) and (**3**) were reacted with an excess of methyl iodide in dried dichloromethane. The reaction mixture was stirred for 2 hrs. The volatiles were removed in vacuo, and the residue was washed with 2-ml portions of diethylether, and dried in vacuo. The residue of the methylation reactions was spectroscopically pure **Tt**Zn–I (Ibrahim et al., 2005a). The solvent of the washed diethyether was removed. The residue was picked up in $CDCl_3$. The ^{1}H NMR measurement of the produced thioether is also shown in Table 2.

2.4. Kinetic measurements

2.4.1. Kinetic measurements for the reaction of thiolate complexes (*2*) and (*3*) with CH_3I

All experiments were performed under pseudo-first-order conditions with large excess of methyl iodide. In a typical experiment, 10 mM of the thiolate complex was dissolved in $CDCl_3$ followed by addition of 5–15 equivalents of MeI. All the reactions were monitored by ^{1}H NMR spectroscopy at 300 K. Whereas for complex (**2**), the measurements have been done at 290 K. The ^{1}H NMR signals of the three thioimidazolyl protons of the reactant thiolate complexes (**2**) or (**3**) and the produced iodo complex (Ibrahim et al., 2005c) were used as an integral standard. The increase in the intensity of the ethyl protons of the produced methylthioether was recorded and integrated relative to the standard thioimidazole protons.

2.4.2. Kinetic measurements for the reaction of complex (*1*) with $(CH_3O)_3PO$

The experiment was carried out under pseudo-first-order condition with large excess of (**2**). In a typical experiment, a solution of (**2**) [4.5 mg(6 μmol)] and trimethylphosphate $(CH_3O)_3PO$ [9.6 μl (0.48 μmol, 0.05 M)] was incubated in $CDCl_3$ (600 μl) at 40 °C for 4 weeks. The concentrations of the reactant [$(CH_3O)_3PO$] and products [$(CH_3O)_2PO_2^-$ & $CH_3SCH_2CH_3$] were determined by referencing peak integrals to the internal standard, TMS. The ^{1}H NMR measurements were done at time intervals of 24 h. The first order rate constants were calculated from the slopes of the linear plots of ln ($1–I_t/I_o$) versus time.

3. Results and discussion

The zinc perchlorate complex **Tt**Zn–$OClO_3$ (**1**) was obtained by treating the $Zn(ClO_4)_2$ with an equivalent amount of the ligand K**Tt** in methanol (Ibrahim et al., 2005a). The existence of complex (**1**) was proved by its structure determination. We designed and synthesized the zinc(II) thiolate complexes (**2**) and (**3**) as structural models for the active site of *Ada* repair protein (Lindahl, 1993) providing (i) tripodal ligands, which correspond to three cysteine amino

Table 2 Procedure and assignments of the methylation reactions of the thiolate complexes **2** and **3** with methyl iodide.

Thiolate complex (mg, mmol)	CH_3I (μl, mmol)	Iodo complex Yield (mg, %)	Thioether ^{1}H NMR ($CDCl_3$)
1 (32 mg, 0.043 mmol)	(11 μl, 0.17 mmol)	(33 mg, 94%)	**[$CH_3SCH_2CH_3$]** 1.27 [t, J = 7.40 Hz, 3H, CH_3(Et)], 2.11 [s, 3H, SMe], 2.52 [q, J = 7.40 Hz, CH_2(Et)]
2 (24 mg, 0.028 mmol)	(8 μl, 0.12 mmol)	(19 mg, 85%)	**CH_3S-carbamate** 1.45 [s, 9H, Me (*t*-but)], 2.11 [s, 3H, SMe], 2.63 [t, J = 6.6 Hz, 2H, CH_2 (CH_2N)], 3.33 [m, 2H, CH2 (CH2S)], 4.86 [m, 1H, NH]

acids, (ii) hydrophobic pockets, which specify the formation of 1:1 zinc(II) complex, and changeable thiolate coligands to achieve the formation of S_4Zn tetrahedral environment, as mentioned in Scheme 2.

*3.1. 1. X-ray structure determination of complex (**1**)*

Complex (**1**) crystallizes in monoclinic crystal system in the space group $P2_1/c$. An ORTEP representation of its molecular structure is shown in Fig. 1 with selected bond lengths and angles contained in Table 3. The Zn[S_3O] coordination sphere in complex (**1**) includes three thione donors from the ligand **Tt** and one oxygen donor from the perchlorate coligand in ideally tetrahedral arrangement around the zinc center. The average Zn(1)–S(thione) bond length, 2.344 , is in the same range to those found in **Tt**Zn-bound acetate and nitrate complexes (Ibrahim et al., 2005a). The Zn(1)–O(1) bond length of 1.917 is shorter than that found in the tetrahedral zinc-bound perchlorate complexes of the related ligand system tris(tertbutylthioimidazolyl) (Tesmer et al., 2001) [2.040] and close to the other related system {[Tm^{Me}]Zn(mim^{Me})}····($OClO_3$)} (2.709) Morlok et al., 2004, in which the $OClO_3^-OClO_3^-$ serves as a hydrogen bond acceptor. The relatively high value of R factor that we observe of 10.6% may be due to the disorder of the perchlorate oxygen atoms and the methanol molecules. I have tried to refine the structure with different space groups.

3.2. 1. Methylation reactions

The reactions of methyl iodide with complexes **(2)** and **(3)** were run in dichloromethane at 300 K (Scheme 3) on a preparative scale and were essentially quantitative according to ^{1}H NMR. The methylation reactions with both complexes were fast and went into completion within minutes. The methyl thioethers thus formed are not coordinated to the zinc in the final product and were identified by their known ^{1}H NMR spectra. The produced zinc-bound iodide complexes were isolated in each case by crystallization, while the methyl thioethers were normally removed with the volatiles. In an attempt to apply more 'natural' methylating agents, complex **(2)** was treated with trimethyl phosphate, TMP, as a mimic of the organophosphates in the *Ada* process (Scheme 3). The reaction of **(2)** with an equimolar ratio of TMP in chloroform yielded the zinc(II)-dimethyl phosphate, TtZn-OP(O)$(OCH_3)_2$, and methyl thioether, $CH_3SCH_2CH_3$, as indicated by ^{1}H NMR spectroscopy.

Table 3 Bond lengths [Å] and angles [°] of complex **1**.

Zn(1)–O(1)	1.917
Zn(1)–S(1)	2.339
Zn(1)–S(2)	2.346
Zn(1)–S(3)	2.349
O(1)–Zn(1)–S(1)	114.4
O(1)–Zn(1)–S(2)	107.5
S(1)–Zn(1)–S(2)	108.2
O(1)–Zn(1)–S(3)	111.4
S(1)–Zn(1)–S(3)	107.1
S(2)–Zn(1)–S(3)	108.0

3.3. Kinetic investigation for the methylation reactions

Reaction of (**2**) and (**3**) with CH_3I in deuterated chloroform results in the quantitative formation of methylthioethers and **Tt**Zn(II)-bound iodide complex (Ibrahim et al., 2005c) indicated in Scheme 3. The pseudo-first-order constants k_{obs} were calculated.

The reaction of (**2**) with methyl iodide was followed in ^{1}H NMR at 290 K by monitoring the decrease and increase in the intensities of the methyl and methylene resonances of the consumed (**2**) and the produced methyl ethyl thioether. The proton chemical shifts of the resulting $CH_3SCH_2CH_3$ are identical to those of a genuine sample, indicating that the thioether product is not coordinated to zinc(II) ions as identified by ^{1}H NMR (Ibrahim et al., 2005a,b,c; Ibrahim, 1989; Ibrahim and Vahrenkamp, 2006; Rombach et al., 2006; Ibrahim, 2006a,b; Shaban et al., 2007; Ibrahim, 2009, 2010; Ibrahim and Shaban, 2009; Ibrahim et al., 2009; Morlok et al., 2004; Grapperhaus et al., 1998; Brand et al., 1998; Burth and Vahrenkamp, 1998; Brand et al., 2001; Seebacher et al., 2003; Ji and Vahrenkamp, 2005; Ji et al., 2005; Bridgewater et al., 2000; Parkin, 2004; Hammes and Crrano, 1999, 2000a,b, 2001; Chiou et al., 2000, 2003; Morlok et al., 2005). The smoothness of the alkylation reactions and the non-polar reaction conditions provide strong evidence that the thiolates are alkylated in the zinc-bound state. A time dependent ^{1}H NMR spectra for the reac-

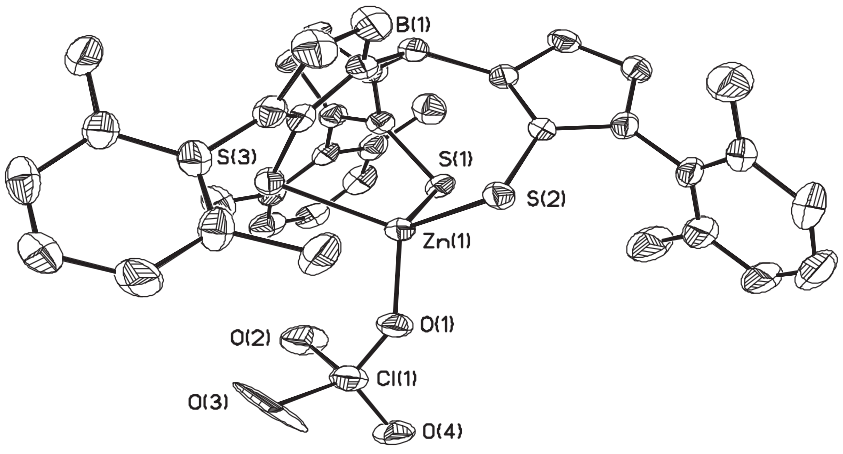
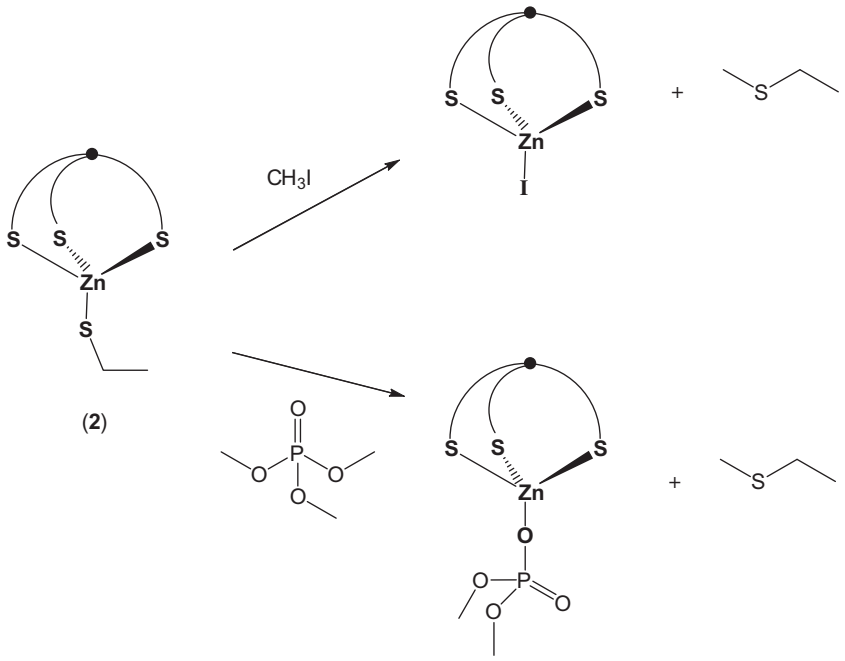


Figure 1 ORTEP drawing of molecular structure of **Tt**Zn–$OClO_3$ **1**. Ellipsoids are depicted at 30% probability level.



Scheme 3 Reaction pathways of the thiolate complex (**2**) with the methylating agents methyl iodide and tri(methyl)phosphate.

tion between **2** and CH_3I in $CDCl_3$ as a representative example is shown in Fig. 2. The reaction of (**2**) with CH_3I was too fast to the point that we could not follow the kinetic measurements at high concentrations of CH_3I and the pseudo-first order rate constant (Fig. 3) at concentration of 50 mM of CH_3I was calculated to be 1.4×10^{-3} s^{-1} at 290 K and it was estimated to be 8.6×10^{-1} s^{-1} at 300 K.

Due to the high reactivity of (**2**) toward methylation by using methyl iodide, we applied trimethylphosphate, $(CH_3O)_3PO$, as a methylating agent. The methyl transfer from $(CH_3O)_3PO$ to (**2**) was followed in NMR at 314 K by recording the decrease in the intensities of $(CH_3O)_3PO$ and the increase in the intensities of $(CH_3O)_2PO_2^-$. A time dependent

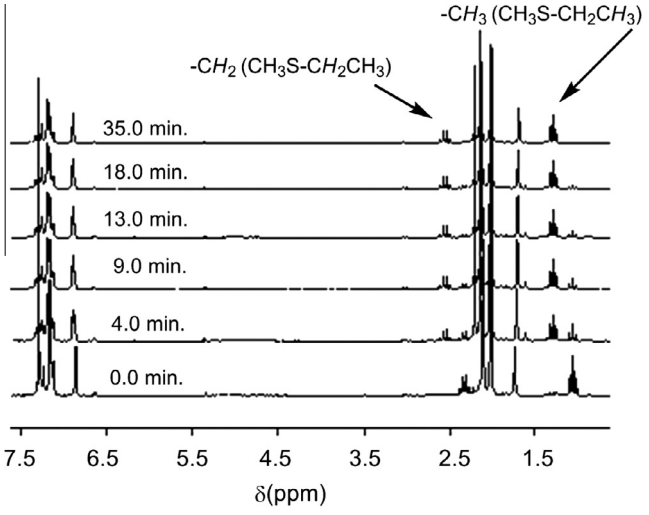


Figure 2 ^1H NMR spectra for the reaction of **2** (10 mM) with CH_3I (50 mM) in $CDCl_3$ at 290 K as a function of time.

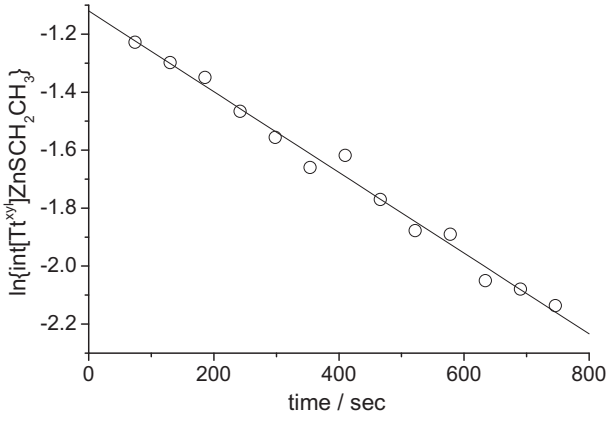


Figure 3 Semilogarthmic plot for the methylation of **2** (10 mM) by using CH_3I (50 mM) in $CDCl_3$ at 290 K.

^1H NMR spectra for the reaction between **2** and $(CH_3O)_3PO$ in $CDCl_3$ as a representative example is shown in Fig. 4. The ^1H NMR spectra displayed two doublet peaks at 3.71 and 3.26 ppm, which were assigned to the trimethyl phosphate and bound dimethyl phosphate, respectively. As shown in Fig. 5 the plots of $(CH_3O)_3PO$ concentration versus time gave the value of k_{obs} at 314 K as 4.04×10^{-6} s^{-1}.

The structural details of zinc thiolate complex (**3**) provided intramolecular NH···S hydrogen-bonding interactions (Ibrahim, 2006b). The reaction of (**3**) with CH_3I was kinetically measured at 300 K. It was followed in ^1H NMR by recording the decrease and increase in the intensities of the methylene resonances of the consumed (**3**) and the produced methyl tert-butyl *N*-(2-mercaptoethyl)carbamate thioether, $(CH_3)_3CO–C(O)NH–CH_2CH_2SCH_3$. Fig. 6 shows a representative set of the methylene proton resonances.

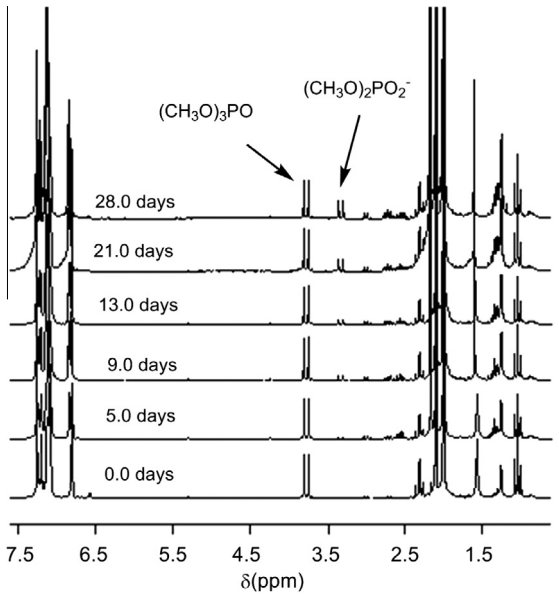


Figure 4 ^{1}H NMR spectral changes used to follow the reaction of **2** (1.0×10^{-3} M) with $(CH_3O)_3PO$ (0.8×10^{-4} M) in $CDCl_3$ at 40 °C.

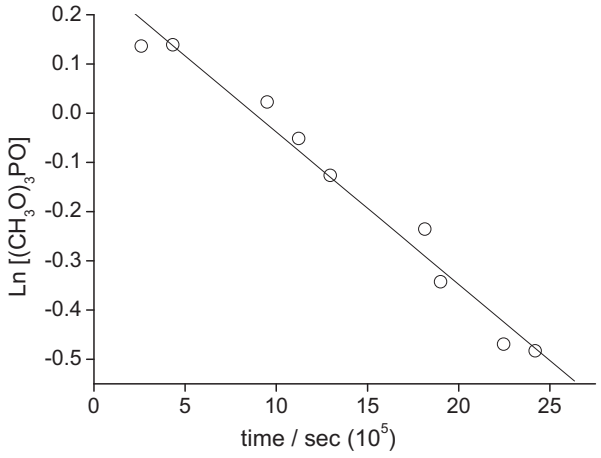


Figure 5 Plot of the logarithm intensity versus time for the methylation of **2** (1.0×10^{-3} M) by using $CH_3O)_3PO$ (0.8×10^{-4} M) in $CDCl_3$ at 40 °C.

The value of the first-order rate constant, k_{obs}, for the methylation of (**3**) at a concentration of 50 mM at 300 K, Fig. 7, was calculated to be 3.13×10^{-3} s^{-1}. From the comparison of the reactivity between the thiolate complexes (**2**) and (**3**), we found that the rate of methylation for the complex (**3**) reduced *ca.* 2 order of magnitude than that found in the case of complex (**2**). This indicates that the NH···S hydrogen-bonding interactions between the thiolate sulfur and amide NH provided a quantitative assessment in altering its reactivity. For example, Riordan and Carrano (Hammes and Crrano, 1999, 2000a,b, 2001; Chiou et al., 2000, 2003; Morlok et al., 2005) reported rates for methyl iodide reaction to both [Ph(PztBu)]Zn(SC_6H_4-o-NHC(O)tBu) of 1.3×10^{-4} M^{-1} s^{-1} and [L1O] Zn(SC_6H_4-o-NHC(O)Me) of ca. 1.2×10^{-4} M^{-1} s^{-1}, respectively. This difference in reactivity is due in a

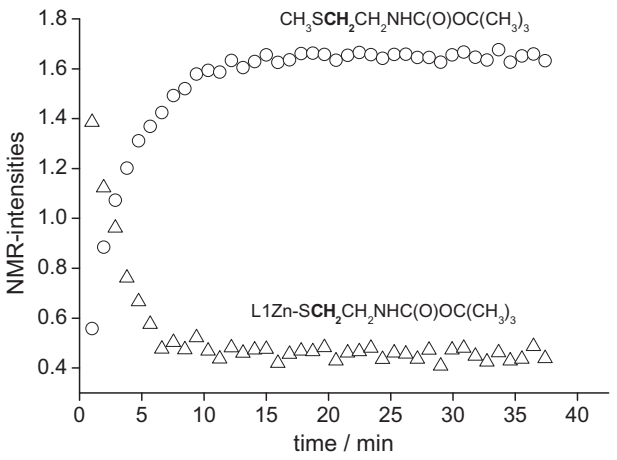


Figure 6 ^{1}H NMR intensities of the methylene protons of **3** and $(CH_3)_3COC(O)NHCH_2CH_2SCH_3$ as a function of time for the reaction of **3** (10 mM) with CH_3I (50 mM) in $CDCl_3$ at 300 K.

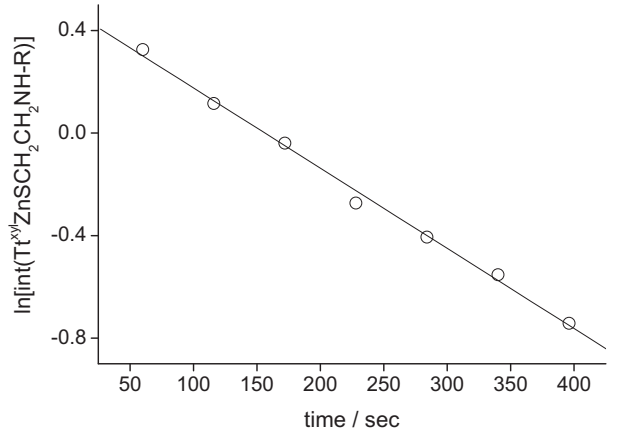


Figure 7 Semilogarthmic plot for the methylation of **3** (10 mM) by using CH_3I (50 mM) in $CDCl_3$ at 300 K.

part to the nature of the electron-releasing property of the hydroxo/amino versus amido substituents and in other part to the coordination environment of the zinc ion in the thiolate-alkylating enzymes. Most of these enzymes have a sulfur-rich coordination of zinc. It suggests that coordination of zinc by sulfur donors is the most efficient way to increase its electron density and hence the nucleophilicity of the zinc bound thiolate coligands (Rombach et al., 2006).

4. Conclusion

The reactivity of both **Tt**Zn–SCH_2CH_3 (**2**) and **Tt**Zn–SCH_2CH_2–NH(C═O)$OC(CH_3)_3$ as model complexes for the active sites of *Ada* repair protein toward methylation reactions showed that the presence of such a NH···S hydrogen-bond provides a quantitative assessment in altering the reactivity of the zinc-bound thiolate. Specifically, the nucleophilicity of (**3**) is decreased by the intramolecular hydrogen-bonding, and hence (**3**) is methylated by an order of magnitude slower than its non H-bonding analog (**2**).

Acknowledgment

The author gratefully acknowledges Professor Heinrich Vahrenkamp for his valuable discussions during this work.

References

Brand, U., Rombch, M., Vahrenkamp, H., 1998. Methylation of zinc bound thiolates; a model for cobalamine independent methionine synthase. J. Chem. Soc. Chem. Commun., 2717–2718.

Brand, U., Rombach, M., Seebacher, J., Vahrenkamp, H., 2001. Functional modeling of cobalamine-independent methionine synthase with pyrazolylborate-zinc-thiolate complexes. Inorg. Chem. 40, 6151–6157.

Brand, U., Rombach, M., Seebacher, J., Vahrenkamp, H., 2001. Functional modeling of cobalamine-independent methionine synthase with pyrazolylborate-zinc-thiolate complexes. Inorg. Chem. 40, 6151–6157.

Bridgewater, B.M., Fillebeen, T., Friesner, R.A., Parkin, G., 2000. A zinc thiolate species which mimics aspects of the chemistry of the Ada repair protein and matrix metalloproteinases: the synthesis, structure and reactivity of the tris(2-mercapto-1-phenylimidazolyl)hydroborato complex [Tm^{Ph}]ZnSPh. J. Am. Chem. Soc., Dalton Trans., 4494–4496.

Burth, R., Vahrenkamp, H., 1998. Monomere Tripod-Zink-Thiolat-Komplexe. Z. Anorg. Allg. Chem. 624, 381–385.

Chiou, S.J., Innocent, J., Riordan, C.G., Lam, K.C., LiableSands, L., Rheingold, A.L., 2000. Synthetic models for the zinc sites in the methionine synthases. Inorg. Chem. 39, 4347–4353.

Chiou, S.J., Innocent, J., Riordan, C.G., Lam, K.C., Liable-Sands, L., Rheingold, A.L., 2000. Synthetic models for the zinc sites in the methionine synthases. Inorg. Chem. 39, 4347–4353.

Chiou, S.J., Riordan, C.G., Rheingold, A.L., 2003. Synthetic modeling of zinc thiolates: quantitative assessment of hydrogen bonding in modulating sulfur alkylation rates. Proc. Natl. Acad. Sci. USA 11, 3695–3700.

Grapperhaus, C.A., Tuntulani, T., Reibenspies, J.H., Darensbourg, M.Y., 1998. Methylation of tethered thiolates in $[(bme\text{-}daco)Zn]_2$ and $[(bme\text{-}daco)Cd]_2$ as a model of zinc sulfur-methylation proteins. Inorg. Chem. 37, 4052–4058.

Habazettl, J., Myers, L.C., Yuan, F., Verdine, G.L., Wagner, G., 1996. Backbone dynamics, amide hydrogen exchange, and resonance assignments of the DNA methylphosphotriester repair domain of *Escherichia coli Ada* using NMR. Biochemistry 35, 9335–9348.

Hammes, B.S., Crrano, C.J., 1999. Synthesis and characterization of pseudotetrahedral N_2O and N_2S zinc(II) complexes of two heteroscorpionate ligands: models for the binding sites of several zinc metalloproteins. Inorg. Chem. 38, 4593.

Hammes, B.S., Crrano, C.J., 2000a. Methylation of (2-methylethanethiol-bis-3,5-dimethylpyrazolyl)methane zinc complexes and coordination of the resulting thioether: relevance to zinc-containing alkyl transfer enzymes. Chem. Commun., 1635–1636.

Hammes, B.S., Crrano, C.J., 2000b. Structure and physical properties of several pseudotetrahedral zinc complexes containing a new alkyl thiolate heteroscorpionate ligand. J. Chem. Soc., Dalton Trans., 3304–3309.

Hammes, B.S., Crrano, C.J., 2001. Methylation of (2-Methylethanethiol-bis-3,5-dimethylpyrazolyl)methane zinc complexes and coordination of the resulting thioether: relevance to zinc-containing alkyl transfer enzymes. Inorg. Chem. 40, 919–927.

Ibrahim, M.M., 2006a. Phosphate triester hydrolysis promoted by S_3-Zinc(II) complexes with bridged hydroxide: the crystal structure of $TtiZn{-}OP(O)(OC_6H_4\text{-}p\text{-}NO_2)_2$, Tti = hydrotris(N-xylyl-2-thioimidazolyl)-borate. Inorg. Chem. Commun. 9, 1215–1218.

Ibrahim, M.M., 2006b. The influence of hydrogen bonding on the rate of thiolate alkylation in tripod-zinc thiolate complexes. Inorg. Chim. Acta. 359, 4235–4242.

Ibrahim, M.M., 2009. Functionalized $S_4Zn(II)$ complexes as structural modeling for the active site of thiolate-alkylating enzymes: the crystal structure of $[TtiZn\text{-}SPH]_2{\cdot}HClO_4$ [Tti = tris(thioimidazolyl)borate and SPyH = pyridine-2-thiol)]. J. Mol. Struct. 937, 50–55.

Ibrahim, M.M., 2010. S_4Zn (II) complexes-containing Cysteine derivatives as Structural Methionine Synthase Models: their ctalytic activities toward methylation reactions. J. Sulfur Chem. 31, 395–403.

Ibrahim, M.M., Shaban, S.Y., 2009. Synthesis, characterization, and molecular structures of hydrotris(2-mercapto-1-xylyl-imidazolyl)borate-based Zn(II) and Cu(I) complexes. Inorg. Chim. Acta 362, 1471–1477.

Ibrahim, M.M., Vahrenkamp, H., 2006. Unusual formation and structure of a O-sulfinato zinc complex. Z. Anorg. Allg. Chem., 1083–1085.

Ibrahim, M.M., Shu, M., Vahrenkamp, H., 2005a. New tris(thioimidazolyl)borate ligands and some zinc complexes thereof. Eur. J. Inorg. Chem., 1388–1397.

Ibrahim, M.M., He, G., Seebacher, J., Benkmil, B., Vahrenkamp, H., 2005b. Biomimetic thiolate alkylation with pyrazolyl-bis(thioimidazolyl)borate zinc complexes. Eur. J. Inorg. Chem., 4070–4077.

Ibrahim, M.M., Seebacher, J., Steinfeld, G., Vahrenkamp, H., 2005c. Tris(thioimidazolyl)-borate-zinc-thiolate complexes for the modeling of biological thiolate alkylations. Inorg. Chem. 44, 8531–8538.

Ibrahim, M.M., Olmo, C.P., Tekeste, T., Seebacher, J., He, G., Calvo, J.A.M., Böhmerle, K., Steinfeld, G., Brombacher, H., Vahrenkamp, H., 2006a. Zn–OH2 and Zn–OH Complexes with hydroborate-derived tripod ligands–a comprehensive study. Inorg. Chem. 45, 7493–7502.

Ibrahim, M.M., Gaied, S.S., Al-Qahtani, M.M., 2009. Synthesis and characterization of 2-mercapto-1-cyclohexylimidazole-based zinc(II) and cadmium(II) bromide complexes: the crystal structure of $[Zn(Hmim^{chexyl})_2(Br)_2]$ with N–H(((Br intermolecular hydrogen bonding interactions. Phosphorus, Sulfur Silicon Relat. Elem. 185, 2324–2332.

Jeremias, H.R.K., Vallee, B.L., 1960. The role of zinc in alcohol dehydrogenase. J. Biol. Chem. 235, 3188–3192.

Ji, M., Vahrenkamp, H., 2005. Zinc-thiolate complexes of (N,N,S)-tridentate ligands for the modeling of thiolate alkylating enzymes. Eur. J. Inorg. Chem., 1398–1405.

Ji, M., Benkmil, Vahrenkamp, H., 2005. Zinc-thiolate complexes of the bis(pyrazolyl)-(thioimidazolyl)hydroborate tripods for the modeling of thiolate alkylating enzymes. Inorg. Chem. 44, 3518–3523.

Ji, M., Benkmil, B., Vahrenkamp, H., 2005. Zinc-thiolate complexes of the bis(pyrazolyl)(thioimidazolyl)hydroborate tripods for the modeling of thiolate alkylating enzymes. Inorg. Chem. 44, 3518–3523.

Lindahl, T., 1993. Instability and decay of the primary structure of DNA. Nature 362, 709–713.

Matthews, R.G., Goulding, C.W., 1997. Enzyme-catalyzed methyl transfers to thiols: the role of zinc. Curr. Opin. Chem. Biol. 1, 332–339.

Melnick, J.G., Zhu, G., Buccella, D., Parkin, G., 2006. Thiolate exchange in [Tm^R]ZnSR′complexes and relevance to the mechanisms of thiolate alkylation reactions involving zinc enzymes and proteins. J. Inorg. Biochem. 100, 1147–1154.

Morlok, M.M., Docrat, A., Janak, K.E., Tanski, J.M., Parkin, G., 2004. The molecular structure of the tris(2-mercapto-1-tolylimidazolyl)hydroborato zinc(2-mercapto-1-tolylimidazole) complex, {[Tmp-Tol]Zn(mimp-Tol)}[ClO4]: intermolecular N–HO···ClO3 versus intramolecular N–H···S hydrogen bonding interactions of the mercaptoimidazole ligand.. J. Chem. Soc., Dalton Trans., 3448–3452.

Morlok, M.M., Janak, K.E., Zhu, G., Quarless, D.A., Parkin, G., 2005. Intramolecular N-H···S hydrogen bonding in the zinc thiolate complex [Tm^{Ph}]$ZnSCH_2C(O)NHPh$: a mechanistic investigation of thiolate alkylation as probed by kinetics studies and by kinetic isotope effects. J. Am. Chem. Soc. 127, 14039–14050.

Parkin, G., 2004. Synthetic analogues relevant to the structure and function of zinc enzymes. Chem. Rev. 104, 699–768.

Rombach, M., Seebacher, J., Ji, M., Zhang, G., He, G., Ibrahim, M.M., Benkmil, B., Vahrenkamp, H., 2006. Thiolate alkylation in tripod-zinc complexes: a comparative kinetic study. Inorg. Chem. 45, 4571–4575.

SAINT, 1999. V6.02, Bruker AXS, Madison, WI.

Seebacher, J., Ji, M., Vahrenkamp, H., 2003. (Neocuproin)zinc thiolates: attempts at modeling cobalamin-independent methionine synthase. Eur. J. Inorg. Chem., 409–417.

Shaban, S.Y., Ibrahim, M.M., Heinemann, F.W., 2007. A new sterically loaded pentadentate N_3S_2 ligand and its zinc complexes. Inorg. Chim. Acta 360 (2007), 2929–2934.

Sheldrick, G.M. 1996. SADABS, Area-Detector Absorption Correction, Göttingen.

Sheldrick, G.M. 1997. Program SHELXS, Program for Crystal Structure Determination, Göttingen.

Tesmer, M., Shu, M., Vahrenkamp, H., 2001. Sulfur-rich zinc chemistry: new tris(thioimidazolyl)hydroborate ligands and their zinc complex chemistry related to the structure and function of alcoholdehydrogenase. Inorg. Chem. 40, 4022–4029.

Warthen, C.R., Hammes, B.S., Carrano, C.J., Crans, D.C., 2001. Methylation of neutral pseudotetrahedral zinc thiolate complexes: model reactions for alkyl group transfer to sulfur by zinc-containing enzymes. J. Biol. Inorg. Chem. 6, 82–90.

Wilker, J.J., Lippard, L.S., 1995. Modeling the DNA methylphosphotriester repair site in *Escherichia coli Ada*. Why zinc and four cysteines. Inorg. Chem. 117, 8682–8683.