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THIOLATE *VS* THIONE COORDINATION IN MODEL COMPLEXES OF ZINC (II) METALLPROTEINS

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ABSTRACT

We synthesized and characterized a new S_4-based zinc complex with thione [$Tti^{xyl}ZnSTm^{xyl}$] 2 as sulfur-donor ligand. Structural determination by X-ray diffraction indicated that the coordination geometry around zinc atom is close to regular tetrahedral with S–Zn(1)–S bond angles in the range 106-113^o. The reactivity studies showed that complex 2 is much less susceptible to methylation than that of complex [$Tti^{xyl}ZnSC_6H_5$] 1, which contains thiolate as sulfur-donor ligand. This decrease in the nucleophilicity could be explained by electronic effects of thione *versus* thiolate.

KEYWORDS

Syntheses, Zinc(II) complexes, Repair protein, biomimetics, methylation.

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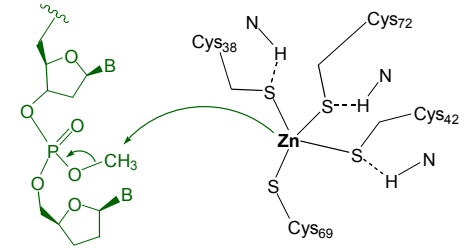
INTRODUCTION

All living organisms have developed complex systems to protect cells from the toxic effects of mutagenic chemicals and radiation. The regulation and function of DNA repair mechanisms have been characterized extensively in Escherichia coli. The E. coli Ada protein a key player in the adaptive response of bacteria to methylating agents, repairs methyl phosphotriesters in DNA by direct, irreversible transfer of the methyl group to one of its cysteines [1], Cys_{69} (Scheme 1). This protein contains zinc(II) ion tightly bound to four cysteine residues, one of which is Cys_{69}, the methyl acceptor. Alkylation on Cys_{69}, showing that this particular cysteine ligand is electronically activated relative to the other three cysteines [2].

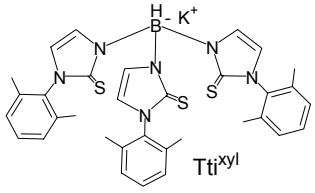
Scheme 1

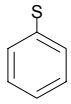
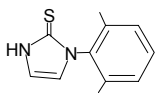


S_p-methylphosphotriester

As part of our studies in biomimetic zinc chemistry [3] and in order to mimic the zinc(II) coordination structure as well as the function of the zinc(II) ion at the active site, several monomeric zinc(II) complexes have been designed and investigated to elucidate the detailed reaction mechanism in these thiolate-alkylating zinc metalloproteins [4].

Scheme 2



$Tti^{xyl}ZnSR$	1	2
SR		

The ligand, potassium hydrotris tris(2-mercapto-1-xylylimidazole)borate, Tti^{xyl} was used to emulate the $[S_3]$ coordination environment provided by the three cysteine amino acid residues in zinc proteins [5]. We report herein the design, synthesis, characterization and structural properties of a new S_4Zn complex with thione $[Tti^{xyl}ZnSTm^{xyl}]$ **2** as sulfur-donor ligand (scheme 2). Structural determination by X-ray diffraction indicated that the coordination geometry around zinc atom is close to regular tetrahedral with S–Zn(1)–S bond angles in the range 106-113°. The reactivity studies showed that complex **2** is less susceptible to methylation than that of

complex **1**, which contains thiolate as sulfur-donor ligand [6-8]. This is decrease in the nucleophilicity could be explained by electronic effects of thione *versus* thiolate.

2. EXPERIMENTAL SECTION

Synthesis of the model complexes **1** and **2**
The synthesis of the zinc model complexes **1** and **2**, the experimental techniques and the standard IR and NMR equipment were described previously [6]. All other organic reagents were bought from Merck.

Kinetic measurements for the reaction of zinc(II) complexes **1** and **2** with CH_3I

All experiments were performed as previously reported [6-8] . 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 ^1H NMR spectroscopy at 300K. The ^1H NMR signals of the three thioimidazolyl protons of the reactant thiolate complexes **1** or **2** and the produced iodo complex **3** [5] were used as an integral standard. The increase in the intensity of the ethyl protons of the produced methylthioether were recorded and integrated relative to the standard thioimidazole protons.

3. RESULTS AND DISCUSSION

Characterization of the model complexes **1** and **2**
The ligand $KTti^{xyl}$, coordinating through three thione sulphurs, mimics the three sulfur donors in the Ada protein. In each of these complexes, the fourth ligand (thione *vs* thiolate) as we showed in (Scheme 1) serves to represent homocysteine coordination to zinc in the protein. The ligand potassium hydrotris[N-(xylyl)-2-thioimidazolyl)borate $KTti^{xyl}$ and zinc(II) complex $[Tti^{xyl}ZnSC_6H_5]$ **1** were prepared according to published procedures [6]. Complex $[Tti^{xyl}ZnSTm^{xyl}]$ **2** was obtained by the reaction of the previously reported perchlorate complex [5], $Tti^{xyl}Zn–OClO_3$ with one equivalent of N-(xylyl)-2-thioimidazole in anhydrous methanol. The complex was fully characterized by using ^1H NMR, FT-IR, elemental analysis, and X-ray crystallography. The ^1H NMR spectra of **2** showed different chemical environments of the thioimidazolyl methyl groups of the ligand system, Tt, and the coligand.

Crystal Structure determination:

Complex **2** crystallizes as a monomer in monoclinic crystal system in the space group P2(1)/c. An ORTEP representation of the cationic part of the molecular structure of **2** is shown in figure 1 with selected bond lengths and angles contained in Table 1. The zinc atom, wih tetrahedral geometry, is coordinated by the sulfur atom of an HTim coligand and by three sulfur atoms of the tripodal ligand Tti, similar to the arrangement of $[Tti^{Ph}]Zn(HTim^{Ph})(ClO_4)$ [9]. The Zn(1)–S(4) bond lengths of 2.358(3) Å is significantly longer than that found in the thiolate complex $[Tti^{xyl}ZnSC_6H_5]$ **1** (Zn(1)–S(4) 2.248 Å. The average S–Zn(1)–S bond angles are essentially the same as those obtained in of $[Tti^{Ph}]Zn(HTim^{Ph})(ClO_4)$ [9] and $[Cu(Tim)_3](NO_3)$ [10] (average 109.3°). The coordination of the Tim^{xyl} colligand to the $[Tti^{xyl}]Zn$ cenetr is very similar to that of the analogous group of the ligand system, which indicate that the attachement of the three thioimidazolyl group to boron exerts very little perturbation on the ability of the thioimidazolyl coligand to bind to zinc.

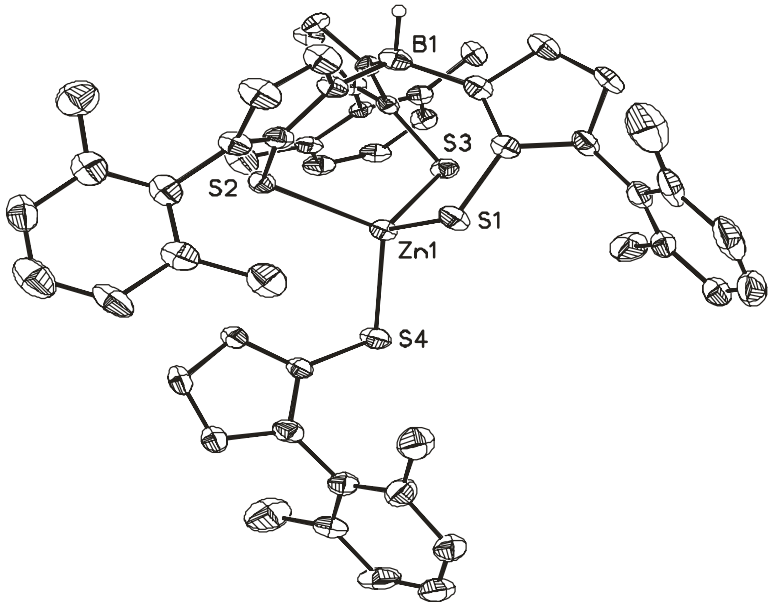


Fig. 1. ORTEP drawing of molecular structure of the actionic part $[Tti^{xyl}ZnSTm^{xyl}]^+$ **2**. Ellipsoids are depicted at 30 % probability level.

Table 1. Bond lengths [Å] and angles [°] of $[Tti^{xyl}ZnSTm^{xyl}]$ 2

Bond length [Å]	Zn(1)-S(1)	2.341(2)
	Zn(1)-S(3)	2.351(2)
	Zn(1)-S(4)	2.358(3)
	Zn(1)-S(2)	2.363(2)
Bond angles [°]	S(1)-Zn(1)-S(3)	106.23(9)
	S(1)-Zn(1)-S(4)	108.93(9)
	S(3)-Zn(1)-S(4)	115.25(9)
	S(1)-Zn(1)-S(2)	106.70(9)
	S(3)-Zn(1)-S(2)	106.57(8)
	S(4)-Zn(1)-S(2)	112.65(9)

Kinetik investigation for the methylation reactions

Reactions of **1** and **2** with CH_3I in deuterated chloroform results in the quantitative formation of methylthioethers and $Tti^{xyl}Zn$(II)-bound iodide complex **3** as indicated in equation 1. The pseudo-first-order constants k_{obs} were calculated.

$$Tti^{xyl}Zn\text{-}SR + CH_3I \longrightarrow \underset{\mathbf{3}}{Tti^{xyl}Zn\text{-}I} + RSCH_3 \qquad (1)$$

The methyaltion reactions were followed in ^{1}H-NMR at 300 K by monitoring the decrease

and increase in the intensities of the methyl resonances of the consumed **1 or 2** and the produced methyl ethyl thioether. The proton chemical shifts of the resulting $CH_3SC_6H_5$ and CH_3STm^{xyl} are identical to those of a genuine sample, indicating that the thioether product is not coordinated to zinc. A typical ^1H- NMR spectra for the methylation reaction of complex **1** as a function of time is shown in Figure 2. The log plots for five different concentrations of CH_3I are linear with correlation coefficients > 0.995. the resulting k_{obs} values, plotted against the CH_3I concentration, define a regression line which passes through the origin with correlation coefficient of 0.985. the second order rate constant, obtained according to $k_{obs} = k``[CH_3I]$, resulted as = 0.10 $M^{-1}s^{-1}$ for complex **1**. Whereas the kinetic reaction was too slow to follow in the case of complex **2** under the same reaction conditions. The clean second order reaction and the occurrence of the alkylations in completely non polar media, i.e., lack of salvation of intermediate anionic species are good arguments in favour of the intramolecular nature of the alkylation process [CH_3I].

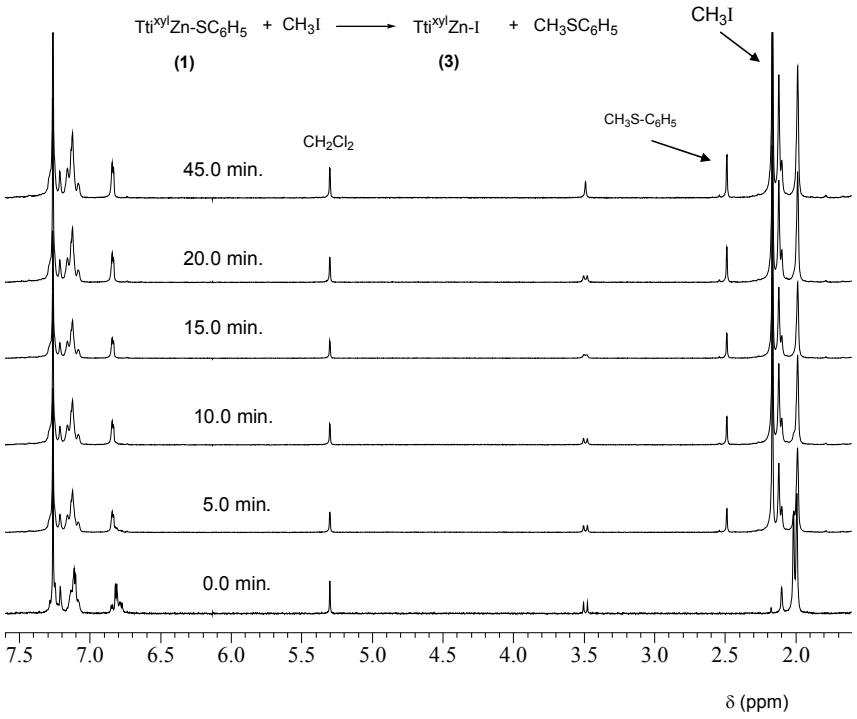


Fig. 2. Time dependent ^1H NMR spectra for the reaction between $Tt^{xyl}Zn–S\ C_6H_5$ 1 (10 mM) and CH_3I (50 mM) in $CDCl_3$ at 300 K under pseudo-first-order conditions.

The rate constant observed for the thiolate methylation in **1** is much higher than that the thione coligand in **2** under the same conditions [8], it provides a means to determine whether the inertness of the sulfur atoms of the Tti^{xyl} ligand of **1** is associated with the constraints imposed by attachement to the boron center. It is therefore, notable that whereas **1** reacts immediately with methyl iodide to give **3**, the corresponding reaction of **2** occurs over a period of days. This results indicate that the corrdinated thione Tm^{xyl} ligand is leass susceptible to electrophilic attack than the thiolate ligand, presumably a reflection of the thione *versus* thiolate nature of the sulfur atom [11].

CONCLUSION

The preparation and characterization of this particular family of thioimidazolylborate zinc complexes $Tti^{xyl}ZnSR$ **1**, **2** (where R = C_6H_5 and $HTm^{xyl,}$ respectively) has enabled us to evaluate how the nature of thiolate coligand affect the methyl transfer reaction. The driving force for the methylation reactions lies in the high nucleophilicity of $TtiZn^{xyl}$-bound thiolate in **1** than that of bound thione in **2**. and the low donor qualities of the resulting thioethers. This decrease in the nucleophilicity could be explained by electronic effects of thione *versus* thiolate.

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REFERENCES

[1] J. Habazettl, L. C. Myers, F. Yuan, G. L. Verdine, G. Wagner, *Biochemistry* 35 (1996) 9335.

[2] D. Swenson, N. C. Baenziger, D, Coucouvanis, J. Am. Chem. Soc. 100 (1978) 1932.

[3] (a) K. Ichikawa, K. Nakata, M. M. Ibrahim, and S. Kawabata Advances in Chemical Conversations for Mitigating Carbon Dioxide Studies in Surface Science and Catalysis, 114, 309 (1998); (b) K. Ichikawa, K. Nakata, and M. M. Ibrahim, Chem. Lett. 2000, 796; (c) M. M. Ibrahim, N. Shimomura, K. Ichikawa, M. Shiro, Inorg. chim. Acta, 2001, 313, 125-136; (d) M. M. Ibrahim, K. Ichikawa, M. Shiro, Inorg. chim. Acta, 2003, 353, 187-196, (e) M. M. Ibrahim, K. Ichikawa, M. Shiro, Inorg. chem. Commun., 2003, 6, 1030-1034, (f) T. Echizen, M. M. Ibrahim, K. Nakata, M. Izumi, K. Ichikawa, M. Shiro, J. Inorg. Biochem., 2004, 98, 1347-1360.

[4] (a) S. J. Chiou, J. Innocent, C. G. Riordan, K. C. Lam, L. Liable-Sands, A. L. Rheingold. Inorg. Chem. 39 (2000) 4347; (b) B. M. Bridgewater, T. Fillebeen, R. A. Friesner, G. Parkin, J. Am. Chem. Soc., Dalton Trans. (2000) 4494; (c) B. S. Hammes, C. J. Crrano. Chem. Commun. (2000) 1635; (d) B. M. Bridgewater, T. Fillebeen, R. A. Friesner, G. Parkin, Chem. Soc., Dalton Trans. (2000) 4494; (e) C. R. Warthen, B. S. Hammes, C. J. Carrano, D. C. Crans, J. Biol. Inorg. Chem. 6 (2001) 82; (f) B. S. Hammes, C. J. Crrano, Inorg. Chem. 40 (2001) 919; (g) U. Brand, M. Rombach, J. Seebacher, H. Vahrenkamp, Inorg. Chem. 40 (2001) 6151; (h) M. Ji, B. Benkmil, H. Vahrenkamp, Inorg. Chem. 44 (2005) 3518; (i) M. M. Morlok, K. E. Janak, G. Zhu, D. A. Quarless, G. Parkin, J. Am. Chem. Soc. 127 (2005) 14039.

[5] M. M. Ibrahim, M. Shu, H. Vahrenkamp, Eur. J. Inorg. Chem. (2005) 1388.

[6] M. M. Ibrahim, J. Seebacher, G. Steinfeld, H. Vahrenkamp, Inorg. Chem. 44 (2005) 8531.

[7] M. M. Ibrahim, G. He, J. Seebacher, B. Benkmil, H. Vahrenkamp, Eur. J. Inorg. Chem. (2005) 4070.

[8] U. Brand, J. Seebacher, M. Shu, M. Ji, M. M. Ibrahim and B. Benkmil, Inorg. Chem. submitted.

[9] (a) A. Docrat, M. M. Morlok, B. M. Bridgewater, D. G. Churchill, G. Parkin, Polyhedron 23 (2004) 481; (b) M. M. Morlok, A. Docrat, K. E. Janak, J. M. Tanski, G. Parkin, J. Chem. Soc., Dalton Trans. (2004) 3448.
[10] E. S. Raper, Inorg. Chim. Acta, 98 (1985)35.
[11] S. Laufer, G. Wagner, D. Kotschenreuther, Angew. Chem. Int. Ed. Engl. 41 (2002) 2290.