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Trapping and crystallographic characterization of Valsartan intermediate (tetrazole–zinc complex)

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ABSTRACT

4′-Methylbiphenyl-2-tetrazole (HMBT) is an important intermediate to the synthesis of Valsartan while HMBT is obtained by the decomposition of Zn-complex (organic–inorganic polymer) containing HMBT. This is the first example of crystallographic characterization of Zn-complex with HMBT produced during in situ [2+3] cycloaddition between 4-methylbiphenyl-2-carbonitrile (MBC) and NaN_3 in the presence of $ZnCl_2$. Also, crystal structural determinations of HMBT and impurity produced during hydrothermal hydrolysis reaction of MBC were reported.

Valsartan [(*S*)-2-[(2′-tetrazoyl-biphenyl-4-ylmethyl)-pentanoyl-amino]-3-methyl-butyric acid] due to its superior efficacy, protection, tolerability and patient compliance profile has been the leading antihypertensive therapy in the class called angiotensin II receptor blockers (ARBs) [1]. Additionally, beyond hypertension, in the Valsartan heart failure trial [Val-HeFT] and other investigations dealing with some 50,000 patients, the cardioprotective role of Valsartan in patients with heart attacks and heart failure was also demonstrated [1]. With medical advances producing more effective treatment, more patients are surviving cardiovascular diseases, leading to increasing incidence and prevalence of chronic heart failure (CHF), which is now becoming a global problem. Many clinical investigations have demonstrated that ARBs have fewer side effects than calcium channel blockers [2]. Thus, Valsartan is becoming more and more need for treating this cardiovascular disease. Recently, the synthesis method regarding Valsartan intermediate (HMBT) has received great attention in which a representative example presented by Nobel Prize winner K.B. Sharpless, involves a mild and green synthesis of a key intermediate compound, 4-methyl biphenyl-2-tetrazole (HMBT) [3]. Due to the synthesis of HMBT involving the decomposition of zinc tetrazole complex (a intermediate produced during the cycloaddition reaction between 4-methylbiphenyl-2-carbonitrile (MBC) and NaN_3 in the presence of $ZnCl_2$), it is very important for us to characterize zinc tetrazole complex so that we can optimize this reaction to reduce side reactions occurred or enhance the reaction yield. On the other hand, we can reduce the environment pollution comparison with its old synthesis method involving very toxic chemical agent use, such as tributylin azide [3].

As a continuation of our systematic studies on novel metal complexes produced during in situ [2+3] cycloaddition reaction systems [4,5], we have carried out the cycloaddition reaction of 4-methyl biphenyl-2-carbonitrile with NaN_3 in the presence of $ZnCl_2$ and crystal structural determination of a intermediate zinc tetrazole complex (bis(4-methyl biphenyl-2-tetrazoylato))zinc-monohydrate solvent monohydrate $[Zn(BMT)_2(H_2O)]H_2O$ (1). Herein, we report the crystallographic characterization of zinc tetrazole complex and very useful information regarding the side product crystal structures as well as crystal structure of HBMT.

Compound **1** was obtained by the reaction of MBC with NaN_3 in the presence of $ZnCl_2$. IR spectrum shows that two typical peaks at 1440 and 1380 cm^{-1} further confirms the formation of tetrazole group. However, there is still a very weak peak at 1600 cm^{-1}, suggesting the raw intermediate precipitate may contain carboxylic compound which identified as amide later.

The crystal structural determination of **1** reveals that the local coordination geometry around Zn center can be best described as a slightly distorted five-coordinated trigonal bipyramid defined by an equatorial plane composed of three N atoms from three different BMT ligands and two apical positions occupied by one N atom from fourth BMT ligand and water molecule depicted in Fig. 1. Thus, each in situ produced BMT ligand acts as bidentate chelating spacer to bridge two different Zn centers while each Zn center needs four BMT ligand to result in the formation of 1D infinite chain, as shown in Fig. 2. To clarify this chain, the omission of 4-methyl biphenyl group, the chain clearly shows that each repeating unit is consists of six-membered ring defined as two Zn atoms and two μ_2-tetrazole groups while another 6-ring almost is perpen-

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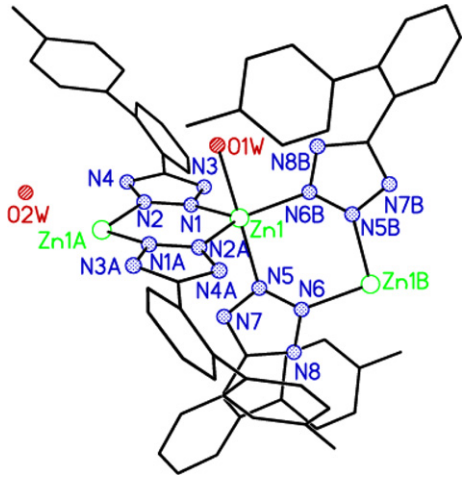

Fig. 1. An asymmetric unit representation of $[Zn(BMT)_2(H_2O)]H_2O$ (**1**) in which the local coordination environment around Zn center can be best described a slightly distorted trigonal bipyramid. Crystal data: $C_{28}H_{26}N_8O_2Zn$, $M = 571.94$, Monoclinic, $P2_1/n$, $a = 15.190(2)$ Å, $b = 7.5253(11)$ Å, $c = 23.672(4)$ Å, $\alpha = \gamma = 90°$, $\beta = 93.114(2)°$, 2701.9(7) Å^3, $Z = 4$, $D_c = 1.406$ Mg m^{-3}, $R_1 = 0.0358$, $wR_2 = 0.0965$, $T = 293$ K, $\mu = 0.950$ mm^{-1}, $S = 0.658$.

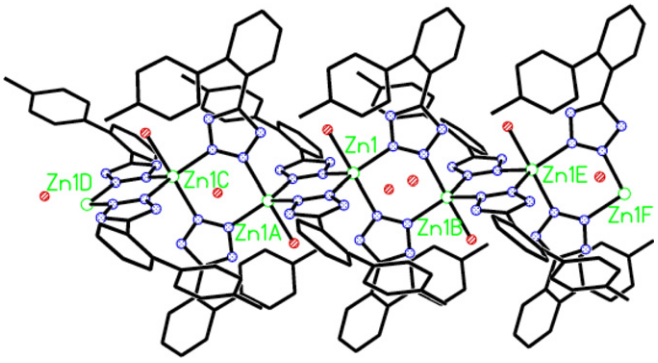

Fig. 2. 1D chain representation of $[Zn(BMT)_2(H_2O)]H_2O$ (**1**).

dicular to this ring as shown in Fig. 3. This describes why Zn center adopts a trigonal bipyramidal coordination mode.

To testify what we got is really HBMT ligand, we have carried out the decomposition of $[Zn(BMT)_2(H_2O)]H_2O$ (**1**) using NaOH and the extraction of HBMT ligand by chloroform. The crystal structural determination shows the formation of a tetrazole 5-membered ring, as depicted in Fig. 4.

Furthermore, to testify what the impurity in the raw precipitate is, we have carried out the collection of the impurity and got the single crystals. The crystal structural determination reveals that the impurity is an amide, as depicted in Fig. 5.

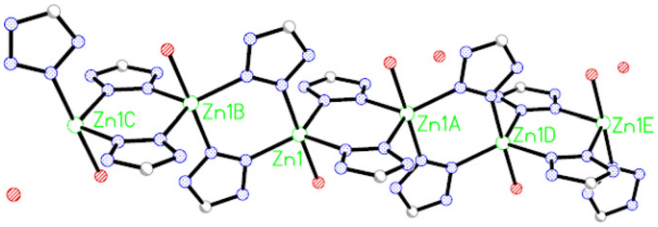

Fig. 3. A simplified 1D chain representation of $[Zn(BMT)_2(H_2O)]H_2O$ (**1**) in which chain is extended by six-membered ring defined as two Zn atoms and four N atoms from two different μ_2-tetrazole groups.

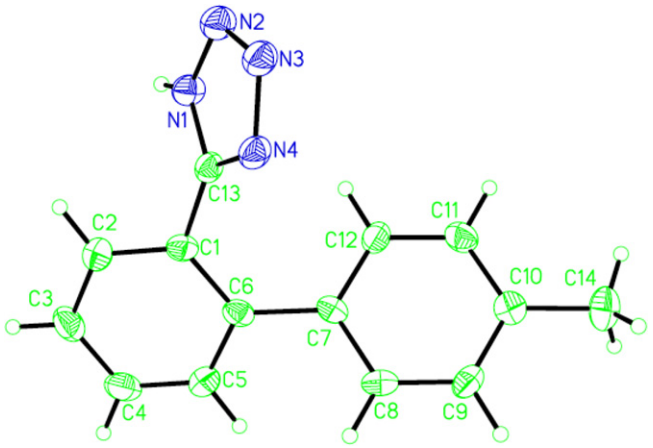

Fig. 4. Solid state structure of HBMT. Crystal data: $C_{14}H_{12}N_4$, $M = 236.28$, Monoclinic, $P2_1/n$, $a = 5.0146(18)$ Å, $b = 16.599(6)$ Å, $c = 15.090(5)$ Å, $\alpha = \gamma = 90$, $\beta = 108.9$-69(10), $V = 1187.8(7)$ Å^3, $Z = 4$, $D_c = 1.321$ Mg m^{-3}, $R_1 = 0.0410$, $wR_2 = 0.0864$, $T = 293$ K, $\mu = 0.083$ mm^{-1}, $S = 0.931$.

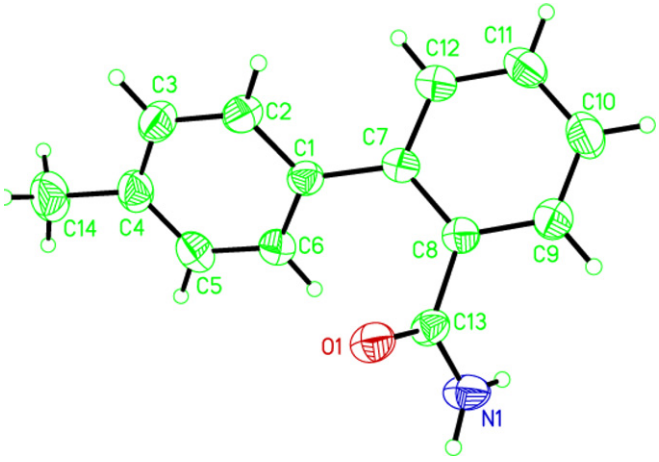

Fig. 5. Solid State structure of the impurity. Crystal data: $C_{14}H_{13}NO$, $M = 211.25$, Monoclinic, $P2_1/c$, $a = 15.746(14)$ Å, $b = 5.145(5)$ Å, $c = 15.746(14)$ Å, $\alpha = \gamma = 90°$, β - = 109.22°, $V = 1204.5(19)$ Å^3, $Z = 4$, $D_c = 1.165$ Mg m^{-3}, $R_1 = 0.0606$, $wR_2 = 0.1697$, $T = 293$ K, $\mu = 0.073$ mm^{-1}, $S = 0.623$.

In conclusion, the crystallographic characterizations of intermediate Zn–tetrazole complex produced during [2+3] cycloaddition between cyano group and azide in the presence of Lewis acid, such as Zn^{2+} and in situ produced tetrazole ligand as well as impurity must provide an useful insight into the optimization of cycloaddition reaction and how to avoid the formation of impurity to reduce chromatographic procedures.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2008.02.031.

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