Tetrazole Synthesis

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Uncovering the Role of Metal Catalysis in Tetrazole Formation by an In Situ Cycloaddition Reaction: An Experimental Approach

Di-Chang Zhong, Ya-Qiong Wen, Ji-Hua Deng, Xu-Zhong Luo,* Yun-Nan Gong, and Tong-Bu Lu**

Abstract: *Using an experimental approach, the role of metal catalysis has been investigated in the in situ cycloaddition reaction of nitrile with azide to form tetrazoles. It has been shown that metal catalysis serves to activate the cyano group in the nitrile reagent by a coordinative interaction.*

Uncovering reaction mechanisms are very important for chemists to delicately control reaction processes and target products. As the majority of reaction intermediates are too unstable to be captured and characterized, a large number of reaction mechanisms currently are unclear. Single-crystal X-ray diffraction is a powerful analytical technique used for the investigation of reaction mechanisms, by which detailed information about the formation and nature of reaction intermediates can be provided.[1] The only difficulty with this method is that we have to capture these intermediates in their crystalline states.

5-substituted 1*H*-tetrazoles are a type of nitrogen heterocyclic compound that have found a wide range of applications in coordination chemistry, medicinal chemistry, and material science.[2] The most convenient synthetic route to 5-substituted 1*H*-tetrazoles is the addition of azide ions to nitriles. Initially, this transformation was achieved by laborious methods using tin or silicon azides or by using strong Lewis acids.[3] A safe, convenient, and environmentally friendly procedure was then reported by Sharpless and co-workers.[4] They found that with Zn^{II} salts as Lewis acid catalysts, this [2+3] cycloaddition reaction of azide with nitriles, for the syntheses of a variety of 5-substituted 1*H*-tetrazoles, can be easily realized in water, an environmentally friendly system. The role of Zn^{II} ions in this reaction was unclear, but it was suggested that an intermediate, composed of a Zn^{II}–tetrazole complex, had been formed. This speculation was confirmed by Xiong et al., who captured this Zn^{II}–tetrazole complex by an in situ synthetic method and characterized its structure by single-crystal X-ray diffraction analyses.[5] In addition to the Zn^{II} ion, other metal ions, such as Co^{II}, Mn^{II}, and Cd^{II}, also showed catalytic activity for this [2+3] cycloaddition reaction under hydrothermal reaction conditions.[6] Noodleman and Sharpless et al. investigated the reaction mechanism by DFT calculations. They concluded that activation of the nitrile substrate by zinc(II) is the crucial factor for tetrazole formation.[7] However, no experimental data had been obtained to corroborate these calculated results, and thus the catalytic mechanism of metal ions in this cycloaddition reaction requires further investigation.

To this end, we constructed an in situ reaction system that was used to monitor step-by-step the formation of bitetrazole by the cycloaddition reaction and to investigate the catalytic behavior of metal ions. The reaction system employed metal salts, terephthalonitrile, and NaN_3 in solution in water as the reactants. By controlling the molar ratio of terephthalonitrile and NaN_3, the cycloaddition reaction of two CN groups in terephthalonitrile with NaN_3 would proceed consecutively. Fortunately, we captured the intermediate products $[Cd(BDT)(H_2BDT)_{0.5}]_n{\cdot}2n\,H_2O$ (**1**), $[Cd(BDT)(H_2O)_2]_n{\cdot}2n\,H_2O$ (**2**), $[Cd(BNT)_2(H_2O)_2]_n{\cdot}3n\,H_2O$ (**3**), and $[Cu(BNT)]_n$ (**4**; H_2BDT = 1,4-benzeneditetrazole; HBNT = benzonitrile-4-tetrazole), and determined their structures by single-crystal X-ray diffraction analysis. The results clearly demonstrate that during the cycloaddition reaction process, the metal ion first coordinates with the CN group, which leads to the activation of the CN group and promotes the [2+3] cycloaddition reaction. This experimental result confirms the calculated one obtained from the pioneering work of Sharpless and co-workers.[4,7]

Under hydrothermal conditions, $Cd(NO_3)_2{\cdot}4\,H_2O$ reacts with terephthalonitrile and NaN_3 in water in a molar ratio of 1:1:2.5 at 110 °C for 72 h leading to the formation of brown block-shaped crystals of **1** in 67 % yield (see the Supporting Information). As expected, with Cd^{II} ions as the Lewis acid catalyst, the ligand H_2BDT was generated in situ through the cycloaddition reaction of one equivalent of terephthalonitrile with two equivalents of NaN_3. The subsequent Cd-H_2BDT complex **1** crystallizes in the *Fddd* space group. In the asymmetric unit of **1**, Cd1 coordinates with six N atoms from six individual BDT^{2-} ions, resulting in an octahedron geometry (Figure 1 a).[10] The ligand H_2BDT is present in two forms, one as H_2BDT itself and the other as the BDT^{2-} ion in which both tetrazolyl rings are deprotonated. The BDT^{2-} ion coordinates with Cd^{II} through the N atoms in the 1,2-positions, and H_2BDT ligand bonds with Cd^{II} by the N atoms in the 2,3-positions (see Scheme S1 a in the Supporting Information, modes I and II). Through the bridge of BDT^{2-} ions, Cd^{II} ions are connected together to form a 3D porous framework. H_2BDT molecules are located in the

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[*] Dr. D. C. Zhong, Y. Q. Wen, J. H. Deng, Prof. Dr. X. Z. Luo, Y. N. Gong
School of Chemistry and Chemical Engineering
Gannan Normal University, Ganzhou 341000 (P.R. China)
E-mail: zhong_dichang@hotmail.com
luoxuzhong@hotmail.com
Prof. Dr. T. B. Lu
School of Chemistry and Chemical Engineering
Sun Yat-Sen University, Guangzhou 510275 (P.R. China)
E-mail: lutongbu@mail.sysu.edu.cn

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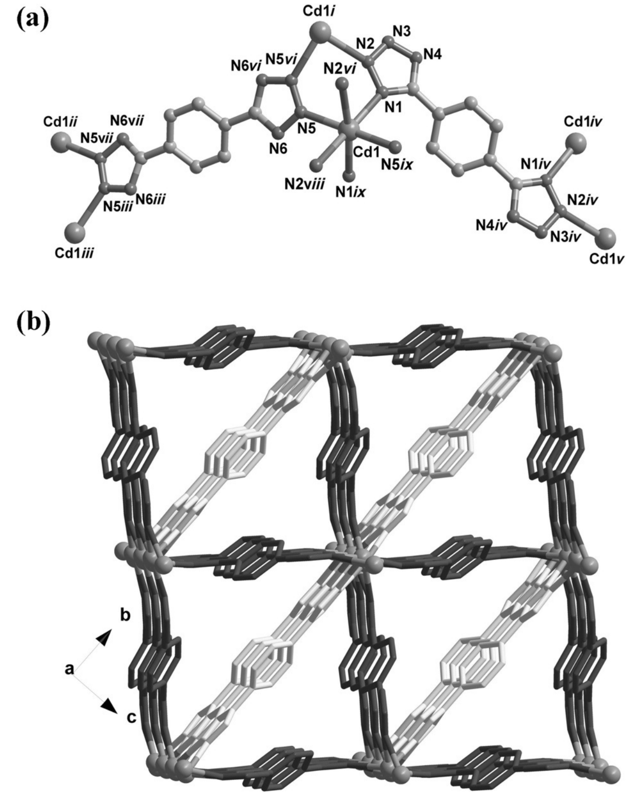

Figure 1. a) X-ray crystal structure of **1** showing the coordination environment of the Cd^{II} ion and the coordination modes of the BDT^{2-} ions. (Symmetry codes: *i* = −0.5 + *x*, 1.75−*y*, 0.25−*z*; *ii* = −0.5 + *x*, −0.5 + *y*, *z*; *iii* = *x*, 1.25−*y*, 0.25−*z*; *iv* = 1−*x*, 2−*y*, −*z*; *v* = 1.5−*x*, 0.25 + *y*, −0.25 + *z*; *vi* = 0.25−*x*, *y*, 0.25−*z*; *vii* = 0.25−*x*, 1.25−*y*, *z*; *viii* = 0.5 + *x*, 1.75−*y*, 0.25−*z*; *ix* = 0.75−*x*, 1.75−*y*, *z*). b) Packing diagram showing the 3D crystal structure of **1**. Lattice H_2O molecules have been omitted for clarity.

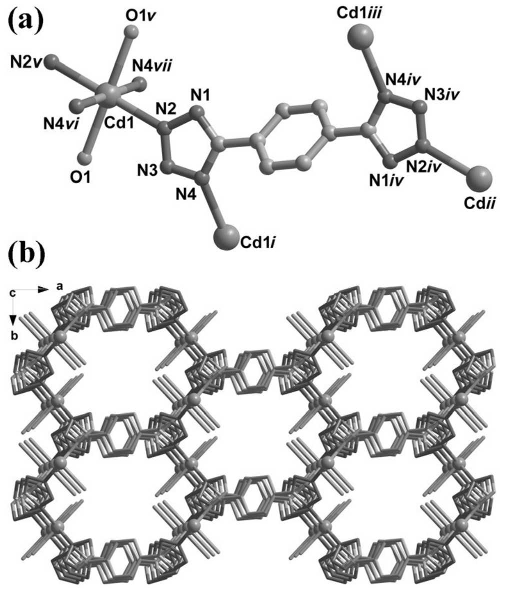

Figure 2. a) X-ray crystal structure of **2** showing the coordination environment of the Cd^{II} ion and the coordination modes of BDT^{2-} ions. (Symmetry codes: *i* = 0.5−*x*, −0.5 + *y*, 1.5−*z*; *ii* = 0.5 + *x*, −0.5 + *y*, −1 + *z*; *iii* = 1−*x*, *y*, 1.5−*z*; *iv* = 1−*x*, −*y*, 1−*z*; *v* = 0.5−*x*, 0.5−*y*, 2−*z*; *vi* = *x*, −*y*, 0.5 + *z*; *vii* = 0.5−*x*, 0.5 + *y*, 1.5−*z*). b) The 3D porous structure of **2**. Lattice H_2O molecules have been omitted for clarity.

channels and further reinforce the porous framework by coordination with Cd^{II} ions, resulting in the formation of a 3D coordination polymer (Figure 1 b).

Replacement of $Cd(NO_3)_2{\cdot}4H_2O$ with $Cd(Ac)_2{\cdot}2H_2O$ as the reagent leads to the formation of a second Cd-H_2BDT complex **2** in 71 % yield (see the Supporting Information). **2** crystallizes in the C_2/c space group. As shown in Figure 2 a, the Cd1 center coordinates with four N atoms from four individual H_2BDT ligands and two O atoms from two H_2O molecules, forming a six-coordinated octahedral geometry.[10] The H_2BDT ligand, with two tetrazolyl rings deprotonated, bonds with four Cd1 ions (Scheme S1 a, mode III). Through bridges composed of BDT^{2-} ions, Cd1 ions are connected together to generate a 3D porous framework with a 1D channel along the *c* axis. The coordinated H_2O molecules are located at the pore surface and point to the pore center, and the lattice H_2O molecules fill the pores of the framework (Figure 2 b).

These results show that under similar reaction conditions, compounds **1** and **2** have been synthesized from the ligand H_2BDT which was generated in situ. It should be noted that in both cases, sufficient quantities of NaN_3 were used for complete reaction with terephthalonitrile. Therefore, under Lewis acid catalysis ($Cd(NO)_3$ or $Cd(Ac)_2$), the cycloaddition reaction of terephthalonitrile with NaN_3 proceeds almost completely. Both cyano groups of terephthalonitrile undergo cycloaddition with two molar equivalents of N_3^- ions leading to the generation of the H_2BDT ligand in situ and the formation of the corresponding coordination polymers, which is consistent with previous reports.[8] Although the structures of the final products are different owing to the different metal precursors, cycloaddition of both cyano groups with N_3^- ions to generate H_2BDT in situ provides clear evidence for the catalysis of the Cd^{II} ions. The conjectured/theoretical results have suggested that the catalytic mechanism of metal ions is the activation of the CN groups in terephthalonitrile by coordination. To obtain experimental evidence, we increased the molar ratio of terephthalonitrile and NaN_3 from 1:2.5 to 1:1. In this case, as the amounts of N_3^- is insufficient, only one of the cyano groups in terephthalonitrile would undergo cycloaddition with N_3^- ions, generating in situ instead the ligand benzonitrile-4-tetrazole (HBNT). Subsequently, new metal–HBNT reaction intermediates would be formed, from which the activation of the cyano groups by the metal ions may be detected and the role of the metal center as a catalyst would be clearly revealed.

We tried to capture the possible reaction intermediate containing Cd^{II} and HBNT by in situ ligand synthesis. After a large number of experiments, we found that reaction of $Cd(NO_3)_2{\cdot}6H_2O$ with terephthalonitrile and NaN_3 in a ratio of 1:1:1 under hydrothermal conditions afforded complex **3** (see the Supporting Information). As shown in Figure 3 a, the central metal Cd1 center coordinates to four N atoms from four individual BNT^- ligands and to two H_2O molecules, resulting in a slightly distorted octahedral geometry about the Cd1 center.[10] Each HBNT ligand, with the tetrazolyl ring

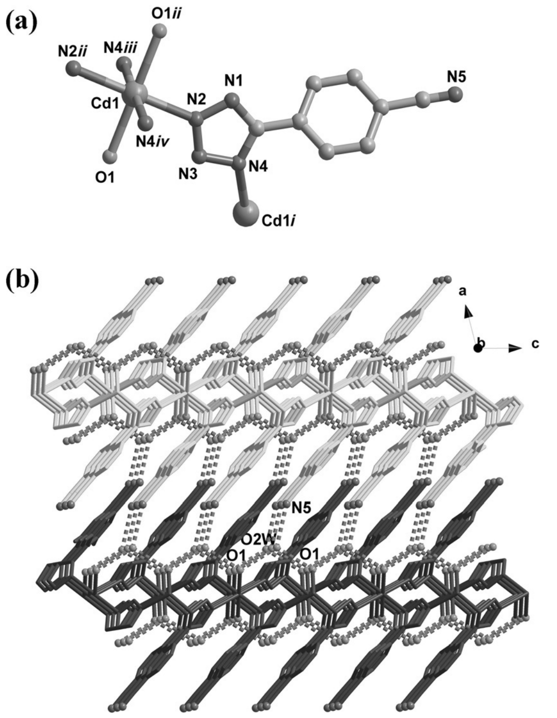

Figure 3. a) X-ray crystal structure of **3** showing the coordination environment of the Cd^{II} ion and the coordination modes of the BNT^{2-} ions. (Symmetry codes: *i* = −*x*, 0.5 + *y*, 1.5−*z*; *ii* = −*x*, −*y*, 1−*z*; *iii* = −*x*, −0.5 + *y*, 1.5−*z*; *iv* = *x*, 0.5−*y*, −0.5 + *z*). b) The 3D supramolecular structure of **3**.

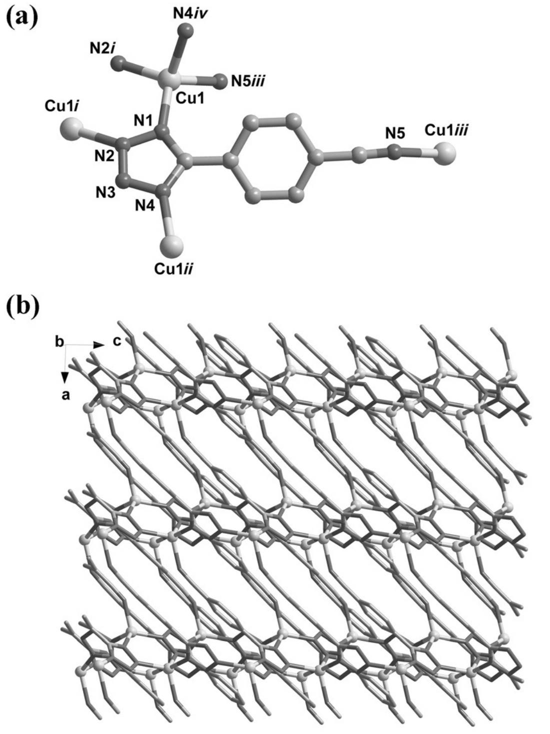

Figure 4. X-ray crystal structure of **4** showing the coordination environment of the Cu^{I} ion and the coordination modes of the BNT^{-} ions. (Symmetry codes: *i* = 1−*x*, −*y*, −*z*; *ii* = 1−*x*, −0.5 + *y*, 0.5−*z*; *iii* = 2−*x*, 2−*y*, 1−*z*; *iv* = 1−*x*, 0.5 + *y*, 0.5−*z*). b) The 3D structure of **4**.

deprotonated, bonds with two Cd1 ions (Scheme S1 b, mode I). Through the bridges of the BNT^{-} ions, Cd1 ions are connected together to generate a 2D layered coordination polymer. The adjacent layers are further linked together by intermolecular hydrogen bonds between coordinated H_2O molecules within each layer, and between layers through interactions between lattice H_2O molecules and between cyano groups, forming a 3D supramolecular structure (Figure 3 b). It should be noted that the CN group does not coordinate with the Cd^{II} center and the length of the C≡N bond is 1.107(13) Å.

Although based on HBNT, we have not directly detected the activation of the CN group by the Cd^{II} ion as a Lewis acid catalyst in **3**, as the ligand HBNT bonds with Cd1 through the tetrazolyl ring, whereas the CN group does not coordinate with Cd1. The reason may be ascribed to the fact that the expected Cd–HBNT intermediate, in which both the tetrazolyl ring and the cyano group in HBNT coordinate to the Cd^{II} center, has low stability. Thus the intermediate cannot be successfully captured, either under the same or different reaction conditions. Next, we tried to use other types of Lewis acids, such as Zn^{II}, Co^{II} or Cu^{II}, instead of the Cd^{II} ion. Fortunately, under the same reaction conditions $Cu(NO_3)_2 \cdot 6\,H_2O$ reacts with terephthalonitrile and NaN_3 leading to the formation of complex **4** (see the Supporting Information). In the asymmetric unit of **4**, the central metal center Cu^{I}, reduced from Cu^{II}, coordinates with four N atoms from four individual BNT^{-} ions, generating a tetrahedron geometry (Figure 4).[10] The in situ generated HBNT ligand, having a deprotonated tetrazole ring, bonds with four Cu1 ions through the tetrazolyl ring and the cyano group (Scheme S1 b, mode II). Through the bridges of the BNT^{-} tetrazolyl ring, Cu^{I} ions are connected together to form a 2D layer structure. These 2D layers are further linked together by the remainder of the BNT^{-} ions generating a 3D coordination polymer. Herein, the coordination of the cyano group to Cu^{I} is clearly detected. The C≡N bond has a length of 1.157(5) Å, which is longer than that in **3**, indicating that the C≡N is significantly weakened by Cu^{I} coordination.

It is clear that when a sufficient quantity of N_3^{-} ions are present, both cyano groups in terephthalonitrile undergo cycloaddition with N_3^{-} ions, generating in situ the ligand H_2BDT and two subsequent coordination polymers of **1** and **2**. With a decreased quantity of N_3^{-} ions present, only one cyano group in terephthalonitrile can undergo cycloaddition with an N_3^{-} ion, resulting in the formation of the intermediate ligand HBNT and two subsequent coordination polymers of **3** and **4**. These results indicate that by controlling the molar ratio of terephthalonitrile to NaN_3, the cycloaddition reaction of the two cyano groups in terephthalonitrile with NaN_3 can be controlled. Furthermore, from the structure of the captured complex **4**, it is clear that the cyano group in terephthalonitrile is activated by coordination to a Cu^{II} ion, which was also confirmed by IR spectroscopy. The IR spectra for **3** and **4** clearly show strong bands at 2235 and 2217 cm^{-1}, respectively (see the Supporting Information), corresponding to a cyano stretching vibration within compounds **3** and **4**. The cyano stretching vibration in **4** (when the cyano group is coordi-

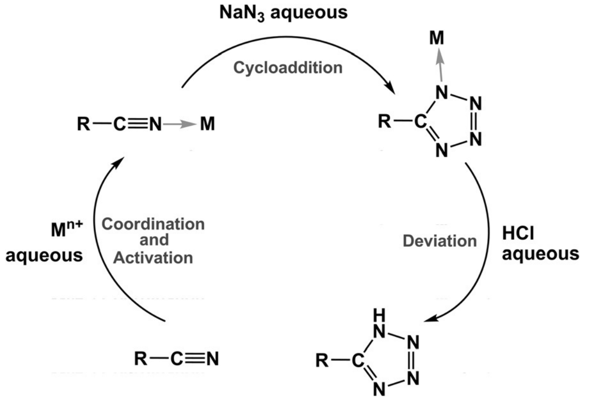

Figure 5. The proposed mechanism for the formation of tetrazolyl compounds through the cycloaddition reaction of nitrile with azide.

nated) is detected at a markedly lower energy wavenumber than that in **3** (where the cyano group is not coordinated), further proving that the cyano group of terephthalonitrile in **4** is activated by Cu^{II} coordination. The activation of the cyano group promotes the [2+3] cycloaddition reaction (Figure 5). This result strongly supports the theoretical results of Sharpless et al.[7]

It is unfortunate that intermediates for other metal ions where cyano coordination could be detected could not been captured because of their low stabilities. The cycloaddition mechanism may occur through different metal-dependent pathways. However, the activation of the CN group by metal coordination may also be an important step during the tetrazole formation (Figure 5). Although comparison of the cyano-group electron densities in **3** and **4** does not provide clear evidence for their activation by Cu^{I} coordination (see the Supporting Information), the differences between the C≡N bond lengths in **3** (1.107(13) Å) and **4** (1.157(5) Å), together with the difference of C≡N IR absorption bands in **3** (2235 cm^{-1}) and **4** (2217 cm^{-1}), confirm that the cyano group is activated by Cu^{I} coordination in **4**.

Complexes **1**–**4** have also been characterized by powder X-ray diffraction (PXRD) and thermogravimetric analysis (TGA). PXRD spectra for the bulk phases of **1**–**4** show that all the peaks displayed in the measured patterns closely match to those in the simulated spectrum generated from single-crystal diffraction data (Figure S1 in the Supporting Information), which indicates that single phases of **1**–**4** were formed. The thermogravimetric curve of **1** shows a weight loss of 7.9% from room temperature to 143 °C, corresponding to the removal of two lattice H_2O molecules per formula unit (calculated 7.7%). After this point no obvious weight loss is observed until 335 °C and with increasing temperature, the frameworks decompose through three steps of continuous weight loss (Figure S2a). Compound **2** lost two lattice H_2O molecules and two coordinated H_2O molecules from room temperature to 125 °C, demonstrated by the weight loss of 22.4% measured which is consistent with the calculated loss (21.9%). After 125 °C, no marked weight loss is observed until 310 °C. Upon further heating, the dehydrated framework decomposes after another three steps of continuous weight loss (Figure S2b). The photoluminescence properties of **1** and **2** in the solid state were investigated at room temperature. As depicted in Figure S3, compounds **1** and **2** exhibit fluorescence upon excitation at $\lambda = 335$ and 322 nm, respectively. As the free ligand H_2BDT shows a broad emission band at $\lambda = 459$ nm upon excitation at 288 nm,[9] the fluorescence emission maxima at $\lambda = 426$ and 408 nm for **1** and **2** can be tentatively ascribed to ligand-to-ligand charge transfer (LLCT).

In summary, by employing an experimental approach we have demonstrated for the first time that the role of the metal in the in situ cycloaddition reaction for the formation of tetrazoles is to activate the cyano group by coordination. This result provides significant insight into the mechanism of metal catalysis in the formation of tetrazolates and may be useful for controlling the syntheses of target tetrazolate compounds in the future.

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