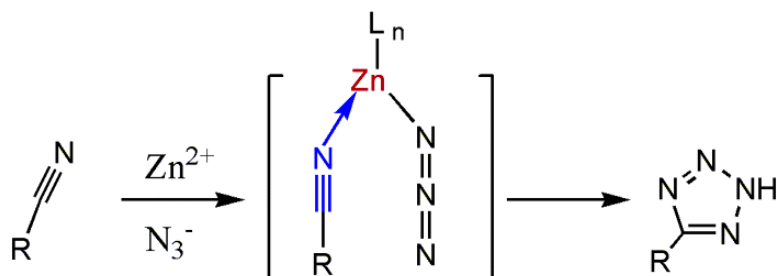Article

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Why Is Tetrazole Formation by Addition of Azide to Organic Nitriles Catalyzed by Zinc(II) Salts?

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Abstract: The mechanism by which zinc(II) catalyzes the union of an azide ion with organic nitriles to form tetrazoles is investigated by means of density functional theory using the hybrid functional B3LYP. The calculations indicate that coordination of the nitrile to the zinc ion is the dominant factor affecting the catalysis; this coordination substantially lowers the barrier for nucleophilic attack by azide. Relative reaction rates of catalyzed and uncatalyzed tetrazole formation also provide experimental support for this conclusion.

I. Introduction

Tetrazoles are an increasingly popular functionality[1] with wide ranging applications. They have found use in pharmaceuticals as lipophilic spacers[2] and carboxylic acid surrogates,[3] in specialty explosives,[4] photography, and information recording systems,[5] not to mention as precursors to a variety of nitrogen containing heterocycles.[6] The most direct method to form tetrazoles is via the concerted[1,7] and highly regioselective[8] [2 + 3] cycloaddition between an organic azide (R−N₃) and an organic nitrile (R−CN) as shown in Scheme 1.[9] However, this cycloaddition is too slow to be synthetically useful except when potent electron-withdrawing groups activate the nitrile component.

Scheme 1. [2 + 3] Cycloaddition of an Organic Azide and an Organic Nitrile
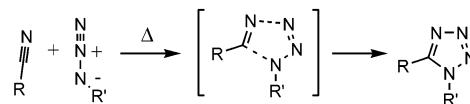
Scheme 2. Addition of an Inorganic Azide to an Organic Nitrile
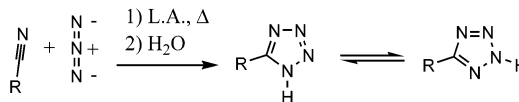
Of greater concern to us here is the mechanism behind the formally similar addition of azide salts and nitriles giving 1*H*-tetrazoles (Scheme 2). This variant is of greater synthetic interest since the range of nitriles which are competent dipolarophiles is much broader and a wide variety of metal-azide complexes can serve as azide donors.[10] Mechanistically, however, these transformations are less straightforward. In the case where hydrazoic acid or an amine salt of hydrazoic acid acts as the dipole, both an anionic two step mechanism[11] and a concerted [2 + 3] cycloaddition[12] have been posited in the literature. More recently, we have suggested a different mechanism[13] that involves the activation of the nitrile by protonation, proceeding through a previously unsuspected imidoyl azide intermediate

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Scheme 3. Addition of an Azide Anion to a Nitrile through the Intermediacy of an Imidoyl Azide
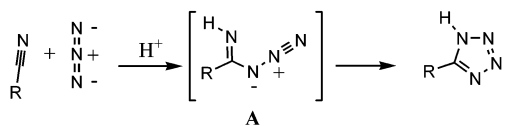
(A, Scheme 3). This pathway is computed to be some 10 kcal/mol lower in energy than the concerted [2 + 3] mechanism. To the best of our knowledge, there are no reports concerning the mechanistic details for the cases where nonprotic Lewis acids are employed as catalysts for the addition of an azide ion to a nitrile.

It has been recently shown that zinc salts are excellent catalysts for this reaction;[14] in fact, they function well even in aqueous media, thereby enabling a more environmentally friendly route to 1*H*-tetrazoles.[15] When we follow this protocol, simple heating (80−170 °C) of an aqueous reaction mixture of nitrile, sodium azide, and catalytic zinc salt provides the 1*H*-tetrazole in good yield following acidic workup. Seeking to understand the mechanism of this catalysis, we have performed model calculations using density functional methods to investigate the role of zinc. A comparison of measured reaction rates of catalyzed with uncatalyzed tetrazole formation, for both intra- and intermolecular cases, seems to corroborate the computational findings.

II. Computational Details

All geometries and energies presented in the present study are computed using the B3LYP[16] density functional theory method as implemented in the Gaussian98 program package.[17] Geometry optimizations were performed using the triple-ζ plus polarization basis set 6-311G(d,p), followed by single-point energy calculations using the larger basis set 6-311+G(2d,2p). To evaluate the zero-point vibrational effects on energy, Hessians were calculated at the B3LYP/lanl2dz level of theory.

Solvation energies were added as single-point calculations using the conductor-like solvation model COSMO[18] at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by a polarizable dielectric continuum. The dielectric constant was chosen as the standard value for water,

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$\epsilon = 80$. Some of the experiments were done in DMF, which has a dielectric constant of $\epsilon = 37$. As the solvation energy to a first approximation is proportional to $(1 - (3/2\epsilon))$ for dipoles and $(1 - (1/\epsilon))$ for charges for large ϵ,[19] the water and DMF values give almost identical solvation energies. Since we are mainly interested in reaction barriers (reactant − transition state) and relative barriers, the differences are not significant.

The energies presented here include solvation effects with $\epsilon = 80$, unless otherwise stated.

III. Experimental Details

To a solution of sodium azide (325 mg, 5 mmol) and zinc bromide (1.12 g, 5 mmol) in water (7 mL) and 2-propanol (3 mL) was added cyanopyrazine (21 mg, 0.2 mmol) and benzyl alcohol (21 mg). The reaction was stirred at 23 °C, and aliquots were removed, added to a biphasic solution of HCl (1 N, 1 mL) and ethyl acetate (5 mL), and shaken. The organic layer was injected onto a GC, and the extent of reaction was determined using benzyl alcohol as the internal standard. The data showed zeroth order kinetics, with a calculated nitrile half-life of 4.0 min. A second reaction was run as above except that no zinc was added, and the reaction was heated in an oil bath set to 80 °C. Zeroth order kinetics were observed again, and the computed half-life was 35 min.

A solution of 2-azidoethyl benzylcyanamide[20] (0.05 mmol) in DMF (5 mL) was heated in an oil bath set at 140 °C. Aliquots were removed and added to ethyl acetate (5 mL), washed with water, dried, evaporated, and analyzed by ^{1}H NMR. Zeroth order kinetics were observed, and a half-life of 24 h was calculated. In a similar experiment, zinc bromide was added to the aforementioned mixture to bring its concentration to 0.05 M, and the resulting solution was heated in an oil bath set to 75 °C. The half-life was found to be 18 h. In a third experiment, aluminum chloride was added to a solution of 2-azidoethyl benzylcyanamide (0.1 M) in 2-methyltetrahydrofuran (10 mL) to bring its concentration to 0.1 M, and the resulting solution was stirred at 23 °C. The half-life was found to be 24 h.

IV. Results and Discussion

The model calculations presented here will focus on the simplest nitrile, namely acetonitrile (CH$_3$CN). The conclusions should, however, be of direct relevance to nitriles in general.

Before discussing the results, the modeling of the Zn^{II} ligand sphere deserves comment. The zinc was modeled by either tetrahedral or octahedral coordination. These two models are electronically very similar, since Zn^{2+} presents an essentially degenerate coordination sphere. However, due to the different steric effects in these two systems, the results can differ somewhat, and the different possible mechanisms are considered individually below.

A. Azide Anion Bound to Zinc. Let us first consider the situation where the azide anion (N$_3^-$) is bound to Zn^{II} and the acetonitrile undergoes the cycloaddition without coordinating to zinc. The optimized transition state structures for this [2 + 3] cycloaddition reaction, modeled using tetrahedrally coordinated zinc (three water ligands and the azide) or octahedrally coordinated zinc (5 water ligands and the azide), are displayed in Figure 1 (A and B, respectively). The energy barriers (enthalpy including solvation) for these reactions are calculated to 33.7 and 35.6 kcal/mol, respectively. Furthermore, making the overall system charge-neutral by substituting one of the water

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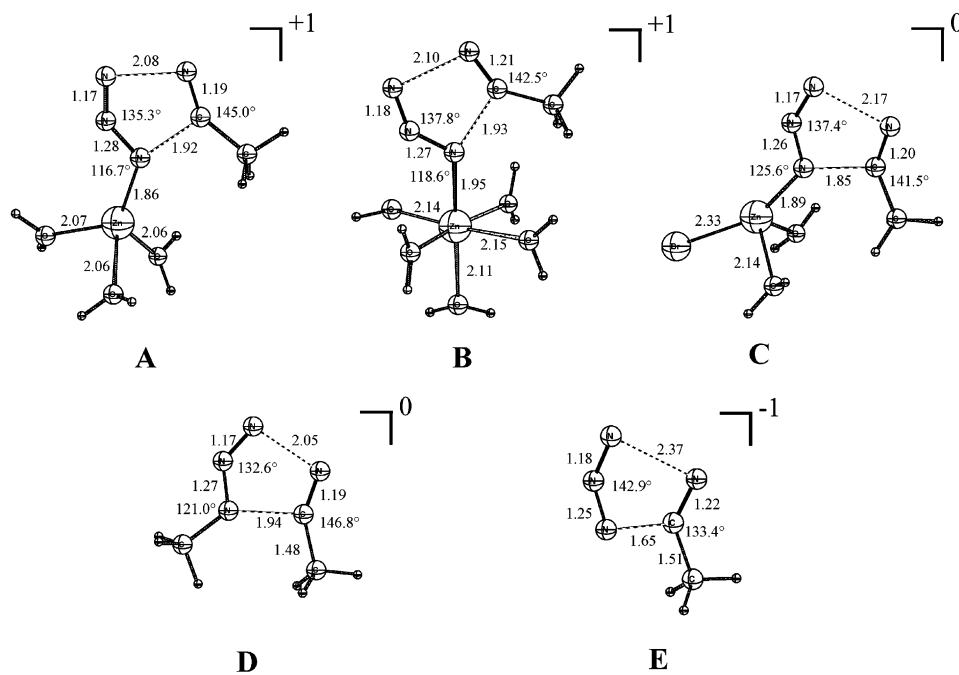(20) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2001**, *3*, 4091−4094.

Figure 1. Optimized transition state structures for various models of the [2 + 3] tetrazole reaction. Bond lengths are given in angstrom. (A) (Tetrahedral zinc) $\Delta H^{\ddagger} = +33.7$ kcal/mol; (B) (octahedral zinc) $\Delta H^{\ddagger} = +35.6$ kcal/mol; (C) (neutral tetrahedral zinc) $\Delta H^{\ddagger} = +34.2$ kcal/mol; (D) (no zinc) $\Delta H^{\ddagger} = +31.6$ kcal/mol; (E) (no zinc, inorganic azide) $\Delta H^{\ddagger} = +33.8$ kcal/mol.
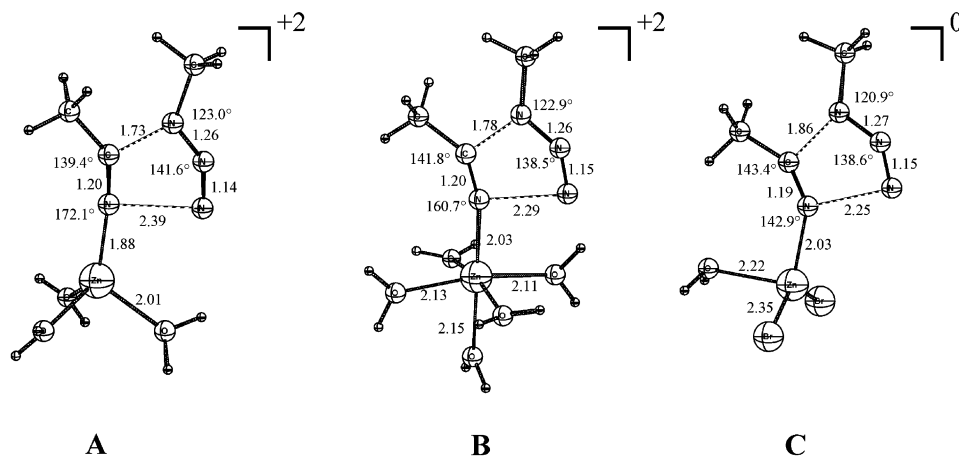

Figure 2. Optimized transition state structures for [2 + 3] cycloaddition reactions of methyl azide and acetonitrile coordinated to zinc. (A) (Tetrahedral zinc) $\Delta H^{\ddagger} = +25.3$ kcal/mol; (B) (octahedral zinc) $\Delta H^{\ddagger} = +28.7$ kcal/mol; (C) (neutral tetrahedral zinc) $\Delta H^{\ddagger} = +29.7$ kcal/mol.

ligands with a Br^- anion (C) gives almost the same barrier, 34.2 kcal/mol.

These barriers are to be compared to the 31.6 kcal/mol barrier for the uncatalyzed concerted cycloaddition of CH_3CN and CH_3N_3 (D) and the 33.8 kcal/mol barrier for [2 + 3] cycloaddition of CH_3CN and N_3^- (E). These calculations indicate that the coordination of an azide anion to Zn does not lead to any significant change in the barrier.

As seen from Figure 1, the local structure of the transition states around the azide and nitrile is quite similar in the zinc-coordinated cases (e.g., A) and in the parent zinc-free cases (D). The $C_{nitrile}-N_{azide}$ bond distance, for instance, is 1.92 Å in Figure 1A and is 1.94 Å in Figure 1D. The $N_{nitrile}-N_{azide}$ bond distance is 2.08 Å in Figure 1A and is 2.05 Å in Figure 1D.

B. Nitrile Bound to Zinc. Next, we consider the situation where the zinc ion is bound to the nitrile instead and methyl
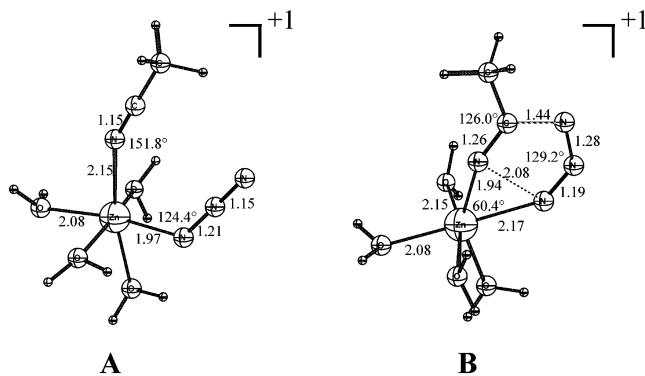

Figure 3. Optimized reactant (A) and transition state (B) structures for the formal [2 + 3] cycloaddition reaction of azide and acetonitrile, both bound to a zinc ion. (A) (Octahedral zinc) [reactant]; (B) (octahedral zinc) [transition state] $\Delta H^{\ddagger} = +27.3$ kcal/mol.
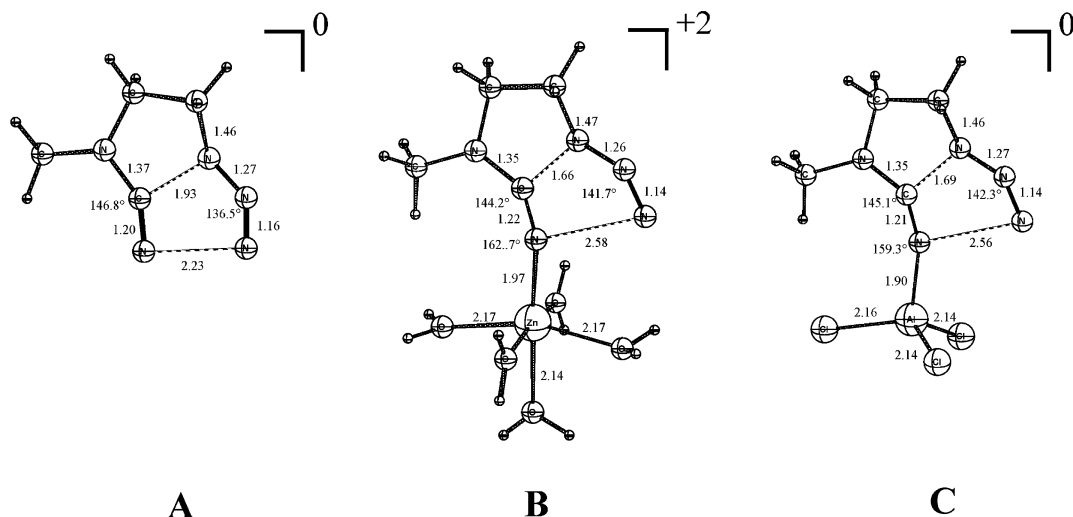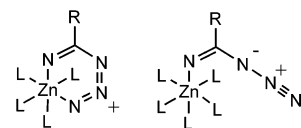
Figure 4. Optimized transition state structures for [2 + 3] intramolecular cycloaddition reaction. (A) Uncatalyzed, (B) octahedral zinc catalyzed, and (C) AlCl$_3$ catalyzed.

Chart 1. Potential Intermediates with the Nitrile Coordinated to Zinc

azide comes from outside the coordination sphere. Three optimized transition state structures modeling these reactions are displayed in Figure 2. In Figure 2A, the zinc is tetrahedral with three water ligands and the acetonitrile, in Figure 2B, the zinc is octahedral (5 water ligands and the acetonitrile), and finally, in Figure 2C, the zinc is tetrahedral (two bromine ligands, one water, and the acetonitrile). The calculated barriers for these reactions are, respectively, 25.3, 28.7, and 29.7 kcal/mol. All the models represent some lowering in the barrier compared to the reactions without the Zn, 31.6 kcal/mol for cycloaddition of CH$_3$CN and CH$_3$N$_3$ (Figure 1D) and 33.8 kcal/mol for cycloaddition of CH$_3$CN and N$_3^-$ (Figure 1E).

For the structures shown in Figure 2, we notice that the local transition state geometries are more asymmetric than those of Figure 1A–D. The C$_{nitrile}$–N$_{azide}$ bond distance is shorter, and the N$_{nitrile}$–N$_{azide}$ bond distance is longer. This is reminiscent of the situation where the nitrile is attached to a strong electron-withdrawing group.[13]

C. Both Reactants Bound to Zinc. So far, the calculations indicate that coordination of the nitrile to Zn reduces the barrier somewhat, while binding of the azide to the Zn does not affect the barrier. What happens when both are bound to Zn?

The reactant and transition state for this cycloaddition reaction are shown in Figure 3. The calculated barrier is 27.3 kcal/mol, which is very close to the barriers obtained when the nitrile is bound to the Zn and the azide is not (e.g., Figure 2B). This suggests that the critical element of the catalysis is the activation of the nitrile by coordination to the metal ion.

As seen from Figure 3, the transition state structure is highly asymmetric, with the C$_{nitrile}$–N$_{azide}$ bond distance being as short as 1.44 Å. Finally, no intermediates of the type shown in Chart 1 could be located.

D. Experimental Corroboration. The results presented above indicate that coordination of the nitrile to the Zn is the

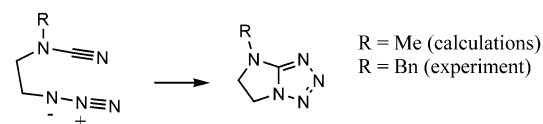**Scheme 4.** Intramolecular [2 + 3] Cycloaddition between Azide and Nitrile

R = Me (calculations)
R = Bn (experiment)

Table 1. Experimental and Theoretical Results of Intramolecular [2 + 3] Cycloaddition of Azide and Nitrile

additive	temperature (°C)	half life (h)	$\Delta G^{\ddagger}$ (kcal/mol) experimental	$\Delta H^{\ddagger}$ (kcal/mol) calculated
none	140	24	35.2 ± 0.2	31.6
ZnBr$_2$	75	18	29.3 ± 0.2	26.3
AlCl$_3$	23	24	25.0 ± 0.2	19.1

main source of catalysis. To test this hypothesis, and to further isolate the effect of zinc, we now consider the intramolecular cycloaddition of the azidocyanamide shown in Scheme 4. This eliminates any possible effects of the charged inorganic zinc–azide complexes, as well as covalent coordination of the zinc and azide. We have calculated the transition states (optimized structures in Figure 4) and performed kinetic studies. The results are presented in Table 1. In the calculations, the benzyl group is substituted by a fully adequate methyl group. Experimentally, Zn^{2+} leads to a decrease in barrier of 5.9 kcal/mol. The calculated barrier reduction is 5.3 kcal/mol, in excellent agreement with experiment.

Zinc's Lewis acidity was previously suspected to be responsible for its catalysis in this reaction. Since most Lewis acids are not water stable, the intramolecular case allowed us to explore stronger, water sensitive Lewis acids. Aluminum chloride proved to be an even more potent catalyst for this reaction, lowering the reaction barrier by an additional 4.3 kcal/mol. The calculations predict a reduction of 7.2 kcal/mol compared to the Zn^{2+} ion.

The calculated absolute barriers are consistently lower than the experimental. The reason for this is that the entropy effect is not included in the calculations. The entropy effect on the intramolecular reaction is estimated from Hessian calculations to be ca. 12 cal/mol·K, corresponding to ca. 4 kcal/mol at room temperature, which when added to the calculated barriers leads

Scheme 5. Intermolecular Addition of Azide to Cyanopyrazine
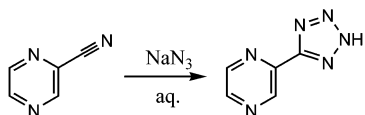
Table 2. Experimental Results of Intermolecular Addition of Azide to Cyanopyrazine

additive	temperature (°C)	half life (min)	$\Delta G^{\ddagger}$ (kcal/mol) experimental
none	80	35	27.2 ± 0.2
ZnBr$_2$	23	4.3	21.5 ± 0.2

to excellent agreement with the experimental barriers. Note that an increase in catalyst concentration in these reactions was not found to significantly increase the rate of reaction.

However, the specific reaction mechanism we are trying to uncover is that for the aqueous conversion of a nitrile to a 1*H*-tetrazole by way of an inorganic azide salt. To assess the similarities of the case shown above, we also performed similar rate studies with the appropriate intermolecular reaction as shown in Scheme 5; the results are shown in Table 2. In this case, the experiments show that Zn reduces the activation barrier by 5.7 kcal/mol. The effect is virtually identical to the intramolecular case, supporting the hypothesis that nitrile coordination to the zinc is the key to catalysis.

V. Conclusions

The mechanism of the zinc catalyzed transformation of nitriles to 1*H*-tetrazoles, in which the presence of zinc lowers the energy barrier of reaction by 5 to 6 kcal/mol, has been studied. Synthetically, this corresponds to a rate acceleration of 3 to 4 orders of magnitude or the fact that the temperature required to achieve comparable rates reaction will drop by some 70−80 °C.

The data presented here strongly support the hypothesis that coordination of the nitrile substrate to the Lewis acidic zinc is the source of the catalysis in the formation of 1*H*-tetrazoles. This point is supported by model calculations using density functional theory and corroborated with experimental rate studies. We were also able to extend our knowledge of the system by looking at another Lewis acid, AlCl$_3$, which catalyzes the reaction to a greater extent than ZnBr$_2$.