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Zinc(II)-Regulation of Hydrazone Switch Isomerization Kinetics

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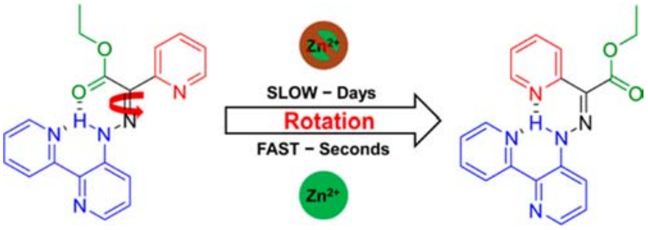
ABSTRACT



The extra H-bond in a bipyridyl-functionalized hydrazone rotary switch slows down its $Z \rightarrow E$ isomerization rate by 2 orders of magnitude ($k = (3.5 \pm 0.2) \times 10^{-6}\ s^{-1}$). The coordination of Zn^{2+} with the bipyridyl subgroup simultaneously 'unlocks' this H-bond and accelerates the isomerization rate by at least 6 orders of magnitude ($k > 6.9\ s^{-1}$). This coordination-regulated kinetic control could open the way to molecular timers that can be used in guiding temporal events.

Biological processes depend on multiple cascades of precisely synchronized and well-programmed chemical reactions.[1] Molecular timers play a pivotal role in this context by regulating physiological events with respect to the temporal order. The prolyl *cis–trans* isomerization,[2] for instance, is an intrinsically slow process; however, it can be catalyzed to proceed several orders of magnitude faster, *i.e.*, from a minute to millisecond time scale, by peptidyl prolyl *cis–trans* isomerases (PPIases).[3] This kinetic modulation leads to a molecular timer that is used in controlling a variety of well-choreographed operations, such as cell cycle, cell signaling, and gene expression.

One of the ultimate goals in the field of artificial molecular motors and switches is to mimic the complexity of biological systems.[4] In order to achieve this goal the control of the timing of molecular events and motions will be crucial. Over the decades, great strides have been made in terms of precisely manipulating thermodynamic states of synthetic molecular switches,[5] with the emphasis being put on the control of spatial order.[4,5] Fewer attempts have been made in terms of precisely regulating the kinetic properties of such molecular systems,[6] which in most cases involve the slowing down of motion, by 'braking' or adding 'bumpers' to the system.[7] However, the stimuli-responsive acceleration of the motion of molecular switches has been less developed.[8] Undoubtedly, the regulation of temporal order, which relies mainly on the control of kinetic properties, will be an important part of

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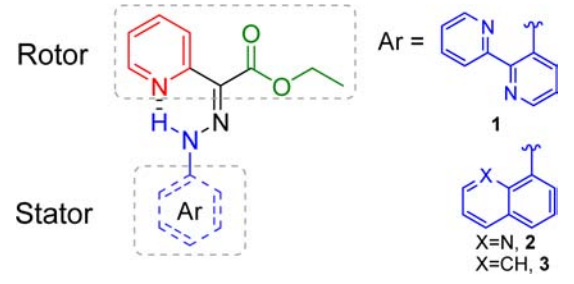
the design of systems that can lead to complexity[4a] and emergent phenomena.[9] Here, we wish to report how such temporal control can be achieved using the bipyridyl-containing hydrazone switch **1**.

Scheme 1. A Schematic Illustration of the Hydrazone-Based Rotary Switches **1**, **2**, and **3**



In an earlier report,[10] we have noted that the extra H-bond in a quinolinyl-based hydrazone switch (**2**) significantly slows down its *Z*→*E* isomerization process (ca. 600-fold), compared to a naphthyl counterpart (**3**, Scheme 1).[11] This remarkable decrease in isomerization rate was attributed to the extra H-bond's stabilization of the *Z* isomer. On the basis of this premise, we envisioned that it will be possible to modulate the isomerization rate of similar systems by using a stator having a tunable H-bond acceptor, one that can be turned "ON" and "OFF" *via* an orthogonal stimulus (*i.e.,* a stimulus other than a proton or base).

2,2′-Bipyridine (BPY) is a versatile bidentate ligand that has been extensively used in various applications.[12] The basic nature of its pyridyl nitrogens makes it also an excellent H-bond acceptor, and therefore, we integrated it into a hydrazone-based switch[13] as a metal-tunable H-bond acceptor (Scheme 1). Compound **1**, which was synthesized in three steps (Supporting Information), crystallizes with tetragonal $P4_3$ symmetry and each asymmetric unit contains two crystallographically independent molecules (Figure S23). Both molecules adopt the *E* configuration, in which the hydrazone N−H forms a H-bond with the pyridyl nitrogen in the rotor. Furthermore, the stator's 2′-pyridyl group is oriented toward the rotor pyridyl ring, forming a second H-bond. However, unlike **2**[10] or **3**,[11] **1** fails to retain its planarity. The pyridyl group is twisted away from the plane defined by the hydrazone skeleton,[14] with the dihedral angles between the rotor and stator pyridyl ring planes being 34.779(141)° and 24.056(137)°. This deviation from planarity is likely caused by the steric overcrowding in the system. Therefore, the strength of the H-bond between the hydrazone N−H and the stator 2-pyridyl nitrogen (2.6752(50) Å, 129.206(246)° and 2.6680(49) Å, 128.621(246)° for the units shown in Figure 1a and b, respectively) is stronger than that between the hydrazone N−H and the rotor pyridyl nitrogen (2.7542(48) Å, 123.938(240)° and 2.7503(48) Å, 124.875(240)° for the units shown in Figure 1a and b, respectively).

The ^{1}H NMR spectrum of **1** in CD_3CN (Figure 1a) initially reveals one set of signals, having a characteristic hydrazone N−H proton resonance at 14.91 ppm, indicating that the sole isomer in solution is the *E* form (**1-*E***). The 1D NOE correlation between protons H8 and H9 confirms that the orientation of the 2′-pyridyl group is as observed in the crystal structure, while the NOE correlation between proton H8 and the hydrazone N−H proton conclusively establishes this configuration (Figure S4). Compound **1-*E*** slowly isomerizes in solution to **1-*Z*** with a first-order rate constant of $k = (1.1 \pm 0.1) \times 10^{-6}\ s^{-1}$ and reaches equilibrium within 10 days (Figures S17−S19), at which time the *E* to *Z* ratio is 78:22. This ratio is close to the one found for **2**,[10] providing additional evidence that the extra H-bond stabilizes the *Z* configuration.

The addition of 8 equiv of trifluoroacetic acid (TFA) to **1** in CD_3CN leads to a new species (Figures S5−S6), which was assigned as **1-*Z*-H**$^+$.[15] Passing this solution through a plug of potassium carbonate (K_2CO_3) yields a new ^{1}H NMR spectrum (Figure 1c), which is identical to the

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(14) The dihedral angles between two pyridyl rings in the bipyridyl groups were 16.409(158)° and 5.076(157)°, and the torsion angles of C=N−N−C were −179.019(407)° and −179.533(403)°, while the torsion angles of N−N=C−C were 0.956(720)° and −0.862(686)°.

(15) Usually up to 2 equiv of acid are required to protonate the rotor pyridyl ring and induce *E*→*Z* isomerization. However, in this system the competition with the free BPY nitrogen increases the amount of TFA required to complete the process.

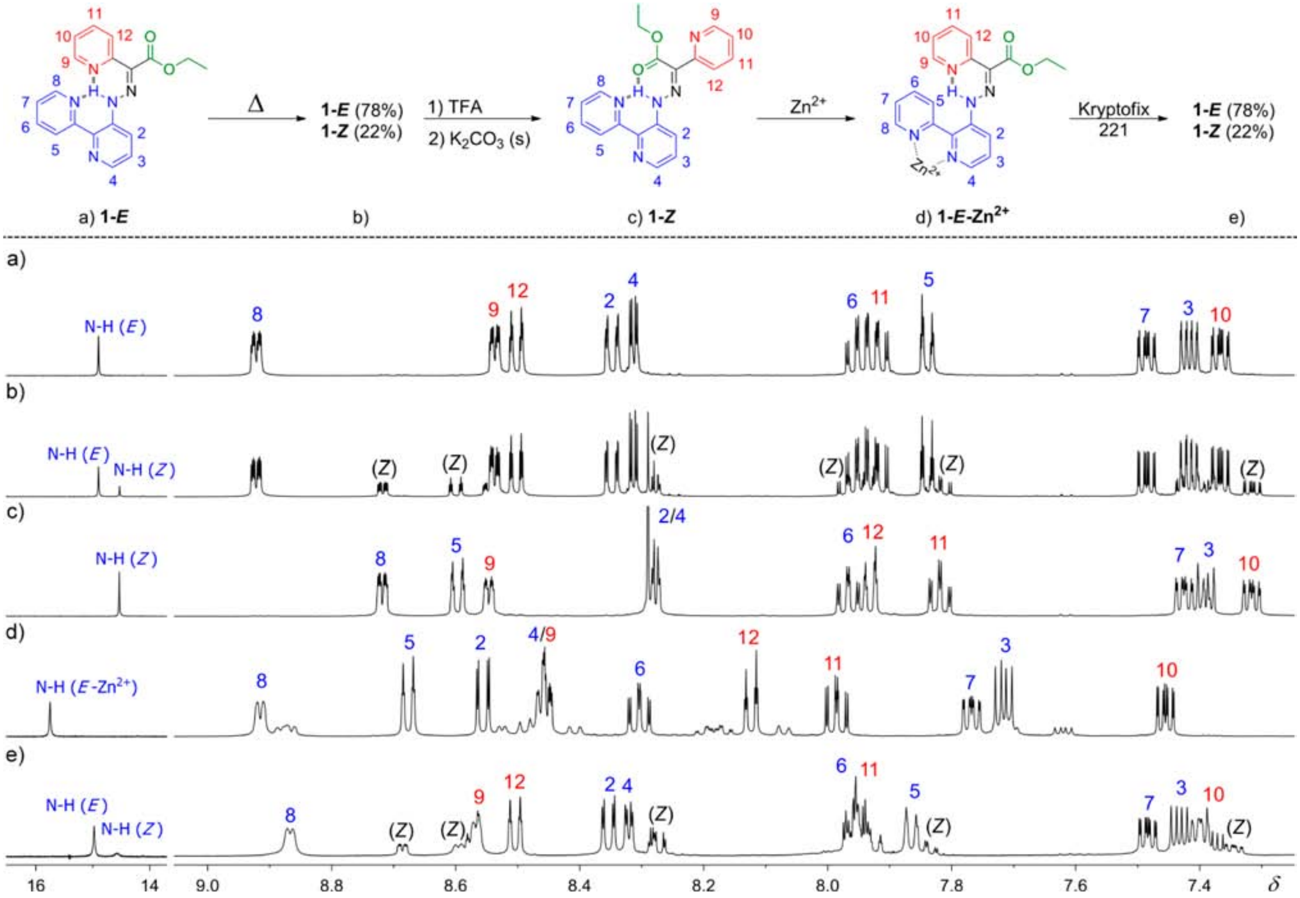

Figure 1. ^{1}H NMR spectra (500 MHz, CD_3CN, 294 K) of (a) **1-*E***; (b) **1** in equilibrium (80% **1-*E*** and 20% **1-*Z***); (c) **1-*Z***, after the addition of 8 equiv of TFA and then passing the solution through a plug of K_2CO_3; (d) **1-*E*-Zn^{2+}**, obtained by the addition of 1.1 equiv of Zn^{2+} to **1-*Z***; and (e) **1** in equilibrium, after the addition of 1.2 equiv of Kryptofix 221 to **1-*E*-Zn^{2+}**.

minor isomer in the equilibrated solution of **1**; *i.e.*, **1-*Z*** is formed. A 1D NOE correlation between the hydrozone N−H and H8 protons (Figure S9) establishes the conformation of the stator, and the presence of a H-bond between the 2′-pyridyl nitrogen and N−H proton. While no NOE correlation was observed between protons H8 and H9, the NOE correlation between the H2 and H12 protons (Figure S10) conclusively confirms the configuration of **1-*Z***. As expected, the isomerization rate from **1-*Z*** to **1-*E*** is extremely slow (first-order rate constant $k_{-1} = (3.5 \pm 0.2) \times 10^{-6}$ s^{-1}; Figures S20−S22), which is comparable to that of **2**. The equilibrium constant K_{eq} (3.2) calculated using k_{-1}/k_1 is consistent with the K_{eq} value (3.5) measured from the ^{1}H NMR spectra integrals.

The addition of 1.1 equiv of zinc(II) perchlorate to the newly formed **1-*Z*** results in a new species (Figure 1d and Figures S11 and S12). The prominent downfield shifts of protons H2−H8, especially of H4 and H8, from 8.29 and 8.73 ppm to 8.47 and 8.92 ppm, respectively, suggest the coordination of Zn^{2+} to the BPY nitrogens. This process is confirmed by the NOE correlation between the hydrozone N−H and H5 protons (Figure S13), which demonstrates not only the breaking of the N−H···N H-bond with the 2′-pyridyl nitrogen but also the change in the conformation of the bipyridyl group. More importantly, the NOE correlation between protons H6 and H9 (Figure S14) reveals that the configuration of **1** switched from *Z* to *E* upon coordination with Zn^{2+}! The new species can therefore be assigned to **1-*E*-Zn^{2+}** (Scheme 2). Such a dramatic change in configuration is rather astonishing because it proceeds almost instantaneously upon coordination with Zn^{2+}. Even in the case of **3**, which lacks the additional H-bond that stabilizes the *Z* configuration, it takes hours (3.5×10^{-4} s^{-1}) for **3-*Z*** to isomerize back to **3-*E***. Therefore, the influence of Zn^{2+} coordination goes beyond the sole effect of 'unlocking' the additional H-bond in the system. It also accelerates the isomerization process by a factor of 10^6, assuming the entire process finishes as a first-order reaction in 1 s (99.9% conversion).[16]

We postulate that Zn^{2+} works on multiple levels in accelerating the *Z*→*E* isomerization in **1**, which proceeds through what we have dubbed a (hydrazone-azo) tautomerization followed by rotation mechanism.[11b] The 'locking' of the hydrazone N−H proton by the 2′-pyridyl nitrogen hinders the tautomerization step, whereas the

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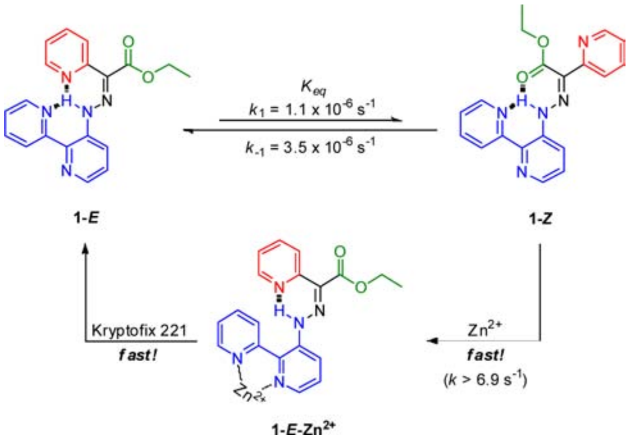
(16) The process is instantaneous and is too fast to follow using NMR spectroscopy.

Scheme 2. The *Z*→*E* Isomerization Rate Is Significantly Accelerate by Zn^{2+} Coordination Followed by Demetalation

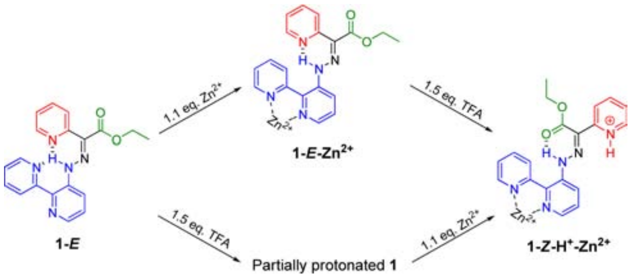


coordination induced ‘unlocking’ greatly reduces the barrier. The metal can also acidify the hydrazone N−H proton, thus facilitating the tautomerization process. Moreover, it can electronically stabilize the transition state.

The removal of Zn^{2+} from the complex **1-*E*-Zn^{2+}** can be achieved by the addition of 1.2 equiv of Kryptofix 221,[17] which is an efficient Zn^{2+}-caging cryptand (Scheme 2). The process instantaneously yields **1** in its equilibrated *E*/*Z* isomer ratio (78:22, Figure 1e). Consequently, the low intensity signals (20%) in the ^{1}H NMR spectrum of **1-*E*-Zn^{2+}** (Figure 1d) can be assigned to **1-*Z*-Zn^{2+}**. Evidently, the coordination to Zn^{2+} does not change the *E*/*Z* equilibrium of **1**, despite its dramatic influence on the isomerization rate.

Interestingly, further investigation disclosed a synergistic effect between protonation and Zn^{2+} coordination in the switching of **1**. The addition of 1.5 equiv of TFA and 1.1 equiv of Zn^{2+}, regardless of the order of addition, results in **1-*Z*-H$^+$-Zn^{2+}** (Figures S15−S16).[18,19] However, adding Zn^{2+} first to **1** gives rise to the formation of **1-*E*-Zn^{2+}**, whereas adding TFA first would simply yield a mixture of (partially) protonated **1** (Scheme 3). This result can be rationalized by the fact that coordination removes the BPY nitrogen from the equation, and so full protonation of the rotor pyridyl ring, and hence isomerization, occurs with only 1.5 equiv of TFA.[15] The deprotonation of **1-*Z*-H$^+$-Zn^{2+}** by the addition of 1.6 equiv of triethylamine (Et$_3$N) leads to the quick formation of **1-*E*-Zn^{2+}** (in addition to the minor isomer **1-*Z*-Zn^{2+}**), which could be converted into **1** using Kryptofix 221.

Scheme 3. Synergy between Zn^{2+} Coordination and Protonation in the Formation of **1-*Z*-H$^+$-Zn^{2+}**



In conclusion, we have demonstrated that the coordination of Zn^{2+} to a bipyridyl-modified hydrazone switch accelerates the otherwise slow *Z*→*E* isomerization process by at least 6 orders of magnitude. Zn^{2+} can then be scavenged by Kryptofix 221, leaving the switched system intact in terms of the thermodynamic equilibrium. This example represents a successful foray into the *in situ* temporal regulation of the motion of molecular switches. We envision that the coupling of this process with multistep switching cascades[13d] will bring us a step closer to realizing the complexity found in biological systems.

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Supporting Information Available. Experimental procedures, NMR spectra, and crystal structural data for **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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[18] The absence of any NOE correlations between the protons on the pyridyl ring and those on the 2′-pyridyl ring suggests that the *E*→*Z* isomerization indeed occurred. As a result of the broadening of the hydrazone N−H proton signal, no NOE correlation is observed between it and any of the stator 2′-pyridyl ring protons.

[19] Almost all the aromatic proton signals of **1-*Z*-H$^+$-Zn^{2+}** are shifted downfield because of the combined effect of protonation of the rotor pyridyl group and the coordination of Zn^{2+} to BPY.