Biomimetic Switches

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Switching through Coordination-Coupled Proton Transfer**

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The binding of transition metals, such as Zn^{2+}, Ni^{2+}, and Cd^{2+}, with protein residues often leads to proton displacement.[1] This process occurs, for example, in the reaction centers (RCs) of photosynthetic bacteria,[2] and leads to conformational changes and modification of the pK_a values of the surrounding amino acid residues. These changes eventually slow down the photosynthetic process. A similar deprotonation event also takes place in cation-diffusion facilitators (CDFs), in which the coordination-coupled deprotonation (CCD) provides the energetic basis for metal efflux.[3] The CCD process has considerable potential for molecular switches,[4] as it opens the way to a new and far-reaching switching mechanism in which acid modulations[5] can be brought about without the addition of protons.[6] This possibility could be of interest, for example, in cases in which molecular switches need to be activated under mild or neutral conditions. The CCD process in RCs and CDFs is associated with metal binding to histidine residues. Therefore, N–H-containing molecular switches, such as the pH-activated hydrazone-based rotary switches[7] that we have been developing, might be suitable for mimicking this bioinorganic process. As it happens, the coordination of transition metals to hydrazones can lead, in certain cases, to N–H deprotonation.[8] With this possibility in mind, we set out to develop a new switching mechanism that takes advantage of the CCD process.

We recently reported the four-step pH-activated switching cycle of a tristable hydrazone-based molecular switch (QPH) with a quinolinyl group as the stator and an ethyl 2-pyridylacetate derivative as the rotor.[7b] This molecular switch can be viewed as a tridentate ligand that can accommodate a transition metal by coordination with either the pyridine or carbonyl moiety in the rotor, the quinolinyl group in the stator, and the imine or N–H nitrogen atoms in the axle. We explored the binding of this molecular switch to Zn^{II}, which has been shown to bring about CCD in RCs, CDFs, and the deprotonation of hydrazones,[8] to discern whether the deprotonation process could be useful in activating the molecular rotor.

The UV/Vis spectrum of QPH in CH_3CN shows an absorption maximum at $\lambda_{max} = 393$ nm (Figure 1). Upon titration with zinc(II) perchlorate ($Zn(ClO_4)_2$), the absorption maximum shifted bathochromically with an accompanying

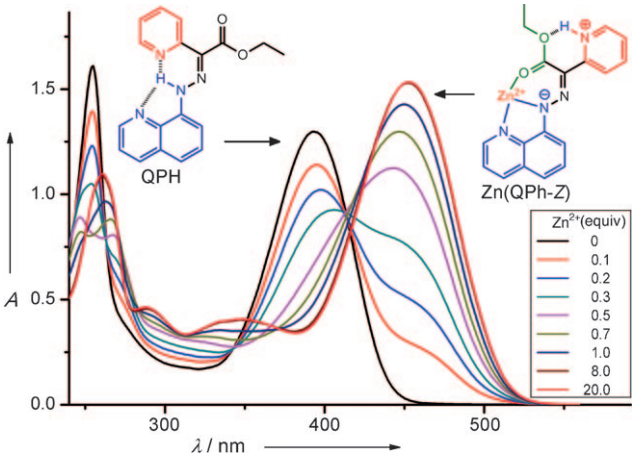

Figure 1. UV/Vis spectra of the titration of QPH (5.0×10^{-5} M) with Zn^{2+} in CH_3CN at room temperature.

hyperchromic change that reached saturation at 8 equivalents of Zn^{2+} ($\lambda_{max} = 452$ nm). This shift in UV/Vis absorption is an indication that Zn^{2+} coordinates strongly with QPH. A Job plot (see Figure S4 in the Supporting Information) derived from the UV/Vis spectra shows a vertex around 0.65, which suggests a 2:1 binding stoichiometry between QPH and Zn^{2+}.[9] The fact that no isosbestic points were observed during the UV/Vis titrations indicates that more than two chromophoric species are involved in the process, and thus the binding stoichiometry cannot be 1:1. Binding constants were determined as $K_1 = 5.7\times10^5\ M^{-1}$ and $K_2 = 7.5\times10^4\ M^{-1}$ by least-square curve fittings (see Figure S5) of the titration data of QPH with Zn^{2+} by using a 2:1 binding model.[10]

When the resulting Zn^{2+} complex was treated with tetra-*n*-butylammonium cyanide (*n*Bu_4NCN), the absorption maximum at $\lambda_{max} = 452$ nm decreased, whereas the signal belonging to QPH at $\lambda_{max} = 393$ nm increased (see Figure S6). After the addition of 12 equivalents of *n*Bu_4NCN, the UV/Vis spectrum returned to its original state. This result indicates that the system can be fully switched back with *n*Bu_4NCN. Satisfactory multiple switching cycles were observed upon the alternate addition of $Zn(ClO_4)_2$ and *n*Bu_4NCN to the QPH solution (see Figure S7).

The ^{1}H NMR spectrum of QPH (Figure 2a) showed drastic changes, especially for the hydrazone and aromatic hydrogen atoms, when Zn^{2+} (0.4 equiv) was added (Figure 2b); the QPH signals decreased in intensity, and a new set

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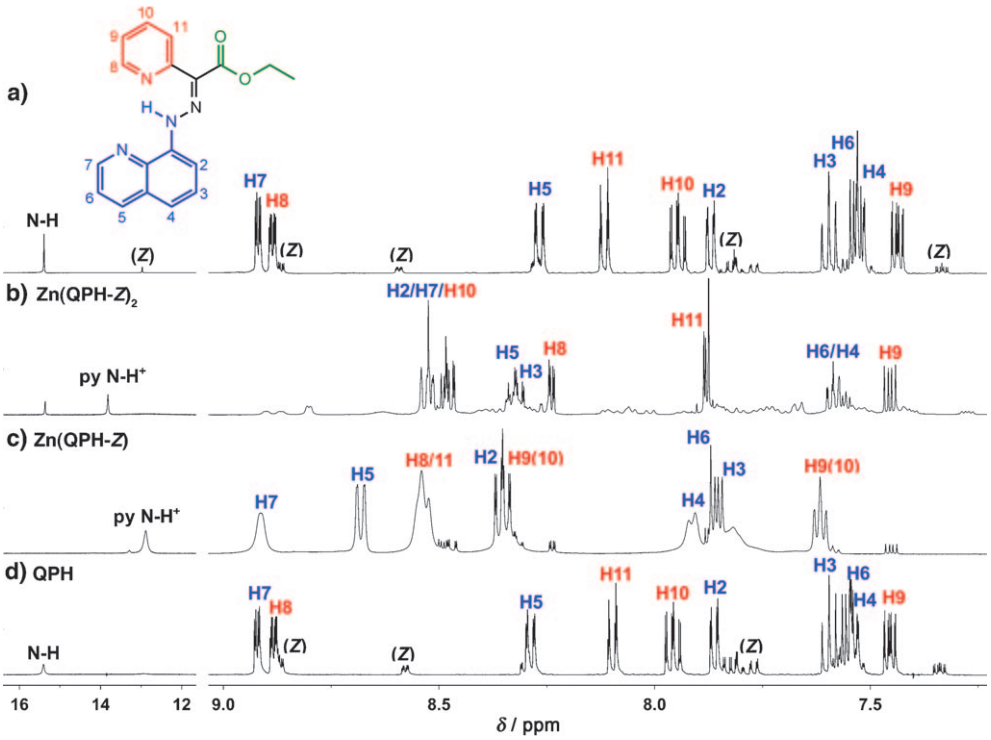


Figure 2. ^{1}H NMR spectra (500 MHz, 294 K) in CD_3CN of a) QPH with peak assignments (the signals of the minor *Z* isomer are also labeled); b) the complex Zn(QPH-*Z*)$_2$ with partial peak assignments (the spectrum was recorded after the addition of $Zn(ClO_4)_2$ (0.4 equiv) to QPH); c) the complex Zn(QPH-*Z*) with peak assignments (the spectrum was recorded after the addition of $Zn(ClO_4)_2$ (1.6 equiv) to QPH); d) QPH (the spectrum was recorded after the addition of nBu$_4$NCN (9.6 equiv) to the complex Zn(QPH-*Z*)).

of peaks emerged, including a peak at $\delta = 13.8$ ppm. The general trend was a downfield shift of the aromatic signals, except for those of hydrogen atoms H7, H8, and H11, which were shifted to higher field. Similar behavior was observed upon protonation of the pyridyl and quinolinyl rings in QPH.[7b] On the basis of the stoichiometry and binding constants, it can be concluded that a 2:1 complex (Zn(QPH-*Z*)$_2$) had been formed at this stage, as expected from the interaction of a tridentate ligand with Zn^{2+}.[11] The signal at $\delta = 13.8$ ppm does not show the typical NOE correlations observed for the hydrazone N–H hydrogen atom. This observation is one indication that this signal does not result from the hydrazone N–H hydrogen atom but rather the nitrogen-bonded hydrogen atom on the protonated pyridyl ring (pyN–H$^+$). Protonation of the pyridyl ring explains the downfield shift of the pyridyl hydrogen atoms. The upfield shift of the signal for H8 can be attributed to its removal from the influence of the quinolinyl ring current. As previously shown,[7] this change is an indication of *E*-to-*Z* isomerization. The lack of any NOE signals from pyN–H$^+$ prevented us from gaining any further structural information about the 2:1 complex in solution.

The changes in the ^{1}H NMR spectrum reached saturation when the amount of $Zn(ClO_4)_2$ was increased to 1.6 equivalents.[12] At this stage, a 1:1 complex (Zn(QPH-*Z*)) is formed. Because of the significant broadening of some of the signals, complete assignment of the peaks was not possible (Figure 2c). In general, the center-of-mass of the spectrum was shifted to lower field, a trend that is again similar to that observed for the fully protonated QPH system.[7b] Interestingly, the signals for hydrogen atoms H7 and H11 were now shifted to low field. These shifts indicate that these atoms were affected by local ring currents in the 2:1 complex. More importantly, the signal at $\delta = 12.9$ ppm, instead of showing the regular NOE correlations, showed a 2D COSY correlation with H8 (see Figure S8). This interaction proves conclusively that the pyridyl group is protonated. Protonation of the pyridyl group has so far led to the *E*-to-*Z* isomerization in these systems. The broadness of key signals and the deprotonation of the hydrazone N–H group hindered the acquisition of NOE interactions that could prove that isomerization also occurred in this instance. However, the upfield shift of the H8 signal is indirect evidence for the isomerization.[7] When the 1:2 and 1:1 complexes were treated with excess nBu$_4$NCN, they reverted back to their original state, and the ^{1}H NMR spectrum of QPH was regenerated (Figure 2d).

Oddly enough, the treatment of the 1:1 complex with potassium carbonate (K_2CO_3) did not lead to the expected deprotonation[7] of the pyridyl N–H group (see Figure S9). A stronger base (nBu$_3$N) was required to effect the deprotonation. It seems that the coordination with Zn^{2+} drastically changed the pK_a value of the system.[13] This result is reminiscent of the changes in the pK_a value that take place when transition metals coordinate with RCs and CDFs.[2,3] It again indicates that this simple QPH system is mimicking the complicated processes that take place in biological systems.

The crystal structures of the Zn^{II} complexes with QPH shed further light on the complexation process. In the 1:1 complex Zn(QPH-*Z*)[14] (Figure 3a), the Zn^{2+} cation is pentacoordinated with one QPH unit, one triflate anion, and one water molecule. The QPH unit still maintains its planar geometry.[15] However, the hydrazone hydrogen atom on N1 is missing, whereas the pyridyl group is protonated and forms a hydrogen bond with the ester carbonyl oxygen atom (N-H···O, 2.6141(487) Å, 131.855(2330)°). The protonation of the pyridyl group is consistent with the 2D COSY NMR spectrum. The C1–N2 and N2–N1 bond lengths are 1.3364(35) and 1.3014(33) Å, respectively. From a comparison with the crystal structure of the monoprotonated QPH

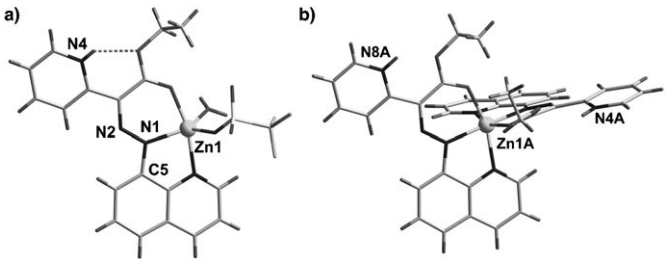
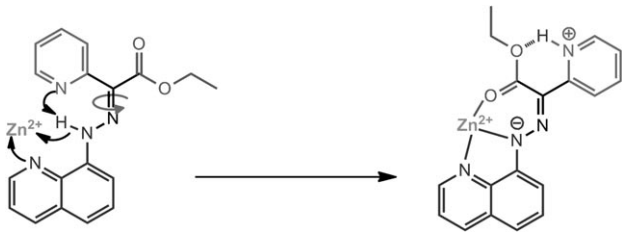


Figure 3. Stick drawings of the crystal structures of complexes a) Zn(QPH-*Z*) and b) Zn(QPH-*Z*)$_2$. The hydrogen atoms are placed in calculated positions, except for those on nitrogen atoms N4, N4A, and N8A, which were refined.

compound (QPH-*Z*-H$^+$),[7b] in which the corresponding bond lengths are 1.3095(23) and 1.3132(22) Å, respectively, it is clear that the C–N bond is elongated and the N–N bond is shortened as a result of deprotonation and coordination with Zn^{2+}. However, the C–N bond still maintains its double-bond character, and the N–N bond maintains its single-bond character. Most importantly, the configuration of QPH is changed from *E* to *Z* as a result of the coordination with Zn^{II} and the protonation of the pyridyl group. These results are consistent with our observations of the system in solution. In the 2:1 complex Zn(QPH-*Z*)$_2$[16] (Figure 3b), the Zn^{2+} cation is hexacoordinated with two QPH molecules that are almost perpendicular to one another. The QPH units in the 2:1 complex have also undergone deprotonation of the hydrazone N–H group, protonation of the pyridyl group, and configurational switching, but remain planar. The changes in bond lengths are similar to those observed for the 1:1 complex; thus, the imine form, rather than the azo form, is still the dominant form of QPH. These results are also consistent with the solution-phase observations and explain the shifts observed for H7 and H8.[17]

On the basis of the above observations, we propose a coordination-coupled proton-transfer switching mechanism (Scheme 1) to rationalize the interaction of QPH with Zn^{2+}.



Scheme 1. Proposed mechanism for switching through coordination-coupled proton transfer.

First, Zn^{2+} coordinates with the quinolinyl nitrogen atom and the hydrazone N–H nitrogen atom, and the hydrazone NH proton undergoes intramolecular transfer to the pyridyl nitrogen atom that is part of the preorganized H-bonded six-membered ring. As a result of the overcrowded positively charged environment, and to satisfy the coordination sphere of Zn^{2+}, the protonated pyridyl group is forced to rotate about the C=N double bond to enable coordination of the ester to Zn^{2+}. This rotation brings about the configurational change observed in solution and in the solid-state structure. When cyanide (CN^-) is added to the solution, competitive coordination of Zn^{2+} by CN^- demetalates the complex, and subsequently, the pyridyl nitrogen atom is deprotonated, and the hydrazone nitrogen atom is protonated. This process brings about *Z*-to-*E* isomerization and thus completes the switching cycle.

To validate the proposed mechanism, we carried out two control experiments. First, we synthesized QPH-NMe by replacing the hydrazone N–H hydrogen atom with a methyl group (see Scheme S1 in the Supporting Information). Upon titration of QPH-NMe with Zn(ClO$_4$)$_2$, the ^{1}H NMR spectrum showed a downfield shift of the aromatic hydrogen atoms, which indicates an interaction between QPH-NMe and Zn^{2+} (see Figure S11). This interaction did not cause any change in the *E*/*Z* isomer ratio: an indication that the N–H hydrogen atom is required to effect isomerization. Moreover, no signal was observed beyond $\delta = 10$ ppm, where the protonated pyridyl group resonates. The lack of a signal in this region is clear evidence that no protonation occurred in this case. It can be concluded that a coordination-coupled intramolecular proton transfer is responsible for the configurational change in Zn(QPH-*Z*) and Zn(QPH-*Z*)$_2$. Second, compound NPH,[7a] which has a naphthyl group instead of a quinolinyl group, was titrated with Zn(ClO$_4$)$_2$. The ^{1}H NMR spectrum showed no significant change, except for signal broadening (see Figure S12). This result suggests that there is no interaction between NPH and Zn^{2+}, and furthermore, that the quinolinyl group is an indispensable prerequisite for the coordination and subsequent reactions between QPH and Zn^{2+}. This experiment also shows that the proton transfer is an intramolecular process coupled with Zn^{2+} coordination.[18] As far as the reverse process is concerned, we hypothesize that an intramolecular proton transfer also takes place from the protonated pyridyl group to the deprotonated hydrazone nitrogen atom. This proton is well-situated to be plucked back by the nitrogen atom once demetalation takes place. However, we have no direct way of studying this process.

In conclusion, we have developed a new switching mechanism that takes advantage of a Zn^{2+}-coupled proton transfer to effect *E*/*Z* isomerization in a hydrazone-based rotary switch. This new mechanism was inspired by, and mimics, the CCD processes in bioinorganic systems. The switching process is full reversible, as the hydrazone-based rotor can be quantitatively switched back to its initial *E* configuration by removing the Zn^{2+} cation with cyanide. This process opens up a broad range of opportunities for the design of switching systems that function under mild (non-acidic) conditions, the study of reactions related to the photosynthetic pathway[2] and CDFs,[3] and the construction of artificial functional mimics of biological systems.[19]

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[12] Because of the equilibrium, the 2:1 complex persists, no matter how much Zn^{2+} is added. This dynamic equilibrium results in the broadening of some of the signals of the 1:1 complex. For the reverse titration of Zn^{2+}, see Figure S10.

[13] A resonance structure can be drawn of an azo form in which the positive charge on the pyridinium nitrogen atom is neutralized. This resonance may explain the change in the pK_a value of this system.

[14] Crystal data for Zn(QPH-*Z*): $C_{20}H_{20}F_6N_4O_{10}S_2Zn$, $M_r = 719.89$, triclinic $P\bar{1}$, $a = 8.1722(8)$, $b = 12.6323(12)$, $c = 13.7757(13)$ Å, $\alpha = 71.611(1)$, $\beta = 86.408(1)$, $\gamma = 81.121(1)°$, $V = 1333.2(2)$ Å^3, $T = 173(2)$ K, $Z = 2$, $\rho_{calcd} = 1.793$ g cm^{-3}, $\mu = 1.182$ mm^{-1}, $2\theta_{max} = 50.24°$, 19397 reflections measured, 4859 unique ($R_{int} = 0.0585$), which were used in all calculations. The final $R_\omega(F^2)$ value was 0.1192 (all data). CCDC 799047 (Zn(QPH-*Z*)) and 799046 (Zn(QPH-*Z*)$_2$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[15] In the crystal structure of Zn(QPH-*Z*), the dihedral angle between the pyridyl ring and the quinolinyl ring is 12.740(63)°, and the torsion angles of N-N=C-C (pyridyl) and C=N-*N*-C (quinolinyl) are 178.801(232) and 178.875(235)°, respectively.

[16] Crystal data for Zn(QPH-*Z*)$_2$: $C_{39}H_{37}C_{l2}N_{9.50}O_{12.25}Zn$, $M_r = 971.05$, monoclinic $P21/c$, $a = 23.867(2)$, $b = 21.720(2)$, $c = 16.6544(16)$ Å, $\alpha = 90$, $\beta = 101.7380(10)$, $\gamma = 90°$, $V = 8453.0(14)$ Å^3, $T = 173(2)$ K, $Z = 8$, $\rho_{calcd} = 1.526$ g cm^{-3}, $\mu = 0.783$ mm^{-1}, $2\theta_{max} = 50.72°$, 81498 reflections measured, 15435 unique ($R_{int} = 0.0667$), which were used in all calculations. The final $R_\omega(F^2)$ value was 0.2125 (all data).

[17] Hydrogen atom H7 of one ligand is oriented perpendicularly to the deprotonated hydrazone functional group of the other; hence, it is shielded.

[18] In an intermolecular proton transfer, the pyridyl nitrogen atom will be available for coordination with Zn^{2+}. We see no evidence of this coordination, thus further supporting the intramolecular pathway. This said, we cannot absolutely rule out intermolecular proton transfer.

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