Enhanced Acidity of Zn²⁺ in the Presence of Small Numbers of Water Molecules

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Experiments performed on gas phase $[Zn(H_2O)_N]^{2+}$ complexes, for N in the range 4–7, show the ions readily undergo unimolecular (metastable) decay with respect to proton release *via* the reaction $[Zn(H_2O)_N]^{2+} \rightarrow Zn^{2+}OH^-(H_2O)_M + H_3O^+(H_2O)_{N-M-2}$. To account for these products, it is proposed that the larger complexes have a stable $[Zn(H_2O)_4]^{2+}$ core to which additional molecules are retained in an outer shell through hydrogen bonding. At $N = 7$, this arrangement would make it possible for proton release to be associated with a chain of up to four water molecules, which equates with ideas proposed for the activity of Zn^{2+} in metalloenzymes.

There is considerable debate in the literature regarding the behavior of the zinc dication, Zn^{2+}, in the presence of water.[1–14] Discussion ranges from subtle differences in geometries adopted by finite numbers of water molecules surrounding the ion,[1–6] through to the anomalous pK_a of water when Zn^{2+} is associated with the enzyme carbonic anhydrase.[7–14] Metalloenzyme chemistry probably represents the single most significant consequence of the acidity of Zn^{2+}, where chemical processes rely on efficient formation of the nucleophile $Zn^{2+}OH^-$. In the case of carbonic anhydrase, it has been proposed that proton loss from coordinated $Zn^{2+}-H_2O$ proceeds *via* the presence of a finite chain of water molecules, and estimates of the number of molecules involved with the active site range from 2 to 12.[9–13]

An important step forward in our understanding of Zn^{2+} in association with water has come from the recent calculations of Bernasconi et al.[7] These authors were able to rationalize differences in acidity between Zn^{2+} and Mg^{2+} in terms of the ability of water as a solvent to preferentially stabilize the $Zn^{2+}(H_2O)_5(OH^-)$ unit, an idea that builds on earlier static calculations by Trachtman et al.[15] and Kluge and Weston.[16] The calculations of Bernasconi et al.[7] also suggest that in the gas phase the difference in acidity between Mg^{2+} and Zn^{2+} should be much larger than that in aqueous solution. The pK_a values for bulk water in the presence of these ions are the following: Mg^{2+} (12.4) and Zn^{2+} (9.2).

This Letter reports the results of observations made on proton transfer reactions in the gas phase complexes consisting of Zn^{2+} in association with small numbers of water molecules, $[Zn(H_2O)_N]^{2+}$ for N in the range 4–7. To illustrate the ability of Zn^{2+} to facilitate proton transfer, we contrast the results with a similar study of $[Mg(H_2O)_N]^{2+}$ complexes. Although six-coordinate structures of Zn^{2+} and Mg^{2+} have comparable ionic radii (~86–88 pm),[17] their chemistries (acidities) are very different. Calculations on Mg^{2+} show the lowest energy structure for $N = 6$ has all of the water molecules in a primary shell.[2]

However, for Zn^{2+}, there are only slight differences in energy between a primary shell $N = 6$ structure and those with up to two molecules in a secondary shell.[2–5] As noted by Glusker et al.,[18] Zn^{2+} has a flexible coordination which may account for the catalytic activity of the ion. In contrast, the coordination of Mg^{2+} is more rigidly bound by energy barriers and so the ion is more suited to maintaining structure rather than promoting reactivity.[18] The results presented here demonstrate that Zn^{2+} has a higher than expected propensity to release a proton from coordinated water, and that the reaction is facilitated by the presence of secondary shell water molecules.

The reactivity of complexes involving both Zn^{2+} and Mg^{2+} with water has been the subject of several earlier experimental investigations by Peschke et al.,[19] Shvartsburg and Siu,[20] and Barran et al.[21] In all cases, fragmentation has been promoted by collision-induced dissociation (CID), which is a very different mechanism from the experiments reported here. In this present series of experiments, size-selected ions have been monitored for the occurrence of unimolecular (metastable) decay at a background pressure of $<10^{-7}$ mbar and on a time scale of $\sim10^{-4}$ s. Because of the existence of competitive shifts, metastable decay is a very sensitive probe of ion stability with respect to the available fragmentation pathways.[22] It is comparatively straightforward to demonstrate that, under conditions where competing processes have similar transition states, metastable decay is exhibited by the lowest energy pathway available to an ion.[23,24] For the examples discussed here, the appearance of metastable decay is used as a measure of the intrinsic instability of a hydrated metal dication with respect to proton transfer. The distinction between metastable decay and CID means that results obtained using the former are frequently different from those studies where collisions have been used to increase the energy content of ions. In the case of Zn^{2+}, this difference has a significant influence on how the results can be interpreted.

The complexes have been prepared using the pick-up technique, details of which have been presented previously.[25] The fragmentation pattern of each size-selected complex has been studied on a VG ZAB-E double focusing, high resolution mass spectrometer using the MIKES technique.[26] In the latter,

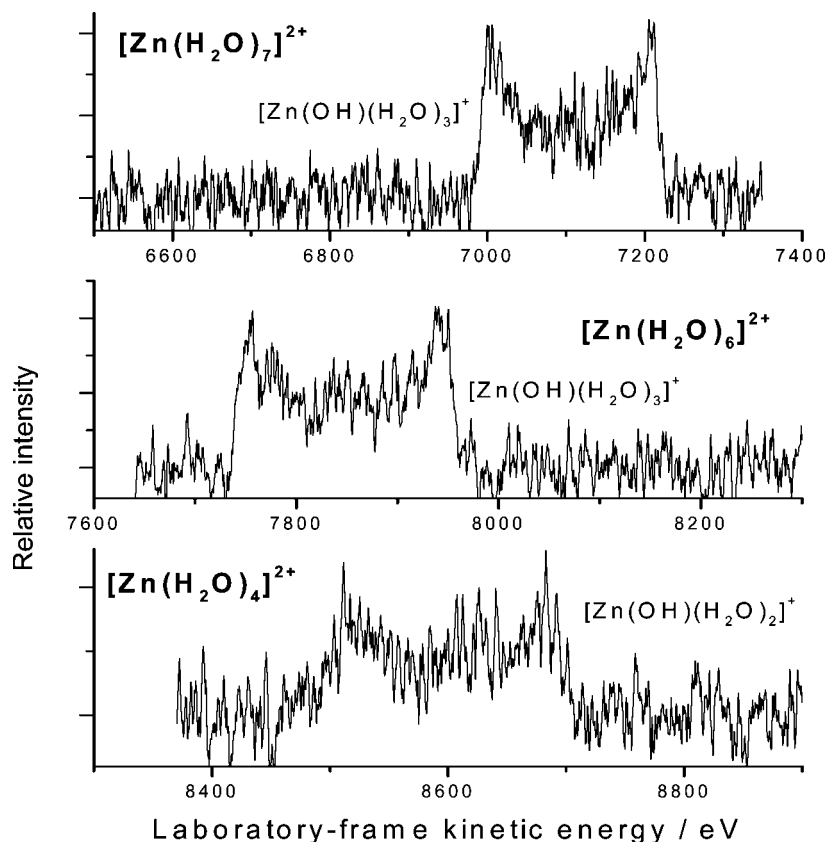**Figure 1.** Kinetic energy profiles recorded for metal-containing fragments following the metastable decay of $[^{64}Zn(H_2O)_N]^{2+}$ complexes. Results are shown for $N = 4$, 6, and 7 together with each proposed counterion.

TABLE 1: Summary of Unimolecular (Metastable) Fragmentation Pathways Observed for $[Zn(H_2O)_N]^{2+}$ and $[Mg(H_2O)_N]^{2+}$ Complexes

N in $[Zn(H_2O)_N]^{2+}$	ZnOH$^+$ fragment	counterion
4	ZnOH$^+$(H$_2$O)$_2$	H$_3$O$^+$
5	ZnOH$^+$(H$_2$O)$_2$	H$_3$O$^+$·H$_2$O
6	ZnOH$^+$(H$_2$O)$_3$	H$_3$O$^+$·H$_2$O
7	ZnOH$^+$(H$_2$O)$_3$	H$_3$O$^+$·(H$_2$O)$_2$
[Mg(H$_2$O)$_3$]$^{2+}$	MgOH$^+$(H$_2$O)	H$_3$O$^+$

ions with a given m/z value are selected using a magnetic sector, and following fragmentation in a field-free region, any charged products are identified by scanning an electrostatic analyzer. Figure 1 shows three examples of unimolecular (metastable) decay where laboratory-frame kinetic energy profiles of ionic fragments have been recorded for reaction 1, which is the gas phase equivalent of the forward step in aqueous hydrolysis.

$$[Zn(H_2O)_N]^{2+} \rightarrow Zn^{2+}OH^-(H_2O)_M + H_3O^+·(H_2O)_K \quad (1)$$
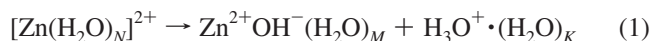
Examples of such behavior have been recorded from complexes where N lies in the range 4−7, M is either 2 or 3, and K is from 0 to 2. In every case, the profile exhibits the classic shape of a fragmentation process that is accompanied by rapid charge separation (Coulomb explosion).[26]

Table 1 summarizes the observed fragmentation patterns, where it can be seen that for the $[Zn(H_2O)_N]^{2+}$ ions given the pathway is very specific and, depending on the initial value of N, leads to the formation of $Zn^{2+}OH^-(H_2O)_{2 \text{ or } 3}$. For $[Zn(H_2O)_N]^{2+}$ ions with $N < 4$, no fragmentation could be observed, and for $N > 7$, Coulomb explosion is replaced by the

loss of a neutral water molecule as the preferred fragmentation pathway. The metal-containing fragment appears to reach an upper size limit and further increases in N are matched by an increase in the number of water molecules that accompany the proton. For reasons of instrumental discrimination, the experiment can only record the metal-containing fragment, and so it is not possible to determine if the loss of H$_3$O$^+$ is always accompanied by bound water molecules. However, if fragmentation involved the loss of H$_3$O$^+$ followed by a sequence of separate water molecules, far more isotropic kinetic energy profiles (cf. Figure 1) would have been expected, as seen, for example, following collision-induced Coulomb explosion.[27] Support for the proposal that H$_3$O$^+$H$_2$O is the counterion when $[Zn(H_2O)_6]^{2+}$ fragments comes from the results of Shvartsburg and Sui,[20] where the ion is observed as the result of a CID experiment. Thermodynamic evidence in support of the formation of H$_3$O$^+$·(H$_2$O)$_K$ units as opposed to H$_3$O$^+$ + KH$_2$O is given below.

To illustrate just how effective Zn^{2+} is at releasing a proton from water, Table 1 also presents the only result recorded from a similar study of $[Mg(H_2O)_N]^{2+}$ complexes.[28] As can be seen, there is a very considerable difference in behavior between the two ions, with Zn^{2+} promoting proton loss even when associated with numbers of water molecules (7) that go beyond what should constitute the first solvation shell. Although proton transfer can be induced in larger $[Mg(H_2O)_N]^{2+}$ complexes, this only happens following collisional activation.[20,21,28] At first sight, there are no obvious reasons why Zn^{2+} and Mg^{2+} should be so different; both ions are closed-shell and the charge densities experienced by individual water molecules in octahedral geometries should be almost identical. However, for Zn^{2+}, there are other $[Zn(H_2O)_4]^{2+}(H_2O)_{N-4}$ structures that are close in energy
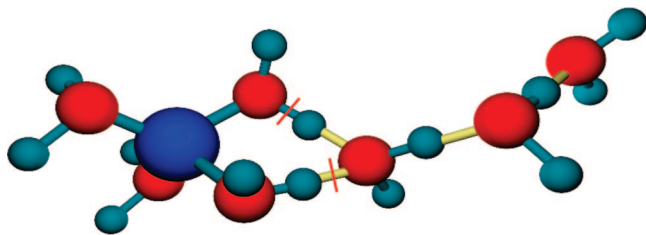
Figure 2. Possible configuration that could lead to the formation of $ZnOH^+(H_2O)_3$ and $H_3O^+\cdot(H_2O)_2$ from $[Zn(H_2O)_7]^{2+}$. Zinc (blue), oxygen (red), hydrogen (gray), and hydrogen bonds (yellow). The red lines show the O−H bond and the hydrogen bond that would have to be broken to form the observed singly charged fragments.

to $[Zn(H_2O)_6]^{2+}$.[2−5] What 4-fold coordination means for Zn^{2+} is that the ionic radius drops to 74 pm,[17] which leads to a significant increase in charge density. As a consequence, the first shell water molecules become more polarized, which in turn increases the magnitude of the positive charge on the H atoms. Such an effect is clearly seen in the calculations by Bock et al.,[2] where H atoms in a six-coordinate Zn^{2+} structure carry +0.51 e of charge, which in $[Zn(H_2O)_4]^{2+}(H_2O)_{1\ or\ 2}$ structures increases to +0.56 e.

From a consideration of the results presented in Table 1, there appear to be two factors determining the composition of products from the fragmentation of $[Zn(H_2O)_N]^{2+}$ complexes. First, with $Zn^{2+}OH^-(H_2O)_M$ as a product, the series converges to $M = 3$, which matches one of the hydrolysis pathways identified by Zhu and Pan as being energetically favorable.[6] This four-coordinate product would also conform to the acknowledged flexibility of Zn^{2+} to adopt configurations other than 6-fold. The smallest (inferred) nonmetallic fragment is the isolated Eigen ion H_3O^+. At $N = 5$, it would have been possible to form the (favored) $Zn^{2+}OH^-(H_2O)_3$ ion, but instead, formation of the Zundel ion, $H_5O_2^+$, is the observed route. This result correlates with what is known regarding relative changes in $\Delta H°$ for these two options; for the addition of H_2O to $Zn^{2+}OH^-(H_2O)_2$, $\Delta H°$ has been calculated as −95 kJ mol⁻¹,[6] whereas, for the addition of H_2O to H_3O^+, $\Delta H°$ has been measured as −151 kJ mol⁻¹.[29] If the same comparison is made for the $N = 6$ products, then the enthalpy change for the addition of H_2O to $H_5O_2^+$ is now −93 kJ mol⁻¹,[29] and thus, the fragmentation pathway switches in favor of forming $Zn^{2+}OH^-(H_2O)_3$.[6] As noted earlier,[22−24] a competitive shift makes metastable pathways extremely sensitive to very small changes in reaction activation energy. Finally, it can be assumed that the $N = 7$ pathway is determined by the underlying structural stability of the $Zn^{2+}OH^-(H_2O)_3$ unit;[6] indeed, the calculated change in $\Delta H°$ for the addition of water to the latter is approximately half that gained in forming the observed ion, $H_7O_3^+$.[29]

A pathway that will yield $ZnOH^+(H_2O)_3$ and $H_3O^+\cdot(H_2O)_2$ as products from the fragmentation of $[Zn(H_2O)_7]^{2+}$ has to involve an initial structure that either has three water molecules in an outer solvation shell or can facilitate the promotion of one or more water molecules during passage along the reaction profile.[30,31] A possible schematic configuration, which is derived from previous calculations,[2,4,5] is shown in Figure 2. The core structure consists of the $[Zn(H_2O)_4]^{2+}$ unit which then has three additional water molecules in a hydrogen bond chain. Clearly, the outermost water molecule could hydrogen bond to the second shell water to give the same result. To achieve the formation of $ZnOH^+(H_2O)_3$ requires breaking just one hydrogen bond and one O−H bond (as shown by the red lines). Were Zn^{2+} to be part of a six-coordinate structure, then an additional two cation−water bonds would have to be broken to achieve the

TABLE 2: Critical Size for the Occurrence of Proton Transfer in Complexes of Zn^{2+} and Mg^{2+} with Water, $[M(H_2O)_N]^{2+}$

| | collision-induced dissociation | | |
dication	Kebarle et al.[a]	Shvartsburg et al.[b]	unimolecular decay[c]
Zn^{2+}	5	6	7
Mg^{2+}	3	4	3

[a] Reference 19. [b] Reference 20. [c] Present work.

TABLE 3: Kinetic Energy Release Measurements

N in $[Zn(H_2O)_N]^{2+}$	$\langle E_t\rangle$/eV
4	1.78
5	1.67
6	1.64
7	1.50
$[Mg(H_2O)_3]^{2+}$	2.17

observed fragmentation pattern. Table 2 summarizes earlier measurements by Peschke et al.[19] and Shvartsburg and Siu[20] on the largest Zn^{2+}/water and Mg^{2+}/water complexes to exhibit proton transfer. For data recorded in the presence of a collision gas, there is clearly some uncertainty, which in the case of Zn^{2+} gives some doubt as to a possible contribution from water molecules in the second solvation shell. That uncertainty is removed by examining the ions for evidence of unimolecular decay.

Table 3 gives values for the average kinetic energy release, $\langle E_t\rangle$, that have been determined from peak widths such as those given in Figure 1. At their maximum, these values would represent the energy difference between the highest point on the reaction profile (the transition state) and the combined potential energies of the reaction products. It is quite possible that $\langle E_t\rangle$ is smaller than this energy difference because some fraction of the reaction exothermicity becomes channeled into internal energy of the products. However, as noted by Solà et al.[1] from their calculations on Zn^{2+}/water complexes, the transition state for proton transfer is located sufficiently far from the starting configuration that it has a geometry which closely resembles that of the final products. For the reaction of a neutral species on such a surface, a significant fraction of the available exothermicity would be predicted to appear in the form of kinetic energy.[32] The Coulomb energy is certainly not being partitioned in a statistical manner because, for that to happen, $\langle E_t\rangle$ at $N = 7$ would have to be approximately half the value of $N = 4$. If it is assumed that $\langle E_t\rangle$ is a reasonable measure of Coulomb repulsion at the point of charge separation, then the distance between the charges can be estimated from $R = 14.4/\langle E_t\rangle$,[26,32] which for $N = 7$ gives ∼9 Å. This value would equate with a chain of four water molecules and also fits within the range estimated for a "water wire" in carbonic anhydrase.[33] However, the simple equation given above is known to overestimate proton transfer distances and more accurate values can be obtained by representing the transfer transition states as a "salt bridge".[30] Finally, Table 3 also gives a value for $\langle E_t\rangle$ measured from the metastable peak associated with the decomposition of $[Mg(H_2O)_3]^{2+}$. As can be seen, this value is larger than would have been predicted from either an extrapolation of the Zn^{2+} data or from a consideration of the relative bond strengths of $ZnOH^+$ and $MgOH^+$.[15] Calculations suggest that for the water dimer of both ions the transition state is close in geometry to the reaction products;[1] however, the difference in $\langle E_t\rangle$ could be due to the geometries adopted by additional molecules when proton transfer occurs.

Zn^{2+} clearly facilitates proton release from coordinated water molecules and does so in a way that is far more effective than Mg^{2+}. The results support the proposal that Zn^{2+} achieves this difference by adopting a four-coordinate structure that serves to increase charge density on the metal cation. As presented in Figure 2, the proton could be part of a chain that is up to four molecules in length; however, these results only apply to water as a ligand. If, as anticipated,[1,11] both the histidine side chains and the molecule receiving the proton in carbonic anhydrase moderate the behavior of Zn^{2+}, then the water chain could be longer than four molecules.

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